The work on which this thesis is based is my own independent work, except where acknowledged.

Nikil Patel

May 2015

Dedicated to the patients who took part in the study

Abstract

'Causes of Brain Injury Associated with Cardiac Interventions'

Nikil Patel

Background & Objective

Brain injury after cardiac surgery is a serious concern for patients and their families. Thousands of air bubbles enter the cerebral circulation during cardiac surgery, but whether these are harmful to the brain and impact adversely on cognition remains subject of speculation.

The purpose of this study was to use MRI to characterise new and pre-existing cerebral ischaemic lesions in patients undergoing cardiac surgery, and to test whether the accumulation of new lesions adversely affects cognition. This study also draws upon recent advances in intra-operative bubble sizing to investigate whether high volumes of macro-bubbles have potential to result in new MRI lesions or increased risk of cognitive decline following surgery.

Methods

The burden of pre-existing versus new ischaemic lesions was quantified based on analysis of 3T MR images and compared with the results of cognitive testing. Intra-operative Doppler ultrasound recordings were used to estimate the number, volume and diameters of bubbles entering the middle cerebral artery during surgery for comparison with MRI and cognitive outcome.

Results

Post-operative lesions were identified in 31% of patients. Patients with pre-existing lesions were 10 times more likely to receive new lesions after surgery. Forty six percent of patients experienced postoperative cognitive decline, which was independent of whether new lesions were present. Intra-cardiac patients received over 16 times the total volume of air, 7 times as many macro-bubbles, 5 times as many emboli following aortic cross-clamp removal, and over twice as many emboli overall than CABG patients, but there were no significant differences in MRI or cognitive outcome.

Conclusions

New MRI lesions and high numbers of intra-operative macro-bubbles are common during cardiac surgery, but we found no evidence of any adverse effect on cognition.

Acknowledgments

I wish to express my deepest gratitude to Dr Emma Chung who has been an outstanding academic supervisor, and would like to take this opportunity to show my appreciation for her time, encouragement and skilful supervision throughout my work. An equally sincere appreciation is also owed to Dr Mark Horsfield for his co-supervision and support with the study; his expert knowledge and ideas have been warmly received and his guidance highly valued. I am indebted to both supervisors for their kindness, generosity and deep knowledge of the subject which has made this journey a very pleasant and rewarding experience.

My grateful thanks are given to the Leicester Cardiovascular Biomedical Research Unit for funding my research. I would also like to thank the nurses and theatre staff at the Leicester Glenfield Cardio-thoracic Unit for their help and support throughout this study.

I owe appreciation to Dr Caroline Banahan and Mr Clément Rousseau for the design and development of the Doppler signal analysis software. My special thanks also go to Dr Mark Horsfield for developing the MRI registration and subtraction software. I would also like to thank Mr David Marshall for measurements of the MCA diameters and Dr Jim Hague for his adapted Monte-Carlo simulations, both of which were valued contributions to the study. The timely support of Dr Caroline Banahan and Mrs Justyna Janus for their assistance with patient recruitment and data collection will always be highly appreciated; both were a pleasure to work with.

My time spent in research has very much heightened my strong friendship with all those working in the Department of Cardiovascular sciences and Medical Physics. I am extremely grateful for your support and making me feel welcome in the department. My friends and colleagues, Bharti, Clément, Nazia, Kunal, Jamie, Kumar, Caroline, Justyna, Sarah, Baris and David are just some of those who have contributed greatly to my professional development and blessed me with their friendship.

I thank my parents for their continual support throughout this journey; their encouragement and pride have been both overwhelming and sustaining. I owe a special thanks to my sister, Gayatri Patel for her unconditional support and guidance throughout my work.

Finally, I will forever be indebted to all the patients who took part in the study. It has been a privilege and pleasure to meet each and every one of you. Your selflessness to participate in medical research is the true driving force of advances in medicine. I have truly been humbled by your spirit, your kindness and your willingness to support research into this challenging disease. To them I dedicate this thesis.

Publications arising from this thesis

Work published in peer-reviewed journals

- **Patel N**, Horsfield MA, Banahan C, Janus J, Masters K, Morlese J, et al. Impact of perioperative infarcts after cardiac surgery. *Stroke*. 2015; 46:680-686

- Chung EML, Banahan C, **Patel N**, Janus J, Marshall DA, Horsfield MA, Rousseau C, Keelan J, Evans DH, Hague JP. Size Distribution of Air Bubbles Entering the Brain During Cardiac Surgery. *PLOS One*. 2014

- **Patel N**, Banahan C, Janus J, Horsfield MA, Evans DH, Egan V, Marshall DA, Chung EML. Air emboli during cardiac surgery are unlikely to be a cause of post-operative neurocognitive dysfunction *(In preparation)*

- Horsfield MA, **Patel N**, Thomas AG, Chung EML. Detection of focal longitudinal changes in the brain by subtraction of magnetic resonance images *(In preparation)*

- **Patel N**, Horsfield MA, Banahan C, Janus J, Evans DH, Egan V, Morelese J, Hague JP, Marshall DA, Chung EML. Comparison of MR data with virtual patient predictions of brain injury during cardiac surgery *(In preparation)*

- **Patel N,** Minhas JS, Chung EML. Risk Factors Associated with Cognitive Decline after Cardiac Surgery: A Systematic Review *(Submitted)*

- **Patel N,** Minhas JS, Chung EML. The presence of new MRI lesions and cognitive decline after cardiac surgery: A systematic review *(Submitted)*

- **Patel N,** Minhas JS, Chung EML. Intraoperative embolisation and cognitive decline after cardiac surgery: A systematic review *(Submitted)*

Conference and Meeting abstracts

- **Patel N**, Banahan C, Janus J, Evans DH, Chung EML. 'Emboli-induced brain injury during cardiac surgery'. *International Conference on the Heart and Brain, Paris, France. March, 2012.*

- **Patel N**, Banahan C, Janus J, Evans DH, Chung EML. 'Why do Emboli take a preferred route through the cerebral vasculature?' *8th International World Stroke Congress, Brasilia, Brazil. October, 2012.*

- **Patel N**, Banahan C, Janus J, Horsfield MA, Spyt T, Evans DH, Chung EML. 'Causes of brain injury during cardiac surgery' *6th NIHR Annual Trainee Meeting, Leeds, UK. November, 2012.*

- **Patel N**, Banahan C, Janus J, Horsfield MA, Spyt T, Evans DH, Chung EML. 'Comparison of the number and timing of cerebral emboli during cardiac CABG and valve surgery in conjunction with post-operative MRI scans and neuropsychological tests' *44th Annual Scientific Meeting of the British Medical Ultrasound Society, Telford, UK. December, 2012*.

- **Patel N**, Banahan C, Janus J, Horsfield MA, Spyt T, Evans DH, Chung EML. 'The number and timing of cerebral emboli during cardiac surgery in conjunction with post-operative MRI scans and neuropsychological tests'. *18th European Society of Neurosonology and Cerebral Haemodynamics & the 3rd meeting of Cerebral Autoregulation Network, Porto, Portugal. May, 2013.*

- **Patel N**, Banahan C, Janus J, Horsfield MA, Spyt T, Evans DH, Chung EML. 'The importance of cerebral emboli during cardiac surgery'. *4th NIHR Infrastructure Experimental Medicine Research Training Camp, Berkhamsted, London. June, 2013.*

- **Patel N**, Banahan C, Janus J, Horsfield MA, Evans DH, Chung EML. 'Cerebral ischaemic lesions on FLuid-Attenuated Inversion Recovery imaging are not associated with neuropsychological decline after cardiac surgery'. *9th International World Stroke Congress, Istanbul, Turkey. October, 2014*

Table of contents

List of tables

List of figures

List of Abbreviations

ACA	anterior cerebral artery
ADC	apparent diffusion coefficient
AS	aortic stenosis
AVR	aortic valve replacement/repair
AxC	aortic cross-clamp
BP	blood pressure
CA	cerebral autoregulation
CABG	coronary artery bypass grafting
CBF	cerebral blood flow
CBFv	cerebral blood flow velocity
$CMRO_2$	cerebral metabolic rate of oxygen
CO_2	carbon dioxide
CPB	cardiopulmonary bypass
CSF	cerebrospinal fluid
CT	computed tomography
dB	decibels
DV	double and triple valve
DWI	diffusion weighted imaging
FFT	fast fourier transform
FLAIR	fluid attenuated inversion recovery
GP	grooved Pegboard
GRE	gradient echo sequences
HADS	hospital anxiety and depression scale
HCL	hypercholesterolemia

HCT	haematocrit
HTN	hypertension
ICA	internal carotid artery
IQR	inter quartile range
KPa	kilopascals
LLA	lenticulostriate artery
LVEF	left ventricle ejection fraction
MAP	mean arterial pressure
MCA	middle cerebral artery
MEBR	measured Embolus-to-blood ratio
MIDCAB	minimally invasive direct coronary artery bypass grafting
MHz	megahertz
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MVR	mitral valve replacement/repair
NSE	neuron-specific enolase
O_2	oxygen
Obvs.	observational study
OPCPB	off-pump cardiopulmonary bypass
$PaCO_2$	partial pressure of carbon dioxide
PCA	posterior cerebral artery
PMEA	poly-2-methoxyethylacrylate
POCD	postoperative cognitive decline
PWI	perfusion weighted imaging
RCT	randomised controlled trial
SCA	superior cerebellar artery
SCOLP	speed and capacity of language processing test

SD	standard deviation
SE	standard error
SE	spin echo
SMK	smoker
SWI	susceptibility weighted imaging
TAVI	transcather aortic valve implantation
TCD	transcranial Doppler
TE	echo time
Temp.	temperature
T_1	Time 1 (MRI)
T_2	Time 2 (MRI)
TI	inversion time
TMA	trail Making Test A
TMB	trail Making Test B
TOF	time of flight
TOF	time of flight
TR	repetition time
TVR	tricuspid valve replacement/repair
WAIS-III	Wechsler Abbreviated Scale of Intelligence
WMS-III	Wechsler Memory Scale-Third Edition
Xe_{133}	$Xenon_{133}$

Chapter 1

1 Brain injury during cardiac interventions part I: Pre- and peri-operative risk factors associated with cognitive decline

1.1 Introduction

Over the past 50 years, the question of whether 'fixing the heart comes at a cost to the brain' has been the subject of considerable research. With advances in anaesthesia, surgical technique, and post-operative care, cardiac surgery is now safer than ever before (Selnes *et al.*, 2006). However, as more complex surgery is now being undertaken in older patients, the incidence of neurological complications following surgery, and potential impact on long term cognition has become a growing concern. It is therefore important to be able to quantify brain injuries and identify their causes.

The era of modern cardiac surgery began in the 1950s when cardiopulmonary bypass (CPB) machines were developed for bypassing the heart and lungs during surgery (GIBBON, 1954). Since then, the safety of cardiac surgery has improved year on year and hundreds of thousands of patients now undergo cardiac procedures worldwide. Despite advances in CPB technology and operative techniques, in recent years clinicians have become increasingly concerned about the potential effects of surgery on the brain. Patients are commonly reported to experience cognitive decline and new ischaemic lesions following surgery, which many researchers believe may accelerate long term neuropsychological dysfunction and vascular dementia. Although injuries are hypothesised to result from emboli entering the cerebral circulation during surgery, the role of emboli in causing cognitive decline is unclear. An embolus is the name given to any object that becomes free-floating in the bloodstream with potential to obstruct, or occlude, a blood vessel leading to ischaemia of the tissue. If periods of brain ischaemia are prolonged, it can eventually result in permanent tissue damage (infarction). In a cardiac surgery setting, emboli typically consist of air bubbles that enter the circulation from the bypass machine or open chambers of the heart, and dislodged pieces of

atherosclerotic plaque released during application and removal of the aortic cross-clamp. Although cardiac surgeons use filters and de-airing procedures to try and reduce the number of emboli reaching the brain, none of these measures are completely effective at eliminating emboli from the cerebral circulation. This thesis focuses on the role of emboli in generating brain injury during cardiac surgery by identifying new brain injuries following surgery and comparing the timing and characteristics of intra-operative emboli with the results of magnetic resonance (MR) scans and neuropsychological testing.

1.2 Cardiac surgery procedures

1.2.1 Coronary Artery Bypass Graft (CABG)

One of the most common major surgical procedures carried out in the UK is coronary artery bypass grafting (CABG). CABG surgery aims to avoid cardiac ischaemia by bypassing diseased regions of the coronary arteries, to restore normal blood flow to the cardiac myocardium. During surgery, a piece of the saphenous vein, radial vein, or mammary artery is grafted to the coronary arteries to bypass regions that have been narrowed by atherosclerosis. In 2010/2011 alone, 16,408 CABG surgeries were performed in the UK (Society of Cardiothoracic Surgery, surgical statistics, 2013).

1.2.2 Valve replacement or repair

The second most common type of cardiac surgery after CABG involves replacement or repair of one or more heart valves. The heart contains four major valves; the tricuspid valve, pulmonary valve, mitral valve and the aortic valve. Over time, valves can become damaged or stenosed (aortic stenosis), or may leak and become inefficient (aortic regurgitation). The most common valve requiring treatment is the aortic valve, positioned at the outlet of the heart. Although in some cases the valve may be repaired, in the majority of operations the valve is completely replaced with a mechanical or biological (tissue) valve. Valve surgery is often performed in combination with CABG, sometimes referred to as combined surgery. According to the UK Society of

Cardiothoracic Surgery, around 5,000 aortic valve surgeries were performed from 2010-2011 (NHS direct website, 2012).

1.2.3 Cardiopulmonary bypass

CABG and valve procedures are both normally performed in conjunction with Cardiopulmonary Bypass. Recognition for the development of modern day cardiopulmonary bypass (CPB) is given to John Gibbon who developed the first functional heart-lung machine at the Mayo Clinic (USA) in the 1950s (GIBBON, 1954). Although early CPB machines were not safe for clinical use as they damaged red blood cells, Gibbon and other researchers gradually refined their methods and the first heart-lung bypass machine was trialled in humans in 1953. Today, CPB is commonly used to take the role of the heart and lungs for many hours during cardiac surgery. Despite advancements in CPB technology, key neurological complications were noted shortly after CPB came into widespread use (CAGUIN & CARTER, 1963; GILMAN, 1965). These complications ranged from; cognitive dysfunction, delirium and focal stroke, to coma and death. As injuries were thought by many clinicians to be associated with the use of CPB, the phenomenon of cognitive decline following cardiac surgery was commonly referred to as ‘pump-head’.

Over time, the demographic characteristics of patients undergoing cardiac surgery have shifted to include a higher proportion of elderly patients, undergoing increasingly complex procedures. The average age of cardiac surgery patients has increased from ~64 years in 2001 to ~67 years in 2010, fig. 1.1(a). The number of patients with neurological disease prior to surgery has nearly doubled from 1.4% in 2001 to ~2.8% in 2010, fig. 1.1(b). Cardiac surgery procedures have also become more complex, with the number of patients undergoing isolated CABG decreasing by almost 20% from 2001-2010, fig 1.1(c). Despite higher patient risk profiles, the mortality rate has fallen slightly from 4.0% in 2001/2002 to 3.1% in 2010/2011 (National Cardiac Surgery Audit, UCL, 2012), suggesting that the overall safety of cardiac surgery is improving.

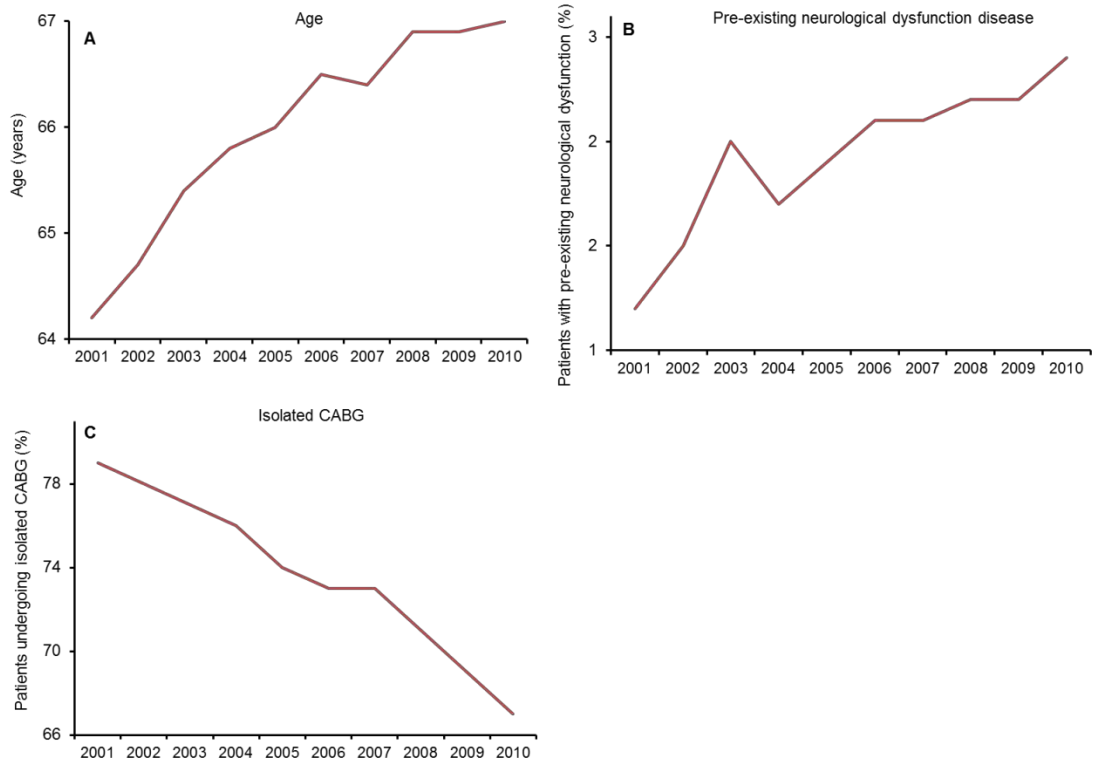


Figure 1.1 In the decade from 2001 to 2011 (A) the mean age, and (B) the incidence of pre-existing neurological dysfunction of cardiac surgery patients both increased. (C) The proportion of patients undergoing isolated CABG decreased, reflecting an increase in the complexity of surgery. These data were taken from the National Office of Statistics, compendium of population health indicators, portal code P00680 (www.indicators.ic.nhs.uk, accessed on 20/01/2013).

1.3 Stroke and neurological complications following cardiac surgery

Neurological complications after cardiac surgery vary from mild/moderate neurocognitive impairment to fatal stroke. As the brain is one of the most complex organs of the human body, even small injuries have potential to lead to symptomatic loss of brain function, while, depending on location, larger lesions may remain asymptomatic.

The World Health Organisation (WHO) defines stroke as; "*suddenly (within seconds) or at least rapidly (within hours), developing clinical signs of focal or global disturbance of cerebral functions, with symptoms lasting for 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin*" (Report of the WHO task force on Stroke, 1989). If the symptoms and signs disappear within 24 hours the event is

defined as Transient Ischaemic Attack (TIA). Symptoms and signs of stroke are caused by interrupted brain perfusion leading to tissue damage.

Previously, a large study investigating the incidence of stroke following cardiac surgery was conducted by Bucerius *et al.* (2003). Based on data from 16,184 cardiac surgery patients, the incidence of stroke was estimated to vary from 2 - 4% for CABG procedures rising to almost 10% for patients undergoing double or triple valve surgery, fig. 1.2.

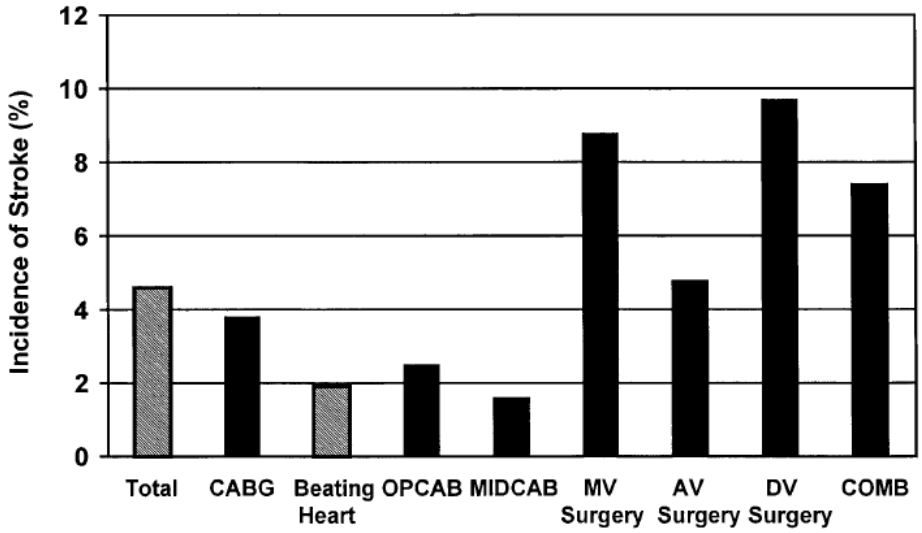


Figure 1.2 The incidence of stroke is related to the type of surgical procedure. AV- aortic valve; CABG- coronary artery bypass grafting; COMB- combined procedures; DV- double and triple valve; MIDCAB - minimally invasive direct coronary artery bypass grafting; MV- mitral valve; OPCAB- off-pump coronary artery bypass grafting. Beating Heart - all patients undergoing beating heart surgery **(Bucerius *et al.*, 2003)**.

1.4 Post-operative cognitive decline

Routine clinical examination covers crucial neurological abnormalities such as; ataxia (disorders affecting co-ordination, balance and speech), visual defects, paresis (paralytic dementia) and hypoesthesia (decreased sensitivity to touch) (Brott *et al.*, 1989). It also includes focal neuropsychological deficits such as; apraxia (motor dysfunction), dyscalculia (arithmetic disorder) and aphasia (communication disorder). However, more global cerebral dysfunction, such as neuropsychological decline, mood and memory disturbances, personality changes, and decline in psychomotor speed are commonly missed because they require more explicit examination using specialised neuropsychological tests (Murkin *et al.*, 1995).

Post-operative cognitive decline (POCD) broadly refers to difficulties associated with memory and general information processing after surgery. At present POCD is not documented in the International Classification of Diseases and is not listed as a diagnosis. The term POCD is used in the literature to describe patients who experience decline in a range of neuropsychological domains such as speed and information processing, executive functioning, short-term and delayed memory. In the International Consensus Statement of Neurobehavioral Outcomes after Cardiac Surgery, POCD was defined as the following:

'*A spectrum of postoperative central nervous system dysfunction both acute and persistent, including subtle neurologic signs, neuropsychological impairment, stroke or brain death'* (Murkin *et al.*, 1995).

According to the American Heart Association and American College of Cardiology, POCD can be divided into two categories. Type I is associated with major focal deficit, apathy or coma. Type II deficits are without detectable focal lesions but are nonetheless associated with diffuse symptoms in terms of confusion, memory loss, agitation and a decline in intellectual ability (Edmunds *et al.*, 1996). Following cardiac surgery, between 2 and 8% of patients are thought to experience a type I deficit. Type II deficits (Wolman *et al.*, 1999; Hogue *et al.*, 1999) are estimated to affect 15-63% of patients, depending on the cognitive testing methods used (Mahanna *et al.*, 1996; Barber *et al.*, 2008). Throughout this thesis the term POCD is used to refer to type II POCD, identified using neuropsychological testing.

1.5 Neuropsychological outcome after cardiac surgery - Literature search

To investigate the incidence and causes of cognitive decline, a systematic literature search was performed drawing on papers from PubMed and EMBASE. All studies published in English between June 1967 and August 2013 and featuring adult human subjects were eligible for review.

Search terms were created by combining the following medical subject headings (MeSH terms):

#1: "Coronary Artery Bypass" OR "Coronary Artery Bypass, Off-Pump" OR "Valve Surgery" OR "Thoracic Surgery" OR "Cardiac Surgical Procedures"

AND

#2: "Cognitive Therapy" OR "Cognition Disorders" OR "Cognition" OR "Neuropsychology" OR "Neuropsychological Tests" OR "Mild Cognitive Impairment"

Abstracts involving both cardiac surgery and cognitive function (#1 AND #2) were independently reviewed by two investigators (N. Patel and E.M.L. Chung) and studies of adult cardiac surgery patients that assessed both pre- and postoperative cognitive function were identified for full manuscript review. Abstracts were excluded if they involved paediatric surgery, operations other than cardiac surgery, or no measurement of cognitive function. Case reports and studies of cardiac procedures such as, angioplasty, angiography, valvuloplasty and Transcatheter Aortic Valve Implantation (TAVI) were also excluded. Studies generating multiple publications from the same cohort were reported only once. Where there was disagreement between investigators the full text was reviewed. Additionally, the reference lists of selected articles were evaluated for any additional articles of interest. Articles short-listed for full manuscript review were summarised in an Excel spreadsheet listing the; study design (observational, RCT, etc.), number of patients, type(s) of surgery, outcome measures, and time point of neurocognitive assessment. Studies that included assessment of anxiety and depression were noted as mood is known to have an impact on cognitive test results.

A total of 638 abstracts were systematically identified using our search criteria of which 426 papers were suitable for full review. Of these, 296 were observational studies and 130 were RCTs, fig 1.3.

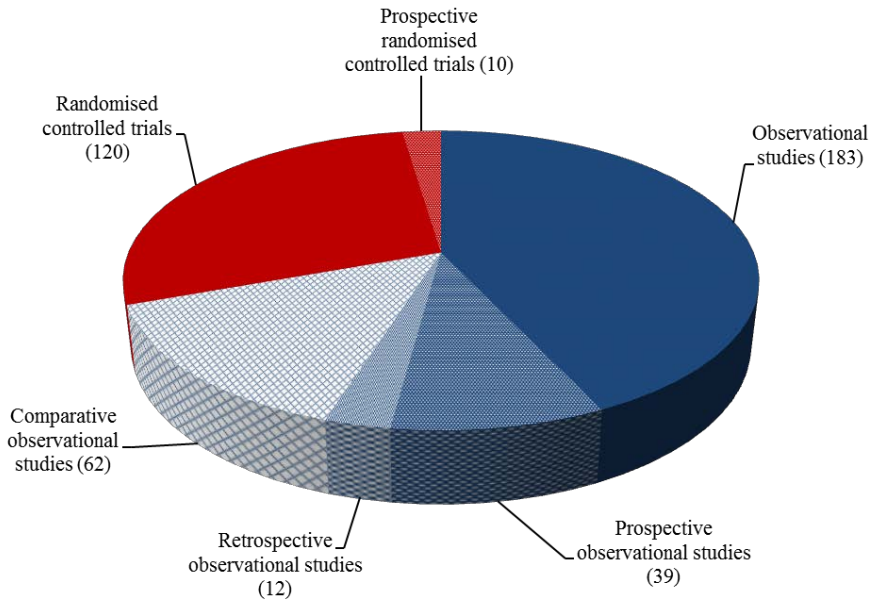


Figure 1.3 Design of original research articles investigating neuropsychological outcome after cardiac surgery. Areas shaded in red indicate RCTs (31% of studies) and areas shaded in blue indicate observational studies (69% of studies).

Although over 420 original research articles were identified as having investigated cognitive decline following cardiac surgery, we found little consensus on the incidence, severity, and time course of symptoms. Differing methodologies used between studies made it difficult to directly compare study findings through systematic meta-analysis. Indeed, some studies suggest that cognitive decline following surgery is transient and that long-term decline in cognition is very similar to that in non-operative controls (Selnes *et al.*, 2003). In a prospective study by Selnes *et al.* (2003) a group of 140 CABG patients were compared with 92 demographically similar patients with diagnosed coronary artery disease but no surgery. Both groups showed improved scores from baseline to 12 weeks with no statistically significant differences between the two groups.

1.6 Timing of assessment for postoperative cognitive decline

Most studies evaluating cognitive decline focus on changes in executive function, learning language, visual spatial skills, attention, and memory (Rudolph *et al.*, 2010). However, neuropsychological tests vary considerably between studies and also appear

to depend on the timing of neurocognitive assessment. By narrowing the search to empirical research articles that studied postoperative neuropsychological assessment as a primary outcome, the number of publications was reduced to 109 articles. Thirty-three of these articles were excluded because the total percentage of patients who declined in cognitive tests was unclear. Four articles had published the same data twice and full-texts were unavailable for 6 articles. A total of 66 articles independently investigating 94 time-points are summarised in figure 1.4 and 1.5. This summarises the estimated percentage decline reported by previous researchers at discharge, 1 week, 2-8 weeks, 3 months, 6 months, 1 year and 3-5 years post-operatively.

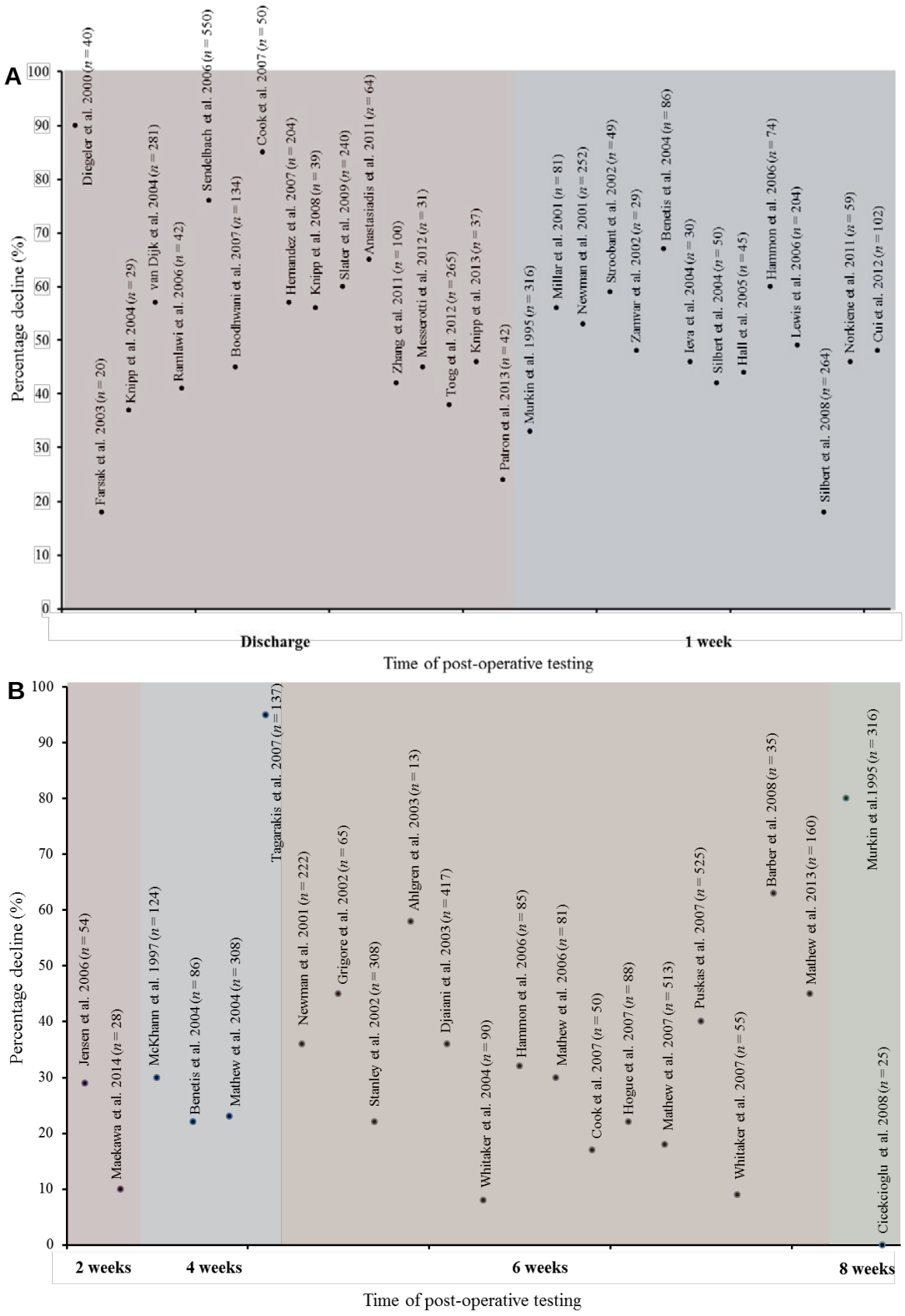


Figure 1.4 Incidence of post-operative cognitive decline measured by previous researchers at (A) discharge and 1 week, (B) 2, 4, 6 and 8 weeks.

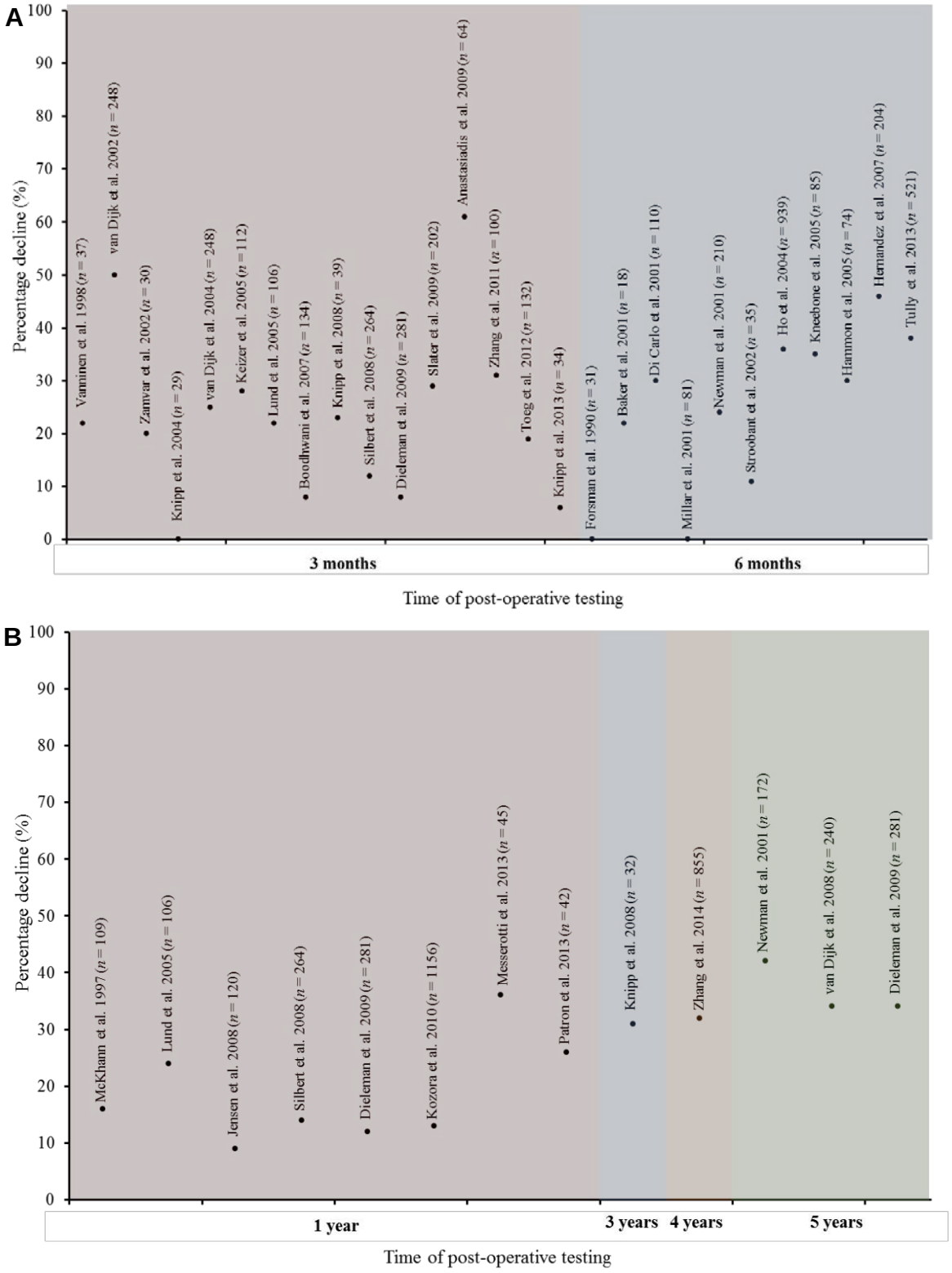


Figure 1.5 Incidence of post-operative cognitive decline measured by previous researchers at (A) 3 months and 6 months, (B) 1, 3, 4 and 5 years.

Grouping studies where assessments were performed at similar time points, and plotting the proportion of patients estimated to be affected by cognitive decline suggests that 40-60% of patients experience cognitive decline when tested within 2 weeks of surgery, falling to 30-40% after 8-10 weeks, recovering to 10-20% at 1 year, with proportion of patients experiencing cognitive decline increasing again at 3-5 years, fig 1.6.

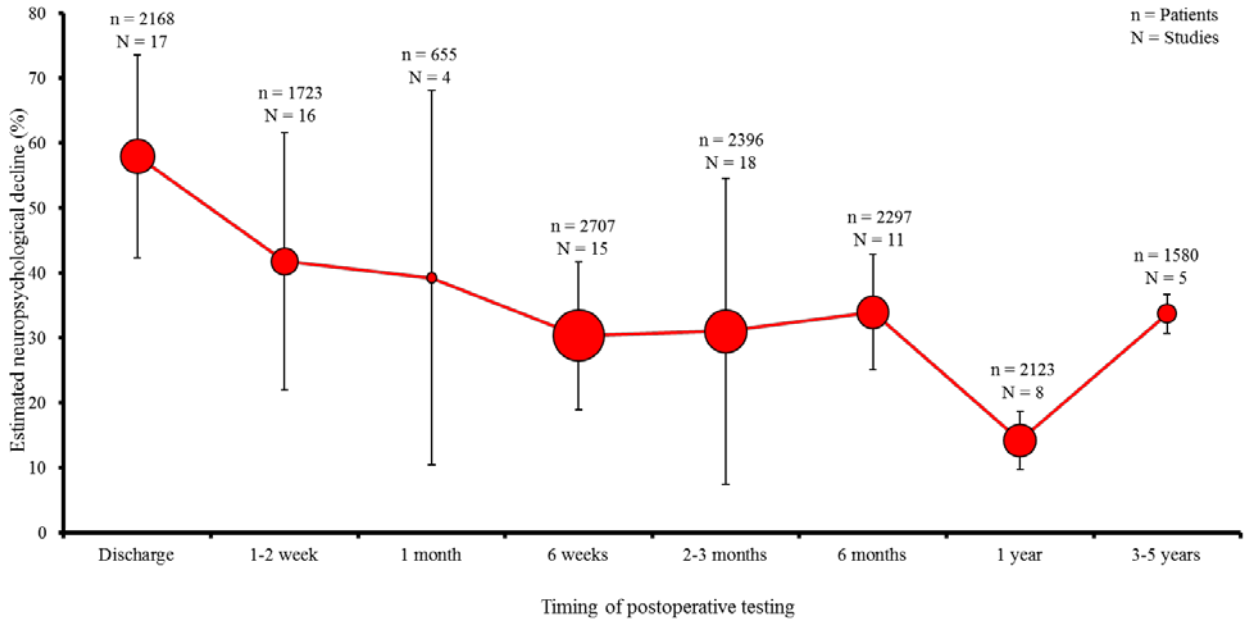


Figure 1.6 Studies attempting to quantify neuropsychological decline at various time points. The weighted mean and standard deviation (number of patients and % decline) is plotted by combining data from a total of 15649 patients and 94 studies; Discharge (17 studies), 1-2 weeks (16 studies), 1 month (4 studies), 6 weeks (15 studies), 2-3 months (18 studies), 6 months (11 studies), 1 year (8 studies), 3-5 years (5 studies).

As can be seen from fig 1.6, large variations in the estimated incidence of post-operative cognitive decline are observed, even after grouping studies where tests were performed at similar time-points. Heterogeneity in assessment methods, patient demographics, and study design may be responsible for these variations.

In a previous study of 261 patients by Newman *et al.*, 40% of patients were found to have cognitive decline 5 years after surgery. The authors also reported that patients who experienced early postoperative decline (~2-3 months) were more prone to experience further decline later in life (Newman *et al.*, 2001). However, that study did not feature a control group, and the few studies that have compared cardiac surgery patients with

non-cardiac surgery controls possessing similar levels of cardiovascular disease suggest that cognition 3-5 years after surgery is similar to that of non-operative controls (Selnes *et al.*, 2003). Most studies, including the study described in this thesis, do not include a control group.

1.7 Patient risk factors for post-operative cognitive decline

Factors thought to be associated with neuropsychological decline include years of education, advanced age, and pre-existing cognitive decline. A prospective longitudinal study investigating patient-related risk factors and the incidence of POCD in 1,064 patients following major non-cardiac surgery found that advanced age was the biggest single risk factor predicting the likelihood of POCD following surgery (Monk *et al.*, 2008). The incidence of POCD is therefore likely to increase as the number of older patients grows (Robinson *et al.*, 2012).

- Age (16 studies found evidence for an association with age and cognitive impairment)
- Pre-existing cognitive impairment (15 studies found evidence for an association with pre-existing cognitive impairment)
- Impaired cerebral autoregulation (2 studies found evidence for an association with impaired cerebral autoregulation)
- Pre-existing cardiovascular disease (10 studies found evidence for an association with cardiovascular disease or aortic stenosis)
- Cerebrovascular disease (9 studies found evidence for an association with pre-existing cerebrovascular disease)

Note that some studies investigated multiple factors.

1.8 Perioperative risk factors for cognitive decline

Studies investigating perioperative risk factors associated with cognitive decline suggest that there is no single causative factor. Potential mechanisms implicated in the pathogenesis of cognitive decline investigated in previous research include (**RCTs**):

- Cardiopulmonary bypass: 59 **(19)** studies
- Inflammation & systemic inflammatory responses: 28 **(4)** studies
- Blood temperature: 23 **(10)** studies
- Rate of re-warming: 4 **(3)** studies
- Embolisation: 27 **(5)** studies
- Neuroprotective agents: 16 **(16)** studies
- Blood pressure: 5 **(3)** studies
- Impaired cerebral perfusion during surgery: 4 **(0)** studies
- Haemodilution: 1 **(1)** studies
- Use of anaesthetics: 18 **(0)** studies

Figure 1.7 summarises the focus and conclusions of studies examining perioperative factors contributing to cognitive decline, weighted by the size of the study.

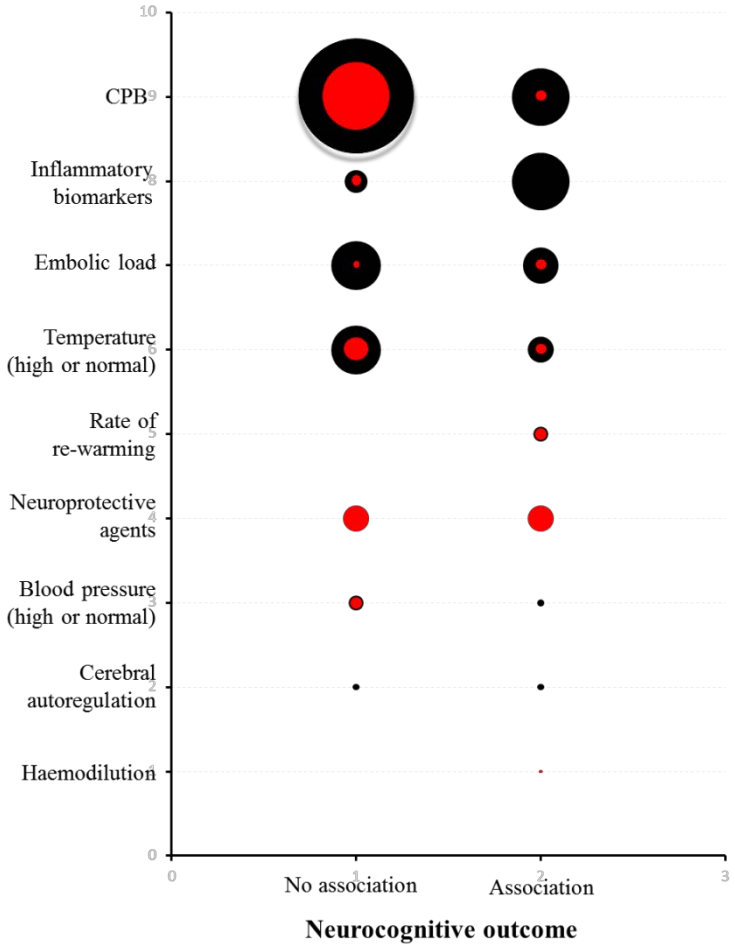


Figure 1.7 Studies examining perioperative factors contributing to cognitive decline. The bubble sizes represent the number of studies investigating each perioperative factor with the area shaded in red indicating the number of RCTs.

1.8.1 Anaesthesia

Sedative and anaesthetic agents with *N-methyl-d-aspartate* receptor antagonist and *γ-aminobutyric acid* mediated properties can temporarily change the neurotransmission of the brain by interacting at a cellular level to achieve deep sedation during surgery (Eckenhoff *et al.*, 2004). Since it would be unethical to perform cardiac surgery without the use of anesthetic agents, the impact of anesthesia on cognition is difficult to study.

Fifteen studies have investigated whether choice of anaesthesia impact neurocognitive outcome after cardiac surgery. Of these, 8 were randomised controlled trials (RCTs), comparing 9 different types of anaesthetic agent. Studies showing an improvement, decline and no difference in postoperative outcome are summarised in table 1.1.

Table 1.1 Studies comparing cognition after cardiac surgery following administration of different types of anaesthetic.

Study	Study design	No. of patients	Type of anaesthesia/drug	Time of post-operative cognitive assessment
Studies showing an improvement in post-operative outcome				
(Dumas *et al.*, 1999)	RCT	48	Fentanyl & Early extubation	8 weeks
(Dowd *et al.*, 2001)	RCT	78	Propofol & lorazepam	6-12 months
(Bottio *et al.*, 2007)	Observational	50	Epidural anaes.	6 months
(Delphin *et al.*, 2007)	Observational	91	Sevoflurane & isoflurane	2 hours and 1 day
(Kanbak *et al.*, 2007)	RCT	40	Isoflurane, sevoflurane & desflurane	3 and 6 days
(Hudetz *et al.*, 2009)	Observational	78	Ketamine	1 week
(Schoen *et al.*, 2011)	RCT	117	Sevoflurane & propofol	2, 4 and 6 days
Studies showing a decline in post-operative outcome				
(Kanbak *et al.*, 2007)	RCT	40	Sevoflurane & desflurane	3 and 6 days
Studies showing no difference in test outcomes				
(Kadoi *et al.*, 2003)	RCT	180	Propofol and fentanyl	6 months
(Silbert *et al.*, 2006)	Observational	300	Fentanyl	1 week, 3 months, 1 year
(Kadoi & Goto, 2007)	Observational	109	Sevoflurane	6 months

(Lehmann *et al.*, 2007)	RCT	66	Sufentanil & midazolam	Discharge
(Evered *et al.*, 2011)	Observational	281	General anaesthetics	1 week and 3 months
(Parra *et al.*, 2011)	Observational	48	Sevoflurane	3 months
(Royse *et al.*, 2011)	RCT	180	Desflurane & propofol	Discharge and 3 months

This research suggests that choice of anaesthetic has potential to affect cognition, particularly when tests are performed soon after surgery. However, in the majority of larger studies, the choice of anaesthetic had no impact on cognitive outcome.

1.8.2 Blood pressure

A number of studies have investigated the association between low blood pressure during cardiac surgery and cognitive decline. Although normal blood pressure in conscious patients is approximately 120/80 mm Hg, it is common for the blood pressure to be much lower during surgery. As the brain has a lower metabolic demand during anaesthesia, this is not thought to adversely affect tissue perfusion; however, low blood pressure may impair embolus clearance and affect the efficiency of cerebral auto-regulation. A total of 5 studies have used neuropsychological tests to investigate whether mean arterial blood pressure had any impact on postoperative cognitive outcome, table 1.2.

Table 1.2 Studies investigating POCD associated with intra-operative blood pressure variation.

Study	Study design	No. of patients	Type of intervention	Time of assessment
Studies showing a decline in post-operative outcome with lower BP (from baseline)				
(Gold *et al.*, 1995)	RCT	248	High (80-100 mmHg) v low (50-60 mmHg) BP	6 months
(Siepe *et al.*, 2011)	RCT	92	High (80-90 mmHg) v low (60-70 mm Hg) BP	2 days
(Gottesman *et al.*, 2007)	Observational	15	Low MAP (50-70 mmHg)	3-5 days & 1 month
(Newman *et al.*, 1995)	Observational	237	Low MAP (50-60 mmHg)	Discharge
Studies showing no difference in post-operative outcome				
(Charlson *et al.*, 2007)	RCT	412	High MAP (57 -90 mmHg) v Custom (capped at 90 mm Hg)	6 months

In the study by Gold *et al.* (1995), a higher mean arterial pressure (80-110 mmHg) during CPB appeared to be associated with a lower stroke rate (2.4%) compared to a low mean arterial pressure between 45-60 mmHg (7.2%), p=0.026. However, at 6 months follow-up the proportion of patients with neuropsychological decline (11% and 12% respectively) were comparable (Gold *et al.*, 1995). In another study, Siepe *et al.* (2011) showed greater proportion of patients with cognitive decline two days following CABG in patients with mean arterial pressure in the range 60-70 mmHg compared to 80-90 mmHg, however cerebral oxygen saturation was similar in both groups (Siepe *et al.*, 2011). The largest RCT by Charlson *et al.* found no difference in cognition between a 'custom' group (average BP: 79 mmHg) and High BP group (average BP: 89 mmHg), however, the average difference in BP between groups was only 10 mmHg, which may not be a clinically significant difference (Charlson *et al.*, 2007). Overall, studies appear to support the idea that maintenance of a sufficiently high mean arterial pressure during cardiac surgery is important for safeguarding perfusion to the brain.

1.8.3 Cerebral autoregulation

Some researchers have proposed that it is not mean arterial pressure (MAP) *per se* that contributes to cognitive decline, but the capacity of the brain's blood flow regulation mechanisms to respond appropriately to blood pressure variations and changes in oxygen saturation. A number of studies have investigated cerebral autoregulation (CA) in response to blood pressure changes during cardiac surgery and found that a significant proportion of patients struggle to autoregulate their cerebral blood supplies intra-operatively (Ono *et al.*, 2012). However, only 4 studies have specifically investigated CA during cardiac surgery in conjunction with pre- and postoperative neuropsychological assessment (table. 1.3).

Table 1.3 Studies investigating cerebral autoregulation during cardiac surgery in conjunction with neurocognitive tests.

Study	Study design	No. of patients	Cerebral autoregulation measures	Time of assessment
Studies showing a decline in post-operative cognitive outcome with impaired cerebral autoregulation				
(Patel *et al.*, 1993)	RCT	70	Xenon-133 isotope clearance, $CMRO_2$, (cerebral metabolic rate for oxygen) $CERO_2$ (cerebral extraction ratio for oxygen)	6 weeks
(Patel *et al.*, 1996)	RCT	70	CBF , CBFv and O_2 saturation were measured during 4 phases of surgery	6 weeks
Studies showing no difference in post-operative cognition				
(Govier *et al.*, 1984)	Observational	67	Partial pressure of arterial carbon dioxide ($PaCO_2$), clearance of xenon 133	Discharge
(Newman *et al.*, 1994)	Observational	215	Xenon-133 clearance, $CMRO_2$, cerebral AV difference ($C[AV]O_2$)	Discharge

All four studies determined pressure-flow and metabolic-flow cerebral autoregulation during cardiopulmonary bypass using the 133Xe clearance cerebral blood flow method. Two studies in table 1.3 by the same author (Patel *et al*.) support the theory that impaired cerebral autoregulation is associated with a decline in postoperative outcome at 6 weeks, whereas two studies showed no association. The largest study by Newman *et al*. investigated CA in 215 patients and concluded that neuropsychological dysfunction at discharge was not explained by impaired CA; however increased oxygen extraction (measured using a thermodilution pulmonary artery catheter) was observed to be associated with a decline in some cognitive tests. They interpreted this as suggesting that an imbalance in cerebral tissue oxygen supply may contribute to POCD (Newman *et al.*, 1994). In a recent trial it has also been proposed that some anaesthetic agents suppress autoregulatory responses more than others (Tanaka *et al.*, 2011). As far as we are aware, no studies have yet looked at the relationship between CA and POCD beyond 6 weeks.

1.8.4 Inflammatory responses

All types of surgery have the risk of developing systemic inflammation; however, in cardiac surgery using CPB the blood is exposed to foreign surfaces which have potential

to stimulate pro-inflammatory responses. Inflammation causes endothelial dysfunction, which can lead to leakage between the blood-brain barrier and tissue oedema (Abbott, 2000). It has been shown that cytokines (e.g. TNF-alpha, Interleukin-1 and Interleukin-6) have been linked to neuropathology (Terrando *et al.*, 2011; Cibelli *et al.*, 2010). These elementary changes are hypothesised to affect the brain regardless of micro-embolic load received during surgery (Reinsfelt *et al.*, 2012; Reinsfelt *et al.*, 2013) and potentially provide an explanation for early cognitive decline (Baufreton *et al.*, 2005).

Bubble oxygenators require direct contact with the blood for gas exchange. One of the earliest advances in the development of CPB was replacement of the bubble oxygenator with the membrane oxygenator. Blauth et al. confirmed the emboli-handling characteristics of the superior membrane oxygenators in 34 patients and concluded that they generated significantly less emboli, as quantified by retinal fluorescein angiography (Blauth *et al.*, 1990). Other investigators also noted that membrane oxygenators generated a reduced inflammatory response (Videm *et al.*, 1989; Cavarocchi *et al.*, 1986). As a result of these studies, the majority of the cardiac centres worldwide now use membrane oxygenators.

Cardiopulmonary bypass components that come into contact with the blood can be coated with biocompatible materials such as; poly-2-methoxyethylacrylate, heparin, trillium, and synthetic proteins. These coatings aim to reduce inflammatory responses triggered during CPB. Heparin-coated circuits, in particular, have undergone considerable investigation in previous research. A total of 26 studies (including 7 RCTs) have used neuropsychological tests to investigate whether there is a strong association between inflammation and cognitive decline, table 1.4.

Table 1.4 Studies investigating whether biomarkers associated with inflammation and/or interventions aimed at reducing inflammation, are associated with changes in cognition after surgery.

Study	Study design	No. of patients	Marker for cerebral damage	Time of assessment
Studies showing improved cognitive outcome when inhibiting complement activation via heparin-coated CPB				
(Fitch *et al.*, 1999)	RCT	35	Inhibition of complement activation by specific antibody & no antibody	Discharge
(Heyer *et al.*, 2002)	RCT	99	Inhibition of complement activation by heparin-coated	5 days and 6 weeks

			CPB	
(Baufreton *et al.*, 2005)	RCT	30	Inhibition of complement activation by heparin-coated CPB	Discharge
(Skrabal *et al.*, 2006)	RCT	39	(PMEA)-coated circuits and no-coated circuits	7-10 days
Studies showing a higher incidence of cognitive decline in the presence of high levels of biomarkers associated with inflammation				
(Wimmer-Greinecker *et al.*, 1998)	Observational	76	>S-100 and NSE	5 days and 2 months
(Jonsson *et al.*, 1999)	Observational	132	>S-100	2 weeks and 2 months
(Kilminster *et al.*, 1999)	Comparative study	130	>S-100	6-8 weeks
(Rasmussen *et al.*, 1999)	Observational	35	>NSE	discharge and 3 months
(Derkach *et al.*, 2000)	RCT	27	>S-100 and NSE (deep and mild hypothermic)	6 months
(Diegeler *et al.*, 2000)	RCT	40	>S-100 (on- & off pump)	1 week
(Georgiadis *et al.*, 2000)	Observational	190	>S-100	Discharge
(Lloyd *et al.*, 2000)	RCT	125	>S-100 (on- & off pump)	3 months
(Basile *et al.*, 2001)	Observational	16	>S-100 and NSE	6 months
(Rasmussen *et al.*, 2002)	Observational	15	>NSE	discharge and 3 months
(Farsak *et al.*, 2003)	Observational	50	>S-100	discharge
(Mathew *et al.*, 2003)	Observational	460	Reduced preoperative endotoxin immunity	6 weeks
(Jonsson *et al.*, 2004)	Observational	56	>S-100	6 months
(Kofke *et al.*, 2004)	Observational	28	Apoepsilon4 allele, >S-100	8 and 24hrs
(Snyder-Ramos *et al.*, 2004)	Observational	64	>S-100 and NSE	Throughout 7 days
(Kalman *et al.*, 2006)	Observational	14	>Cytokine interleukin-6	1 week and 6 months
(Ramlawi *et al.*, 2006)	Observational	42	>C-Reactive protein	6 hours and 4 days
(Lazibat *et al.*, 2012)	Observational	62	>S-100	2 days
(Bayram *et al.*, 2013)	Comparative study	64	>S-100	1 week
Studies showing no difference in post-operative cognitive outcome in the presence of high levels of biomarkers associated with inflammation				
(Westaby *et al.*, 2001)	Observational	1001	>S-100 and NSE	5 days and 3 months
(Mathew *et al.*, 2005)	Observational	440	Statin treatment	6 weeks

(Plaschke *et al.*, 2013)	Observational	151	Preoperative serum anticholinergic activity	3 months

NSE; neuron-specific enolase, PMEA; poly-2-methoxyethylacrylate

All studies that have randomised patients to receive a heparin coated CPB system found neuropsychological outcome was better in patients receiving the heparin-coated circuit (Heyer *et al.*, 2002; Baufreton *et al.*, 2005; Fitch *et al.*, 1999; Skrabal *et al.*, 2006) . In studies investigating inflammatory responses, a Consensus panel has concluded that '*the use of surface-modified circuits might be effective at attenuating the systemic inflammatory response to CPB and improving outcome*' (Shann *et al.*, 2006). Many markers associated with susceptibility to brain ischaemia such as, *S*-100beta and neuron-specific enolase (NSE) have been suggested to be associated with an increased risk of cognitive decline (Lazibat *et al.*, 2012; Bayram *et al.*, 2013; Westaby *et al.*, 2001). Inflammation may also play an important role in our understanding of long-term cognitive function. Biomarkers for inflammation tend to be higher in patients with chronic cardiovascular disease (Bayram *et al.*, 2013). Overall, the role of inflammation in the pathogenesis of cognitive decline appears to warrant further investigation (Carnevale *et al.*, 2012).

1.8.5 Neuroprotective drugs

A number of neuroprotective agents have been investigated to assess whether these could be administered to help preserve neurocognitive function. The results of 17 studies investigating whether neuroprotective agents reduce the incidence of POCD are summarised in table 1.5.

Table 1.5 RCTs investigating the efficacy of neuroprotection, or neuroprotective agents, in reducing cognitive decline after cardiac surgery

Study	No. of patients	Type of neuroprotective drug	Time of assessment
Studies showing a better post-operative outcome with the use of neuroprotective agents			
(Grieco *et al.*, 1996)	29	GM-100 (Ganglioside) or placebo	1 week and 6 months
(Arrowsmith *et al.*, 1998)	171	Remacemide or placebo	2 months

(Svensson *et al.*, 2002)	403	mannitol, thiopental, MgSO4, lidocaine	2-3 weeks
(Wang *et al.*, 2002)	118	Lidocaine or placebo	9 days
(Uebelhack *et al.*, 2003)	64	Piracetam or placebo	3 days
(Szalma *et al.*, 2006)	98	Piracetam or placebo	6 weeks
(Haljan *et al.*, 2009)	32	Erythropoietin or placebo	Discharge and 2 months
(Hudetz *et al.*, 2009)	52	Ketamine or placebo	1 week
(Zhang *et al.*, 2011)	200	Benzyl Alcohols or Saline (placebo)	Discharge and 3 months
Studies showing no difference in post-operative outcome with the use of neuroprotective agents			
(Kong *et al.*, 2002)	245	Chlormethiazole/administration or placebo	4-7 weeks
(Taggart *et al.*, 2003)	150	Imidazoles: low dose (10 mg) or high dose (100 mg) or placebo	5 days and 3 months
(Mathew *et al.*, 2004)	914	Pexelizumab bolus, bolus plus infusion, or placebo	4 days and 1 month
(Mathew *et al.*, 2005)	440	Hydroxymethylglutaryl-CoA Reductase Inhibitors	6 weeks
(Hogue *et al.*, 2007)	174	17beta-Estradiol or placebo	4-6 weeks
(Mathew *et al.*, 2009)	241	Lidocaine or placebo	6 weeks and 1 year
(Mitchell *et al.*, 2009)	158	Lidocaine or placebo	10 weeks and 25 weeks
(Holinski *et al.*, 2011)	88	Piracetam or placebo	3 days

One of the most commonly used neuroprotective agents is Lidocaine, which featured in 4 of the 17 studies. Lidocaine is thought to inhibit inflammatory responses during cardiac surgery by modulation of inflammatory mediators, reduction in cerebral metabolism, and deceleration of ischaemic ion fluxes (Mitchell & Gorman, 2002). Two studies showed improved outcome with the use of the drug (Svensson *et al.*, 2001; Wang *et al.*, 2002), while two studies showed no difference (Mitchell *et al.*, 2009; Mathew *et al.*, 2009). Currently, no trials have demonstrated a reproducible clinically significant benefit conferred by the use of any particular neuroprotective drug.

1.8.6 Hypothermia and rewarming

The patient's temperature during cardiac surgery has long been thought to play a role in neurological outcome. Several studies have focused their trials on whether reducing the metabolic demand of the brain through hypothermia is neuroprotective. Based on our literature search, 41 studies investigating the effects of temperature were identified. Seventeen studies were excluded from the final result due to lack of clarity in neuropsychological assessments and outcomes. Results from a total of 19 studies investigating the effect of temperature on pre- and post-operative neuropsychological tests are summarised in table 1.6.

Some studies suggest that hypothermia is more effective than normothermia in protecting the brain during surgery, however, other studies report no obvious difference between 'mild hypothermia' and 'normothermia' in terms of neuropsychological performance at discharge (49% and 45% respectively) and at 3 months (4% and 8% respectively) (Boodhwani *et al.*, 2007).

Table 1.6 Studies investigating POCD associated with temperature during cardiac surgery.

Study	Study design	No. of patients	Mean temperature (Celsius)	Time of assessment
Studies showing a better post-operative cognitive outcome in favour of normothermia				
(Grimm *et al.*, 2000)	RCT	144	1.Normothermia: 37°C 2.Hypothermia: 32°C	1 week and 4 months
(Shaaban-Ali *et al.*, 2002)	RCT	60	1.Normothermia: 34°C 2.Hypothermia: 28°C	5 days
Studies showing an improvement in post-operative cognitive outcome in favour of hypothermia				
(Nathan *et al.*, 1995)	Observational	30	Maintain ≤ 34°C	1 week
(Grocott *et al.*, 2002)	Observational	300	Post-op hypothermia only	6 weeks
(Kadoi *et al.*, 2004)	RCT	60	1.Normothermia: 37°C 2.Hypothermia: 32°C	1 month
(Boodhwani *et al.*, 2006)	RCT	448	1.Normothermia: 37°C 2.Hypothermia: 34°C	1 week
(Hiraoka *et al.*, 2012)	Observational	11	Hypothermia: 20-22°C	3 weeks and 6 months
Studies showing no difference in post-operative outcome regarding temperature				
(McLean *et al.*, 1994)	RCT	155	1.Hyperthermia: >34°C 2.Hypothermia: <28°C	5 days and 3 months

(Regragui *et al.*, 1996)	RCT	97	1.Normothermia: 37°C 2.Hypothermia: 28°C & 32°C	6 weeks
(Heyer *et al.*, 1997)	RCT	99	1.Normothermia: 34°C 2.Hypothermia: 28°C	Discharge and 6 weeks
(Kneebone *et al.*, 1998)	Observational	50	1.Normothermia: 37°C 2.Hypothermia: 30-32°C	1 week
(Reich *et al.*, 1999)	Observational	149	1.Deep Hypothermia: 12-15°C (< 25 mins) 2.Deep Hypothermia: 12-15°C (>25 mins)	1 month
(Kaukinen *et al.*, 2000)	RCT	36	1.Normothermia: 36-37°C 2.Hypothermia: 28°C	5 days and 11-23 months
(Gorna *et al.*, 2001)	Observational	33	No full text	3-10 days
(Grigore *et al.*, 2001)	RCT	300	1.Normothermia: 35.5-36.5°C 2.Hypothermia: 28-30°C	6 weeks
(Kaukuntla *et al.*, 2004)	Observational	60	1.Normothermia: 35°C 2.Differential temperature management	1 and 8 weeks
(Reich *et al.*, 2004)	Observational	61	Monitoring during deep hypothermic arrest (28°C)	Discharge
(Boodhwani *et al.*, 2007)	RCT	268	1.Normothermia: 37°C 2.Hypothermia: 34°C	Discharge and 3 months
(Kunihara *et al.*, 2007)	Observational	26	1.Normothermia: 34°C 2.Hypothermia: 22°C	1 week

Some researchers have proposed that the brain could be susceptible to insult during rewarming from hypothermia, particularly if cerebral autoregulation mechanisms are unable to compensate for a sudden increase in metabolic activity associated with changes in temperature. Six studies have been conducted to examine the effect of rewarming rate on POCD, and all of these have shown a benefit in post-operative outcome associated with slower rewarming (table 1.7).

Table 1.7 Studies investigating POCD associated with the rate of re-warming during cardiac surgery

Study	Study design	No. of patients	Mean temperature (Celsius)	Time of assessment
Studies showing a better post-operative cognitive outcome in favour of a slower re-warm				
(Mora *et al.*, 1996)	RCT	138	1.Rewarm 1-2°C (per increase) 2.Rewarm 3-5°C (per increase)	1-3 days, 7-10 days & 1 month
(Nathan *et al.*, 2001)	Observational	294	1.Rewarm to 34°C (1°C per increase) 2.Rewarm to 37°C (3°C per increase)	1 week and 3 months
(Grigore *et al.*, 2002)	Observational	100	1.Rewarm to 32°C (max within 3 mins) 2.Rewarm to 37°C (max within 3 mins)	6 weeks
(Kawahara *et al.*, 2003)	RCT	100	1.Rewarm 1-2°C (per increase) 2.Rewarm 4-5°C (per increase)	1 month
(Nathan *et al.*, 2007)	RCT	223	1.Rewarm to 34°C (1°C per increase) 2.Rewarm to 37°C (3°C per increase)	1 week
(Sahu *et al.*, 2009)	RCT	80	1.Rewarm 1-3°C (per increase) 2.Rewarm 3-5°C (per increase)	5 days

1.9 Summary

Interpreting the risk factors associated with postoperative cognitive decline, it seems that efforts to protect the brain during surgery are intrinsically linked with the need to control the progression of cardiovascular disease, especially in older patients. It is possible that patients may be exceeding a 'threshold' of pre-existing vulnerability where the brain's ability to compensate for injuries or inflammation during surgery are absent. In summary, the literature examining underlying risk factors, and perioperative risk factors associated with the pathogenesis of cognitive decline suggests that there is no single factor responsible for postoperative cognitive decline or single intervention capable of protecting the brain during surgery. Overall, the pathogenesis of cognitive decline following surgery still remains unclear.

Chapter 2

2 Brain injury during cardiac surgery part II: Impact of new MRI lesions and embolic events on cognitive decline

2.1 New MRI lesions; Magnetic Resonance Imaging of the brain

Magnetic resonance imaging (MRI) of the brain provides an alternative method of identifying and quantifying brain injury after cardiac surgery (Ebinger *et al.*, 2010; Merino *et al.*, 2013). A range of imaging pulse sequences can be used, including diffusion weighted imaging (DWI) (Crisostomo *et al.*, 2003) and FLuid Attenuated Inversion Recovery (FLAIR) (Ebinger *et al.*, 2010).

The majority of previous studies have used DWI as their imaging modality. An advantage of using DWI is that preoperative assessment is unnecessary as DWI identifies acute ischaemic injury as bright lesions. DWI lesions typically appear within 2-3 hours of onset and are thought to resolve within 2-3 weeks (Crisostomo *et al.*, 2003). A disadvantage of using DWI is that patients need to be scanned very soon after surgery (<48 hours), which is not always possible, and that acute DWI lesions may not reflect clinically significant long-term injuries. New ischaemic brain lesions can also be detected using FLAIR imaging, and once developed are usually permanent. Therefore, in assessing FLAIR images for the presence of new lesions it is important that a preoperative scan is carried out in order to be able to distinguish new lesions from old.

Acute ischaemic changes are visible using DWI MRI in 15-61% of patients following cardiac surgery (Gerriets *et al.*, 2010; Messe *et al.*, 2014) and new chronic ischaemic lesions are found in approximately 13% of patients using FLAIR (Lund *et al.*, 2005). Lesions are typically multiple, small, and spherical, whose radiographic appearance is strongly suggestive of embolisation (Restrepo *et al.*, 2002; Bendszus *et al.*, 2002; Knipp *et al.*, 2005). To the best of our knowledge, no studies have attempted to quantify the accumulation of new ischaemic injuries against a backdrop of chronic pre-existing cerebrovascular disease.

2.2 MRI lesions after cardiac surgery - Literature search

A number of studies have investigated whether there is an association between postoperative MRI brain lesions and cognitive decline after cardiac surgery.

To investigate the incidence of MRI lesions and cognitive decline a systematic literature search, drawing on papers from PubMed and EMBASE was performed. All studies published in English between June 1967 and August 2013 and featuring adult human subjects were eligible for review.

Search terms were created by combining the following medical subject headings (MeSH terms):

> **#1**: "Coronary Artery Bypass" OR "Coronary Artery Bypass, Off-Pump" OR "Valve Surgery" OR "Thoracic Surgery" OR "Cardiac Surgical Procedures"
>
> AND
>
> **#2**: "Cognitive Therapy" OR "Cognition Disorders" OR "Cognition" OR "Neuropsychology" OR "Neuropsychological Tests" OR "Mild Cognitive Impairment"
>
> AND
>
> **#3:** "Brain Infarcts" OR "Cerebral Infarction" OR "Ischaemic lesions" OR "Lacunes"

Abstracts involving cardiac surgery, cognitive function and MRI outcome (#1 AND #2 AND #3) were independently reviewed by two investigators (N. Patel and E.M.L. Chung) and studies of adult cardiac surgery patients that assessed both pre- and post-operative assessments were identified for full manuscript review. Abstracts were excluded if they involved paediatric surgery, operations other than cardiac surgery, or no measurement of cognitive function. Case reports and studies of cardiac procedures such as angioplasty, angiography, valvuloplasty and Transcatheter Aortic Valve Implantation (TAVI) were also excluded. Studies generating multiple publications from the same cohort were reported only once. Where there was disagreement among investigators the full text was reviewed. Additionally, the reference lists of selected

articles were evaluated for any additional articles of interest. Articles short-listed for full manuscript review were summarised in an Excel spreadsheet listing the: study design (observational, RCT, etc.), number of patients, type(s) of surgery, outcome measures, and time point of neurocognitive assessment.

A total of 33 articles were extracted for full text review, and a total of 19 articles were included in our final summary of results, table 2.1. Studies were excluded if patients did not complete a battery of pre- and post-operative neuropsychological tests. Of these, 2 studies observed no MR changes in their patients and 6 studies concluded that postoperative MRI changes were significantly associated with cognitive decline. Eleven studies found no evidence of an association between new lesions and cognitive decline but these studies were mostly small and focussed on acute changes observed using DWI MRI.

Table 2.1 Studies investigating POCD associated with the postoperative MRI lesions (obsv.: observational)

Study	Study Design	Type of surgery (*n*)	MRI scan (Field Strenght)	Incidence of new lesions (%) (time of post-op scan)	Comment
Studies concluding that new ischaemic lesions are associated with neuropsychological impairment					
(Toner *et al.*, 1994)	RCT	CABG (*n*= 15)	T2-weighted spin-echo (0.5T)	26 (1 week)	Patients with new MR changes were more likely to experience significant neuropsychological deficit. However, the sample size is small.
(Goto *et al.*, 2001)	Obsv.	CABG (*n*= 421)	DWI (1.5T)	50 (1 week)	DWI findings immediately after surgery significantly correlated with neuropsychological deficit at 1 week ($p<0.001$).
(Restrepo *et al.*, 2002)	Obsv.	CABG (*n*= 13)	DWI (1.5T)	31 (5 days)	DWI findings were associated with a larger decline in composite z-score (P=0.046) and significantly associated with a decline in >1 test at 5 days (P=0.008).
(Barber *et al.*, 2008)	Obsv.	Valve (*n*= 30) Combined (*n*= *6*)	DWI (1.5T)	43 (5 days)	DWI findings are associated with cognitive decline at 5 days
(Schwarz *et al.*, 2011)	Obsv.	CABG (*n*= 47)	DWI (1.5T)	18 (3 days)	DWI findings are associated with cognitive decline at 3 days and 3 months.
(Ito *et al.*, 2012)	Obsv.	CABG (*n*= 449)	T_1- and T_2-weighted scans	49 (unclear)	Patients with new lesions revealed a high prevalence of neurological impairment to those without.

Studies showing no association between new ischaemic lesions and neuropsychological impairment					
(Sylivris *et al.*, 1998)	Obsv.	CABG (*n*= 28)	T_1- and T_2-weighted scans (1.5T)	18 (1 week)	'There was no relationship between MR changes and neuropsychological deficit.'
(Vanninen *et al.*, 1998)	Obsv.	CABG (*n*= 38) Vascular surgery (*n*= 20)	T_2-weighted (1.5T)	21 (8 days)	'MRI lesions did not correlate with neuropsychological deficit.'
(Bendszus *et al.*, 2002)	Obsv.	CABG (*n*= 35)	DWI (1.5T)	26 (3-5 days)	'There was no significant association between the presence of a new lesions and neuropsychological deficit.'
(Knipp *et al.*, 2004)	Obsv.	CABG (*n*= 29)	DWI (1.5T)	45 (3 months)	'No statistical correlation between the presence of new brain lesions on MRI and neuropsychological deficit.'
(Knipp *et al.*, 2005)	Obsv.	Valve (*n*= 30)	DWI (1.5T)	47 (5 days)	'There was no significant association between the presence of new lesions and neuropsychological deficit at 5 days or 4 months.'
(Lund *et al.*, 2005)	RCT	CABG (*n*= 120)	FLAIR (1.5T)	13 (3 months)	'There was no significant correlation between the presence of a new lesions and neuropsychological deficit.'
(Cook *et al.*, 2007)	Obsv.	Cardiac surgery (*n*= 50)	DWI (1.5T)	32 (5 days)	'There does not appear to be any relationship between early or persistent cognitive change and new MRI lesions.'
(Gottesman *et al.*, 2007)	Obsv.	CABG (*n*= 13)	DWI (1.5T)	46 (3-5 days)	'The relationship between DWI and early cognitive dysfunction is unclear.'
(Knipp *et al.*, 2008)	Obsv.	CABG (*n*= 20)	DWI (1.5T)	51 (discharge)	'An association of early or late cognitive changes to new ischemic brain lesions on DWI was not found in this cohort.'
(Gerriets *et al.*, 2010)	RCT	CABG Embol-X (*n*= 43) Dynamic bubble trap (*n*= 50)	DWI (1.5T)	15 (3 days)	'The number of new lesions did not correlate with early or late POCD.'
(Mirow *et al.*, 2011)	RCT	CABG (*n*= 63)	DWI (1.5T)	20 (discharge)	'The number of new lesions did not correlate with postoperative neurological complications.'
Studies showing no new neuropsychological deficit or MRI abnormalities					
(Eifert *et al.*, 2003)	RCT	CABG (*n*= 17) Valve (*n*= 4) Combined (n= 12)	DWI (1.5T)	0 (5 days)	'No patients developed neuropsychological deficit or MR abnormalities.'
(Agarwal *et al.*, 2010)	Obsv.	CABG (*n*= 11) Valve (*n*= 8)	FLAIR (1.5T)	0 (4-6 weeks)	'No patients developed neuropsychological deficit or MR abnormalities.'

Prior to the advent of DWI, T_2-weighted imaging was used to detect new postoperative lesions (Toner *et al*, 1994). In a study by Toner et al., 4 out of 15 patients with new MRI abnormalities were all found to have significant neuropsychological deficits. Toner *et al.* concluded that these preliminary data suggest a link between structural brain changes and cerebral function after CABG (Toner *et al.,* 1993). More recent studies have used DWI to detect acute cerebral injury. These suggest that acute cerebral injury is common and often more extensive than clinical symptoms would suggest (Wityk *et al.*, 2001).

The earliest DWI study by Goto *et al*. reported new ischaemic lesions in 50% of patients after CABG surgery and concluded that lesions seen immediately after cardiac surgery correlated to cognitive decline (Goto *et al.,* 2001). Another study investigating cognitive decline in relation to DWI lesions immediately after surgery concluded that postoperative lesions were of embolic origin and unrelated to any neurological symptoms or decline in neurocognitive performance (Bendszus *et al.*, 2002). Subsequent trials have confirmed the proportion of patients receiving new ischaemic lesions ranges from 31% (Restrepo *et al.*, 2002) to 51% (Knipp *et al.*, 2008) after CABG surgery and 32% (Stolz *et al.*, 2004) to 47% (Knipp *et al.*, 2005) for valve surgery. In both CABG and valve surgery, the pattern of new lesions is found to be consistent with an embolic pathogenesis (Cook *et al.*, 2007). Atheromatous disease of the aorta may be an important factor in predicting the risk of new MRI lesions. A study of 110 patients by Djaiani *et al.* observed new DWI lesions in 60% of patients who suffered from moderate atherosclerosis in the aorta and the aortic arch, in comparison to 0% of patients with no atherosclerotic disease (Djaiani *et al.*, 2004). It has been shown in various studies that factors linked to the risk of receiving new ischaemic lesions include the patient's age (Djaiani *et al.*, 2004; Stolz *et al.*, 2004), presence of pre-existing lesions or pre-existing white-matter disease (Bendszus *et al.*, 2002; Stolz *et al.*, 2004; Lund *et al.*, 2005), and the presence of atheroma burden (Djaiani *et al.*, 2004).

2.3 Clinical significance of new MRI lesions

Although high proportions of patients experience new lesions after cardiac surgery, the majority of lesions are clinically silent and do not appear to generate any noticeable neuropsychological impairment. Lesion location is crucial in determining the likelihood of generating clinical symptoms (Sudo *et al.*, 2004). Previous studies suggest that only

7% of patients with symptomatic ischaemic lesions peri-operatively showed subsequent neurocognitive impairment once their symptoms had resolved (Kang *et al.*, 2003).

2.4 Embolus detection using transcranial Doppler (TCD)

In a cardiac surgery setting, TCD can been used to measure cerebral blood flow velocity (CBFv) and detect embolic material entering the cerebral circulation. TCD studies suggest that the number of emboli experienced during surgery varies widely between patients. Factors such as length of procedure, type of surgery, and number of surgical and perfusionist interventions are all closely linked with the number and timing of embolic counts. Previous studies have demonstrated that emboli mainly occur during aortic cannulation, removal of the aortic cross clamp, initiation of CPB, during cardiac ejection, and at the end of CPB (van der Linden & Casimir-Ahn, 1991; Barbut *et al.*, 1994; Hartman *et al.*, 1996; Barbut *et al.*, 1996). Potential sources of emboli during surgery are summarised in figure 2.1.

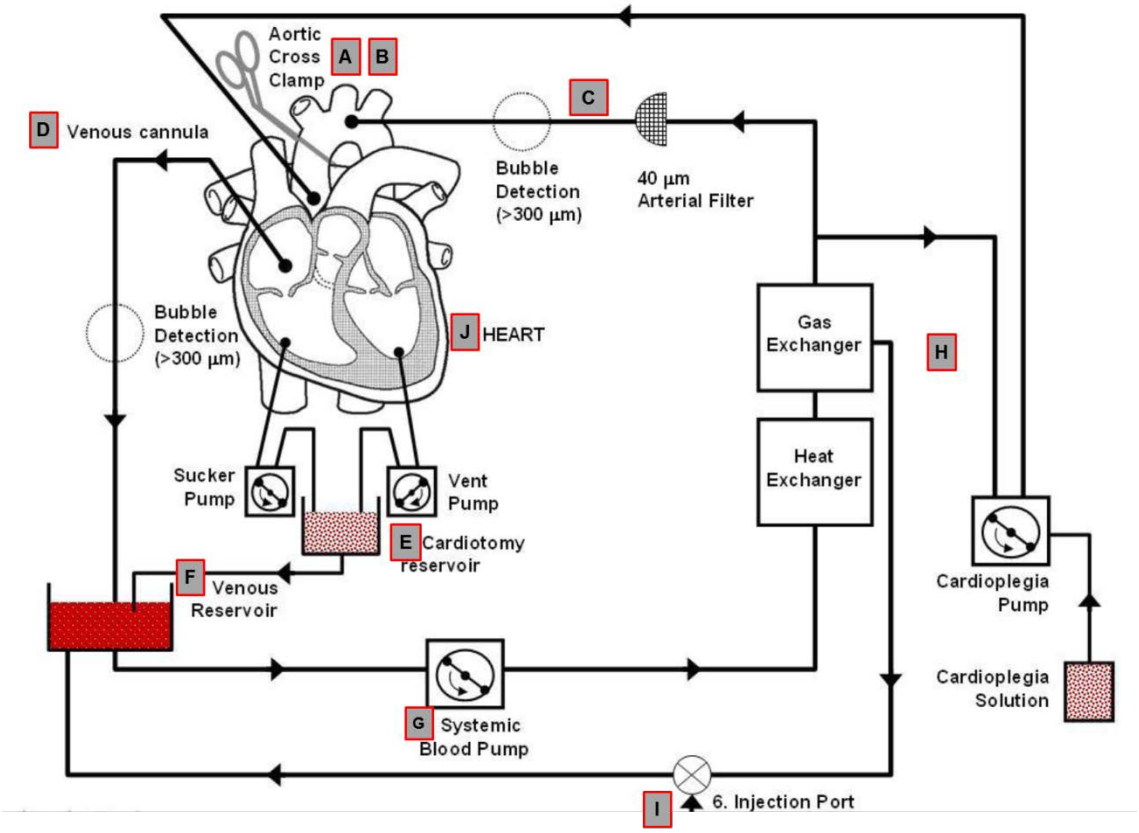


Figure 2.1 Schematic diagram of a cardiopulmonary bypass circuit. Atherosclerotic debris can be dislodged from diseased arteries during surgery. Air bubbles can also be introduced into the circulation via, trapped air in the chambers of the heart, leakage of air into the venous cannula, the cardiotomy reservoir, the venous reservoir, air bubbles generated by the pump and air introduced by injection of drugs or blood sampling. Note that all emboli entering through the arterial line usually pass through a ~40 µm line filter.

A. Application of the aortic cross-clamp - solid emboli

B. Atherosclerotic debris dislodged from diseased arteries during cannulation –solid emboli

C. Air bubbles introduced into the circulation via the cardiopulmonary bypass circuit

D. Leakage of air into the venous cannula – gaseous emboli

E. The cardiotomy suction/reservoir - gaseous emboli & lipid microparticles

F. The venous reservoir - gaseous emboli

G. Air bubbles generated by the pump – gaseous emboli

H. Perfusionist and anaesthetist interventions – gaseous emboli

I. Air introduced by injection of drugs or blood sampling – gaseous emboli

J. Release of trapped air in the chambers of the heart – gaseous emboli

2.4.1 Clamping

Clamp applications when constructing the coronary artery bypass graft are known to be a common source of cerebral emboli (Boivie *et al.*, 2003). In a prospective RCT of 46 patients, Hammon *et al*. showed that the use of a partial occluding (side-biting) clamp was linked with a higher rate of neuropsychological decline 6 months after CABG. In contrast, the use of a single cross-clamping technique was found to significantly (p=0.005) reduce the proportion of patients experiencing cognitive decline from 57% to 33% (Hammon *et al.*, 2006). Hammon *et al.* therefore recommend avoiding the use of partial occluding clamps during CABG whenever possible. The use of a proximal aorta coronary anastomosis device (called 'stitch-less'), which eliminates the need for aortic cross-clamp application, has also been shown to reduce cerebral emboli (Calafiore *et al.*, 2001). Another study by Barbut *et al.* used TCD to detect embolic signals in 20 patients undergoing CABG surgery. Thirty-four percent of embolic signals were reported to be associated with removal of the aortic cross-clamp, and another 24% with removal of aortic partial occlusion clamps (Barbut *et al.*, 1994). This suggests that over half of emboli detected during surgery were associated with the release of clamps. Emboli detected following the removal of clamps are more likely to be clinically significant than emboli during other stages of surgery, as these have potential to contain pieces of aortic atheroma which pass direct to the brain without being captured by the 40 μm arterial line filter.

2.4.2 Cannulation and aortic arch atheroma

The choice of site for aortic cannulation is also thought to influence the numbers of cerebral emboli (Mullges *et al.*, 2001). A study by Borger *et al*. (1999) involving 34 patients undergoing CABG surgery showed that cannulation of the distal aorta was associated with fewer cerebral emboli. The authors concluded that arch cannulation, is associated with lower peak aortic flow velocities than conventional short, right-angled, cannulas (Borger *et al.*, 1999). A decrease in flow velocity, and positioning of the cannula tip below the left subclavian artery, is thought to result in decreased embolisation from the atherosclerotic artery wall. Several studies (Karalis *et al.*, 1991; Toyoda *et al.*, 1992; Katz *et al.*, 1992; Stern *et al.*, 1999) have investigated the relationship between aortic atheroma and perioperative stroke. A study by Katz *et al*

(1992), demonstrated that patients with aortic arch atheroma had a significantly higher incidence of perioperative stroke (15%) compared to patients without significant disease (2%) (Katz *et al.*, 1992). One of the patients studied by Katz *et al.* experienced perioperative stroke after cannulation through an aortic arch plaque. Stern *et al* (1999) investigated the outcome of 268 patients, all of whom had been identified by transesophageal echocardiography (TOE) as possessing significant (>5 mm) aortic arch atheroma, and found that perioperative stroke occurred in 11.6% of patients (Stern *et al.*, 1999).

2.4.3 Number of perfusionist interventions

Perfusionist events have also been linked to the number of embolic signals detected using TCD. Studies by Taylor *et al* and Lynch *et al* demonstrated that cerebral emboli were more likely to be detected during sampling of blood or injection of drugs due to the introduction of small air bubbles to the CPB circuit (Taylor *et al.*, 1999). The number and timing of embolic signals detected by TCD during cardiac surgery is found to be closely linked to the timing of perfusionist and surgical interventions. Taylor *et al.* used TCD to monitor 18 CABG patients and found that perfusionist and surgical interventions both generated a significant rise in embolisation compared to baseline figures (Taylor *et al.*, 1999), table 2.2.

Table 2.2 Embolisation rates associated with surgical and perfusionist interventions **(Lynch & Riley, 2008)**.

Intervention	**Number of emboli / minute**
Baseline embolisation	0.4 ± 0.5
Surgical Interventions	1.5 ± 1.5
Blood sampling	4.5 ± 5.8
Drug administration	10.2 ± 5.0

A study by Borger *et al*. demonstrated that patients experiencing high numbers of perfusionist events had a worse postoperative neuropsychological outcome (Borger *et*

al., 2001). In a small study by Lynch *et al*, 34 patients were monitored during cardiac surgery and it was found that patients receiving more than 10 perfusionist interventions had a greater decline in neuropsychological outcome than the patients who received 10 or fewer interventions (Lynch & Riley, 2008). However, the number of perfusionist interventions may also reflect the complexity of the surgery and is therefore unlikely to be casual.

2.4.4 The cardiopulmonary bypass (CPB) machine

Development of the CPB circuit was critical to the development of modern cardiac surgery techniques. Although, neuropsychological dysfunction, was first noted early after the use of CPB, and has since long been suspected a cause of neuropsychological impairment (sometimes referred to as 'pump-head'), the literature suggests no difference in 'on-pump' and 'off-pump' cognitive decline. Several key components of the CPB circuit and surgical procedures have also been independently investigated, such as CPB filters, coating of the CPB circuit, cell saver and cardiotomy suction, cannulation, clamping and de-airing process during weaning off bypass. However, none of the modifications introduced so far appear to confer significant cognitive benefit.

There are a number of methods the perfusionist can use to minimise introduction of bubbles to the circuit during surgery. For example, Rodriguez *et al*. showed that by removing air from the venous line before starting CPB, the number of emboli is clearly reduced (Rodriguez *et al.*, 2006). A study by Pugsley *et al*, which involved 100 patients undergoing CABG surgery, demonstrated the efficacy of arterial line filtration and showed that filtration was associated with an improved score in postoperative neuropsychological test performance. More patients were found to have neuropsychological deficits in the group without the arterial line filter at both 8 days ($p<0.05$) and 8 weeks ($p<0.03$) after surgery (Pugsley *et al.*, 1994). There are several parts of the CPB machine that are potential sources of small air bubbles. Clinical trials suggest that membrane oxygenators produce less emboli than bubble oxygenators (HELMSWORTH *et al.*, 1963; Deverall *et al.*, 1988). Studies have also shown that avoiding CPB during cardiac surgery reduces the number of emboli (Novitzky & Boswell, 2000; Watters *et al.*, 2000). In a study by Lund *et al*, which compared embolic counts detected using TCD in 60 patients randomised to either off-pump or on-pump

CABG surgery, researchers found a statistically significant reduction in the number of emboli that patients received during 'off pump' surgery compared to the 'on pump' procedure (Lund *et al.*, 2003). An increased number of emboli entering the cerebral circulation were found by Patel *et al* (1996) to be a strong indicator for poorer neuropsychological outcome following arterial blood gas management during CPB.

The two types of pump used during CPB are roller pumps and centrifugal pumps. Roller pumps have the advantage of administering pulsatile flow. A previous study by Scott et al. randomised 103 patients to receive either roller or centrifugal pumps during CABG surgery (Scott *et al.*, 2002). The investigators found a lower incidence of neuropsychological dysfunction with the centrifugal device (33%) over the roller pump (51%) on the fifth day postoperatively, but this was not statistically significant (p=0.08). In a larger retrospective study, 4000 patients undergoing CABG and/or valve surgery were studied over a 5 year period. The investigators found a lower rate of coma and postoperative stroke for the patients who were operated with the centrifugal pump (Parolari *et al.*, 2000). Unfortunately, this larger study did not include detailed neurocognitive testing. At present, it is unclear whether the type of pump used has any impact on cognition.

Venous reservoirs are generally classified as 'open' or 'closed' depending on whether the reservoir is open to air. So far, no clinical studies have studied a difference in cerebral embolisation and neurocognitive outcome between the two types of reservoir. In an *in vivo* study, Mitchell *et al*. used an *ex vivo* model to show that operating the CPB circuit with low volumes in open reservoirs was associated with a higher risk of air embolisation (Mitchell *et al.*, 1997). In 2006, open venous reservoirs were used in over 80% of cardiac surgery centres (Baker & Willcox, 2006).

The introduction of arterial line filters was another important development in reducing cerebral embolic injury during CPB. Loop *et al.* in 1976 used ultrasonic insonation of the arterial line proximal and distal to a 20 µm woven nylon mesh arterial filter and showed a 90% reduction in observed emboli with the use of the filter (Loop *et al.*, 1976). One of the earliest studies which monitored the middle cerebral artery (MCA) using transcranial Doppler during cardiac surgery was by Padayachee *et al*. The investigators demonstrated that arterial line filters resulted in a significant reduction of emboli detected (Padayachee *et al.*, 1988). After a number of years, subsequent studies

with similar results led a consensus group to recommend arterial line filters during the application of CPB (Shann *et al.*, 2006).

The dynamic bubble trap directs gaseous microbubbles to the middle of the CPB tubing flow to aid with removal of bubbles. The efficacy of the bubble trap was demonstrated in a randomised controlled trial (RCT) by Schoenburg *et al* and resulted in a 70% reduction of gaseous microemboli detected in the MCA for patients undergoing CABG (Schoenburg *et al.*, 2003).

Cardiotomy suction is an effective tool for recycling shed blood and reducing the levels of blood loss during CPB. However, drained blood that has been suctioned from the operative field through cardiotomy suction has been shown to contain high levels of lipid microparticles and other cellular debris arising from the sternotomy incision (Kincaid *et al.*, 2000). These lipid microparticles can be found in the cerebral vasculature after cardiac surgery using laser microprobe mass spectrometry (Challa *et al.*, 1998). Liu *et al*. were one of the first groups of investigators to demonstrate a link between cardiotomy suction and the number of emboli in the CPB circuit measured by a Coulter counter (Liu *et al.*, 1992).

The use of blood salvage devices to process the blood before returning it to the venous reservoir may reduce the number of particulate emboli. Two prospective randomised double-blinded clinical trials have investigated the effects of blood processing through the cell saver system, as opposed to cardiotomy suction, on cognitive outcome following cardiac surgery. The first RCT included 264 patients undergoing CABG and/or valve surgery. This failed to show any positive benefit of using a cell saver on POCD (Boodhwani *et al.*, 2007). Ruben *et al.* randomised 268 patients and concluded that there was no difference in the number of observed cerebral emboli or the incidence of neuropsychological dysfunction between the two groups (Rubens *et al.*, 2007). In contrast, a further trial performed by Djaiani *et al.* randomised 226 patients and found a lower risk of neuropsychological impairment 6 weeks after surgery in the cell saver group (6% versus 15%, p=0.04), however, there was no difference in the number of cerebral emboli and their findings of a reduction in the incidence of cognitive decline were of borderline statistical significance (Djaiani *et al.*, 2007). Reduction of both platelet and coagulation factors due to the washing process is an undesirable side effect of processing the cardiotomy blood and both studies showed an increase in bleeding and

requirement for blood transfusion. To date, it is unclear whether the potential benefits of recycling the blood outweigh the disadvantages.

2.5 Neuropsychological outcomes for off-pump and on-pump CPB

Given that neuropsychological impairment is often thought to be associated with the use of CPB, an off-pump surgery technique was developed (Murkin *et al.,* 1999). A systematic review and meta-analysis performed by Marasco *et al*. in 2008 included eight trials incorporating 892 patients in total, and found no significant difference between neuropsychological outcomes when comparing patients undergoing off- and on-pump CABG surgery (Marasco *et al.*, 2008). Since then, an additional 8 RCTs comparing off- and on-pump CABG have been conducted (Hernandez *et al.*, 2007; Yin *et al.*, 2007; Jensen *et al.*, 2008; Tully *et al.*, 2008; Sousa Uva *et al.*, 2010; Kozora *et al.*, 2010; Lamy *et al.*, 2013; Shroyer *et al.*, 2009). Kozora *et al.* investigated neuropsychological outcome up to a year after surgery in 1,156 patients randomised to either off- or on-pump CABG. The study concluded that neither on- nor off-pump surgery adversely impacts long-term neurocognitive function (Kozora *et al.*, 2010). One of the largest of these studies was by Shroyer *et al.* 2009, who investigated neuropsychological outcome in 2203 patients randomly assigned to either on- or off-pump surgery. Neuropsychological outcomes were similar in both groups 1 year postoperatively (Shroyer *et al.*, 2009). Another RCT by Motallebzadeh *et al* investigated neurocognitive outcome on 212 patients randomly assigned to either off- or on-pump surgery concluded that off-pump surgery was linked to a better cognitive outcome at discharge but there was no significant difference at 6 weeks or 6 months (Motallebzadeh *et al.*, 2007). Whilst the neuropsychological outcomes may differ slightly at hospital discharge, these RCTs have found no difference in neuropsychological outcomes between off-pump and on-pump CABG surgery with a postoperative follow-up of up to 6 months to 1 year. The only study to investigate neuropsychological impairment over 2 years postoperatively found no differences between the on- and off-pump groups in CABG surgery at 5 years (van Dijk *et al.*, 2007).

Seventeen RCTs (Van Dijk et al reported 3 times, counted as one) assessing neurocognitive outcome after on- and off-pump cardiac surgery are summarised in table 2.3.

Table 2.3 Randomised controlled trials investigating POCD associated with on- and off-pump cardiac surgery

Study	Total no. patients (on-pump/off-pump)	Outcome measures (postoperative testing)	Comment
Studies favouring the off-pump procedure			
(Diegeler *et al.*, 2000)	40 (20/20)	TCD (embolic load) Cognitive tests (1 week) S-100β serum levels	'POCD seems to be strongly associated to CPB and the occurrence of emboli'.
(Zamvar *et al.*, 2002)	60 (30/30)	Neuropsychological tests (1 week/10weeks)	'Off-pump surgery resulted in less neurocognitive impairment than on-pump surgery'.
(Motallebzadeh *et al.*, 2007)	212 (104/108)	TCD (embolic load) Neuropsychological tests (discharge/6 weeks/ 6 months)	'At discharge, neurocognitive function is better after off-pump surgery, possibly as a result of the lower embolic load. However, the difference in neurocognitive function does not persist at 6 weeks and 6 months.'
(Puskas *et al.*, 2011)	87 (44/43)	Neuropsychological tests (mean of 7.5 years) MRI-FLAIR	'After a mean of 7.5 years of follow-up, patients undergoing off-pump surgery performed marginally better than on-pump technique in several cognitive domains; these differences were small and of uncertain clinical importance. Early MRI showed no significant differences in acute cerebral infarctions between the off-pump and on-pump groups.'
Studies showing no difference in POCD outcome after on- or off-pump surgery			
(Van Dijk *et al.*, 2002)	281 (139/142)	Cognitive tests (3months/1year)	'No statistically significant differences were observed between the on-pump and off-pump groups in quality of life, stroke rate, or mortality at 3 and 1 year'.
(Keizer *et al.*, 2003)	81 (36/45)	Cognitive tests & questionnaire (1year)	'Irrespective of the type of surgical technique (on-pump v off-pump), POCD does not result in substantial impairment 1 year after cardiac surgery'.
(van Dijk *et al.*, 2004)	281 (139/142)	Cognitive tests (4 days/3months)	'Early cognitive decline is not significantly influenced by the use of CPB.'
(Kobayashi *et al.*, 2005)	(167) 81/86	S-100β serum levels Cognitive tests (2 months weeks)	'Off-pump technique was as safe as the on-pump technique.'
(Lund *et al.*, 2005)	106 (52/54)	Neuropsychological tests (3 months/1year)	'Long-term cognitive function and magnetic resonance imaging evidence of brain injury were similar after off-pump and on-pump surgery.'

		MRI- FLAIR (3 months)	
(Ernest *et al.*, 2006)	79 (32/47)	Neuropsychological tests (2 months/6 months)	'The off-pump technique appears to be generally comparable to the on-pump technique in terms of short-term and long-term POCD.'
(Jensen *et al.*, 2006)	105 (51/54)	Neuropsychological tests (3 months)	'Off-pump technique has no improvement in cognitive outcomes at 3 months compared with patients who undergo a surgery with the on-pump technique.'
(Vedin *et al.*, 2006)	70 (37/33)	Neuropsychological tests (1/6 months)	'There is no difference in cognitive outcome after on-pump compared to off-pump surgery.'
(Hernandez *et al.*, 2007)	201 (102/99)	Neuropsychological tests (discharge/6 months)	'Off-pump surgery did not result in decreased frequency of POCD.'
(van Dijk *et al.*, 2007)	281 (139/142)	Neuropsychological tests (5 years)	'Avoiding the use of CPB during surgery had no effect on 5-year cognitive outcome.'
(Jensen *et al.*, 2008)	90 (43/47)	Neuropsychological tests (1 year)	'The results did not suggest that off-pump surgery was associated with significantly better cognitive outcome 1 year after the surgery.'
(Tully *et al.*, 2008)	59 (31/28)	Neuropsychological tests (3 months)	'The off-pump technique did not show fewer cognitive deficits or greater improvement in quality of life.'
(Shroyer *et al.*, 2009)	2203 (1099/1104)	Neuropsychological tests (1 year)	'No significant differences between the techniques were found in neuropsychological outcomes.'
(Kozora *et al.*, 2010)	1156 (581/575)	Neuropsychological tests (1 year)	'Neither the on-pump nor the off-pump technique adversely impacts long-term brain function.'
(Sousa Uva *et al.*, 2010)	150 (75/75)	Neuropsychological tests (1 month/1 year)	'1 month complications, neuropsychological functioning, and one-year clinical and functional outcomes were not statistically different between the off-pump and the on-pump techniques.'

The majority of studies found no evidence to support the hypothesis that use of CPB was associated with worse cognitive outcome, fig 2.2. In the few studies favouring off-pump surgery, sample sizes were small (i.e. the studies were more likely to be underpowered, or differences were either short-term or marginal).

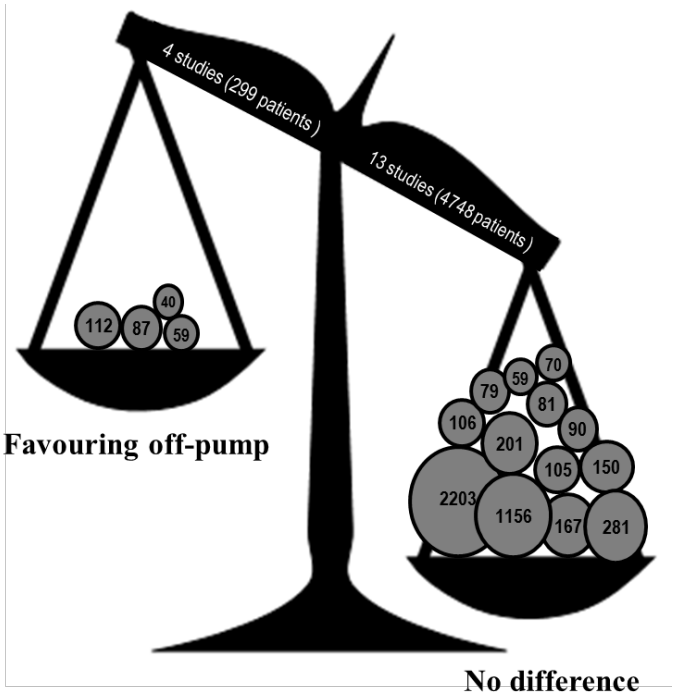


Figure 2.2 Majority of the RCTs showed no evidence that CPB was associated with cognitive decline. Only 4 RCTs (299 patients) favoured off-pump compared to 13 RCTs (4748 patients) showing no difference.

2.6 Cardiac de-airing and weaning from bypass

Large numbers of bubbles are observed by TCD during de-airing of the heart and resumption of cardiac contractions due to the release of air that becomes entrained in the cardiac chambers during surgery. Although several mechanical de-airing techniques can be employed, such as use of the Trendelenburg position, aspiration, and gentle squeezing of the heart, none of these methods is completely effective at eliminating emboli. A further method of reducing air emboli during cardiac surgery is by flooding the operative area with carbon dioxide (CO_2). CO_2 is heavier than air, and therefore sinks to the bottom of the chest cavity. By surrounding the wound with CO_2 rather than air, any bubbles introduced to the circulation consist of fast dissolving CO_2 which is highly soluble and dissolves easily into the bloodstream. A study by Svenarud *et al*. randomised 20 patients undergoing valve surgery to flooding of the operative area with CO_2 and found a 78% reduction in the number of emboli (Svenarud *et al.*, 2004). Another similar study by Martens *et al*. randomised 80 patients to CO_2 field flooding and found 'auditory-evoked potentials' (small electrical voltage potentials originating

from the brain recorded from the scalp in response to an auditory stimulus) were improved in the CO_2 group compared to the control group. However, Martens *et al.* failed to show any significant differences in neuropsychological outcome between the CO_2 group and controls (Martens *et al.,* 2008). A multicentre RCT by Chaudhuri *et al.* compared neurocognitive outcomes 6 weeks postoperatively in 125 patients undergoing open chamber cardiac surgery who were assigned to CO_2 insufflation or placebo (control group). The investigators concluded that CO_2 insufflation did not improve cognitive outcome (Chaudhuri & Marasco, 2011).

2.7 Link between number of emboli detected on TCD and the risk of perioperative stroke

Several observational studies have investigated potential links between the number of emboli detected during surgery and stroke risk (Salazar *et al.*, 2001; McKhann *et al.*, 2002; Ritzl *et al.*, 2004; Lynch & Riley, 2008). The main difficulty of using 'stroke' as an end-point/outcome is that the event rate is low, which means studies are generally underpowered. A study by Lynch *et al.* (2008) comparing the total number of emboli during surgery with the incidence of stroke in 82 CABG patients found that 4 suffered a stroke. Interestingly, the number of emboli recorded in these 4 stroke patients was almost 3 times higher than the average number of emboli detected in the remaining 78 'stroke free' patients. The same study found that patients experiencing greater numbers of emboli also tended to have longer hospital stays. Patients who experienced more than 500 embolic signals spent over 6 times longer in hospital compared to patients with less than 100 embolic signals (table 2.4) (Lynch & Riley, 2008). Again, an explanation for this association may be that high numbers of emboli are associated with more difficult cases in patients with extensive atherosclerosis disease. The longer surgery times and complexity of the procedure have potential to result in both longer hospital stays and more emboli, but the two are not necessarily causally related.

Table 2.4 Higher numbers of embolic signals are associated with longer hospital stay (Lynch & Riley, 2008).

Number of emboli	Number of patients	Number of days in hospital (p = 0.0007)
< **100**	40	8.6
100-300	23	13.5
300-500	16	16.3
>**500**	6	55.8

2.8 Emboli and cognitive decline - Literature search

A number of studies have investigated whether there is an association between intraoperative emboli and cognitive decline after cardiac surgery.

To investigate this question, a systematic literature search drawing on papers from PubMed and EMBASE was performed. All studies published in English between June 1967 and August 2013 and featuring adult human subjects were eligible for review.

Search terms were created by combining the following medical subject headings (MeSH terms):

#1: "Coronary Artery Bypass" OR "Coronary Artery Bypass, Off-Pump" OR "Valve Surgery" OR "Thoracic Surgery" OR "Cardiac Surgical Procedures"

AND

#2: "Cognitive Therapy" OR "Cognition Disorders" OR "Cognition" OR "Neuropsychology" OR "Neuropsychological Tests" OR "Mild Cognitive Impairment"

AND

#3: "Emboli" OR "Transcranial Doppler" OR "Doppler ultrasound" OR "Embolism" OR "Intracranial embolism" OR "Microemboli"

Abstracts involving cardiac surgery, cognitive function and intraoperative emboli (#1 AND #2 AND #3) were independently reviewed by two investigators (N. Patel and E.M.L. Chung) and studies of adult cardiac surgery patients that assessed both pre- and post-operative assessments were identified for full manuscript review. Abstracts were excluded if they involved paediatric surgery, operations other than cardiac surgery, or no measurement of cognitive function. Case reports and studies of cardiac procedures such as, angioplasty, angiography, valvuloplasty and Transcatheter Aortic Valve Implantation (TAVI) were also excluded. Studies generating multiple publications from the same cohort were reported only once. Where there was disagreement among investigators the full text was reviewed. Additionally, the reference lists of selected articles were evaluated for any additional articles of interest. Articles short-listed for full manuscript review were summarised in an Excel spreadsheet listing the; the study design (observational, RCT, etc.), number of patients, type(s) of surgery, outcome measures, and time point of neurocognitive assessment.

A total of 29 articles were extracted for full text review, and a total of 19 studies have investigated whether neuropsychological impairment is related to the number of emboli entering the MCA territories during surgery, table 2.5. Of these, 9 studies observed the incidence of emboli to be significantly associated with cognitive decline. However, the majority of studies had <50 patients and are likely to be underpowered. Nine studies found no evidence of an association between intraoperative emboli and cognitive decline. One study was excluded from further review because of limited information on TCD use and application. The remaining 18 studies are summarised in table 2.5.

Table 2.5 Studies investigating the relationship between POCD and embolic load (obsv: observational)

Study	Study design	Type of surgery (*n*)	Embolus detection criteria	Median/Mean number of emboli (range)	Comment (postoperative testing)
Studies showing a positive association between embolic load and subsequent neuropsychological impairment					
(Clark *et al.*, 1995)	Obsv.	CABG (*n*= 120)	All emboli detected >40 dB	Mean: 22 (0-251)	Patients with the highest number of emboli had the highest incidence of POCD (5-10 days).
(Braekken *et al.*, 1998)	Obsv.	CABG (*n*= 14) Valve (*n*= 26)	All emboli detected >3 dB	Mean: CABG: 1155 (151-3074) Valve: 2083 (251-4541)	A positive association between emboli and POCD was seen in the valve group but not in the CABG group (2 months)
(Sylivris *et al.*, 1998)	Obsv.	CABG (*n*= 41)	All emboli detected >3 dB	Mean: 1,038 ± 4,164 (not stated)	Embolic load during surgery was associated with early POCD. Additionally, patients who showed evidence of strokes during CABG had a higher embolic load during the pre-incision phase than those without cerebral infarction (1 week).
(Fearn *et al.*, 2001)	Obsv.	CABG (*n*= 70)	All emboli detected >8 dB	Median: 225 (not stated)	The number of emboli is linked to the cause of memory deficits. Cerebral hypoperfusion impaired subsequent attention in postoperative tests (1 week, 2 & 6 months).
(Abu-Omar *et al.*, 2004)	Obsv.	CABG (*n*= 12) Valve (*n*= 4)	An additional reference probe to reject artefacts	Median: CABG: 229 (127-314) Valve: 1220 (874-1261)	Embolic load with the use of CPB correlates with postoperative cerebral functional MRI activation (4 weeks).
(Whitaker *et al.*, 2004)	RCT	CABG (*n*= 192)	Not clear	Median: 67 (5-846)	A lower number of emboli showed a strong trend towards improving cognitive performance (6-8 weeks).
(Abu-Omar *et al.*, 2006)	Obsv.	CABG (*n*= 15)	An additional reference probe to reject artefacts	Median: 254 (116-397)	Patients undergoing the use of CPB surgery have a significant relative reduction in prefrontal activation, which correlates with intraoperative cerebral embolic load (4 weeks).
(Bokeriia *et al.*, 2007)	Obsv.	CABG (*n*= 26) Valve (*n*= 36)	All emboli detected >7 dB	Unclear	Embolic load induces specific cognitive impairment in accordance to the brain region to which they are delivered.
(Gerriets *et al.*, 2010)	RCT	CABG (*n*= 91)	Embolic signals defined by detection within 120 secs after event markers	Median: 154 (30-2572)	Embolisation contributes to neuropsychological decline, which is measurable 3 months post-operatively (3 months).
Studies showing no association between embolic load and neuropsychological impairment					
(Thiel *et al.*, 1997)	Obsv.	CABG (*n*= 10)	Full text unavailable	-	Results showed moderate deterioration of neurocognitive function after surgery for both

		Valve (*n*= 15)			surgical groups however POCD was unrelated to number of embolic counts.
(Jacobs *et al.*, 1998)	Obsv.	CABG (*n*= 10) Combined (*n*= 2)	All emboli detected >8 dB	Mean: CABG: 603 (90-876) Combined: 1652 (1516-1710)	Emboli during cardiac surgery can cause alterations in neurocognitive function. The number of emboli and changes in cognitive function were not necessarily interrelated (12 days).
(Browndyke *et al.*, 2002)	Obsv.	CABG (*n*= 20) Valve (*n*= 10)	Not clear	Mean : CABG: 423 (not stated) Valve: 886 (not stated)	Emboli counts were not significantly associated with POCD in either the CABG or the valve group (10 days).
(Mullges *et al.*, 2003)	RCT	CABG (*n*= 60)	All emboli detected >9 dB	Median CABG: 923	Emboli do not appear to influence overall cognitive performance early after surgery (9 days).
(Stroobant *et al.*, 2005)	Obsv.	CABG (*n*= 50)	All emboli detected >9 dB	Mean : 335.5 ± 333.5 (24-1229)	The number of emboli showed no correlation with degrees of early and late POCD (6 months).
(Motallebzadeh *et al.*, 2007)	RCT	CABG (*n*= 104)	All emboli detected >7 dB	Median: 1605 (750-2475)	At discharge, neurocognitive function is better after off-pump surgery, possibly as a result of the lower embolic load. However, the difference in POCD does not persist at 6 weeks and 6 months (6 weeks & 6 weeks).
(Whitaker *et al.*, 2007)	RCT	CABG (*n*= 26)	Not clear	Median: 31 (13-183)	There was no evidence to suggest that emboli are related to neurocognitive change after surgery (Discharge).
(Liu *et al.*, 2009)	Obsv.	CABG (*n*= 59)	All emboli detected >7 dB	Median: 430 (155-2088)	Neither CPB nor emboli was independently associated with the risk of POCD either 1 week or 3 months after surgery (1 week and 3 months).
(Rudolph *et al.*, 2009)	Obsv.	CABG (n=68)	Not clear	Median: 303 (112-1598)	This study found no relationship between intraoperative cerebral micro-embolic load and delirium after CABG surgery (5 days).

Given that neuropsychological impairment is often thought to be associated with intraoperative embolisation, correlations between cerebral emboli with postoperative neuropsychological complications have been shown in a number of studies. Based on the results of this literature search, 9 studies have reported that cerebral emboli do contribute to impaired neurocognitive outcome post-surgery and 9 studies reported no correlation. A study conducted by Bokeriia *et al*. looked at the effects of asymmetric cerebral embolic load of cognitive function using TCD. He examined the cognitive outcome of 30 patients who underwent open heart surgery with completed pre- and postoperative neuropsychological assessments (Bokeriia *et al.*, 2007). He concluded

that a significant embolic load during cardiac surgery induced specific cognitive impairments in accordance to the region of the brain they are delivered. Another study by Gerriets *et al*. investigated embolic load and neurocognitive outcome and concluded that microembolisation contributes to neuropsychological decline measurable at 3 months postoperatively, however this was only of borderline significance (p=0.049) (Gerriets *et al.,* 2010). Many studies have also reported no correlation between embolic load and postoperative neurocognitive dysfunction. A study by Liu *et al*. measured the embolic load in 59 CABG patients with pre- and postoperative neuropsychological tests. The authors concluded that neither emboli nor the duration of CPB was independently associated with neurocognitive dysfunction at 1 week and 6 months (Liu *et al.,* 2009). Another study investigating emboli in 50 CABG with cognitive testing at 1 week and 6 months postoperatively failed to show any correlation between emboli and cognitive decline. It is important to note that the majority of detected emboli do not produce immediate symptoms. Previous studies using intra-aortic filtration and atheroma avoidance techniques suggest that these have potential to reduce the risk of both perioperative stroke and neuropsychological decline.

Overall, there were an equal number of studies reporting a correlation and no correlation between embolic load and cognitive decline, fig 2.3 (9 studies in both groups). However, 2 studies reporting a correlation between emboli and cognitive decline was only of borderline significance (Braekken *et al.*, 1998) (p=0.03), (Gerriets *et al.*, 2010) (p=0.049).

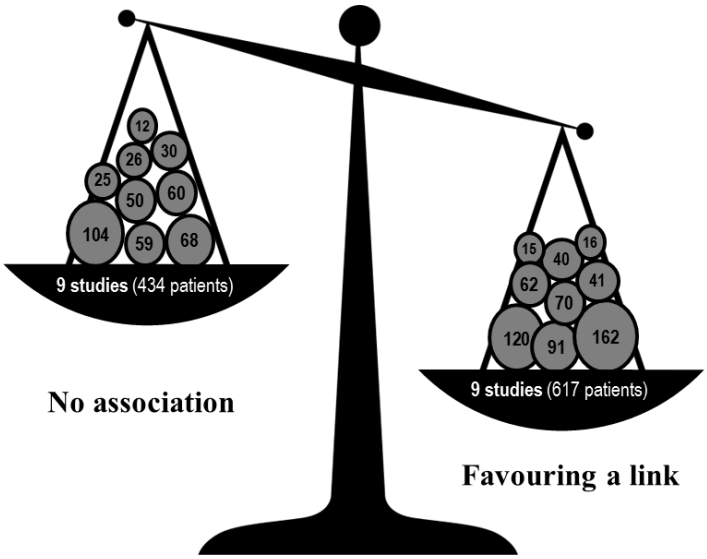


Figure 2.3 Equal number of studies supporting both no association and favouring a link between emboli and cognitive decline. Total number of patients was higher in the studies showing an association (617 patients) compared to studies showing no association (434 patients).

2.9 Overview of literature

Based on previous research, our reading of the literature suggests that we can expect to observe a 1-4% incidence of peri-operative stroke, 0-63% incidence of neurocognitive decline (at 6 weeks), and new MRI lesions on FLAIR in approximately 13% of patients. If new MRI lesions arise from potential solid emboli, then we could expect to see a correlation between new lesions and pre-existing atheroma, pre-existing lesions, and solid emboli detected using TCD (e.g. following removal of the aortic cross-clamp).

Neuropsychological function is a soft outcome measure and has proved challenging to quantify post-operatively. Although neuropsychological tests theoretically provide a highly sensitive means of quantifying changes in cognition, differences in test batteries, timing of assessment and criteria for defining neuropsychological decline generate considerable heterogeneity in the data, which limits our ability to compare the results of different studies. To better understand the incidence, causes, and time course of POCD we performed a systematic literature review incorporating over 426 articles.

Depending on the timing of the neurocognitive tests and the definition used for determining decline, the reported incidence of neurocognitive decline after cardiac

surgery varied extensively. The outcome suggests that 50-70% of patients experience cognitive decline when tested within one week of surgery, falling to 30-50% after 8-10 weeks, recovering to 10-20% at 1 year, and then declines again at 3-5 years. Currently, there is no widely accepted clinical definition of cognitive decline; therefore, it is possible that arbitrary definitions of decline have resulted in an overestimation of the incidence of decline. At present, there is no evidence to suggest that the long-term incidence of cognitive decline differs from that of non-operative controls. Estimating long-term cognitive decline can be difficult, as normal ageing and dementia interfere with studies with older populations.

Interpreting patient risk factors associated with POCD, it seems that efforts to protect the brain during surgery are intrinsically linked with the need to control long-term progression of cardiovascular disease, especially in older patients. Although cognitive decline is common in all ages, the incidence of long-term neurological deficit is consistently higher in older patients who have higher level co-morbidities, regardless of whether they undergo cardiac surgical interventions.

Further research is required to develop a more dynamic and nuanced picture of interactions between underlying pre- and peri-operative risk factors. It is apparent that studies investigating isolated peri-operative factors are insufficient to explain complex interactions between temperature, cerebral autoregulation, oxygen saturation and brain metabolism. To date, isolated interventions and neuroprotective drugs aimed at improving cognitive outcome have proved largely ineffective. Literature examining underlying and perioperative risk factors associated with the pathogenesis of cognitive decline suggests that there is no single causative factor responsible for POCD. It seems likely that the causes are multi-factorial, due to emboli, impaired perfusion, chronic cardiovascular disease, and inflammatory responses. As the majority of studies show no correlation between new lesions on MRI and neurocognitive decline (table 2.1) it seems that clinically silent cerebral infarcts tend not to impair cognitive functions as assessed through neurocognitive testing.

2.10 Study aims

At present, it is difficult to predict which patients will experience stroke or neurocognitive decline as a consequence of cardiac surgery. A major hypothesised cause of brain injury within the literature is from showering the brain with solid and gaseous emboli which become lodged in the cerebral arteries supplying brain tissue. The overarching aim of this thesis was to investigate the causes of brain injury during cardiac surgery by relating measurements of intra-operative emboli obtained using transcranial Doppler ultrasound to MRI and neuropsychological outcome. The current study focuses particularly on the role of large bubbles in generating new lesions on MRI and/or deficits of POCD and utilises a novel algorithm for sizing bubbles entering the MCA territory, which allows us to estimate the volume of air and the likely impact of bubbles on cerebral blood flow. Doppler data were analysed to estimate the sizes of bubbles and volume of air entering the cerebral vasculature during cardiac surgery. The potential impact of air emboli on brain tissue perfusion was then estimated using virtual patient Monte Carlo simulations.

Specific clinical questions addressed in the following chapters of this thesis include:

1. Do the presence, total number, and/or volume of new postoperative FLAIR MRI lesions adversely impact cognition?
2. Does increased embolic load during heart surgery result in a higher incidence of new MRI lesions and/or greater decline in neuropsychological performance?
3. Does size and composition of emboli impact MRI or neuropsychological outcome?

This research was conducted as part of a British Heart Foundation study investigating brain injury following cardiac surgery. The main aim of our study was to investigate the proposed link between large gaseous emboli, cognitive decline, and new lesions on MRI, and to try to quantify the impact of emboli on cerebral blood flow.

Chapter 3 provides technical details describing our embolus detection, MRI and cognitive testing methods, statistical analysis, and simulation techniques.

Chapter 4 outlines the clinical study protocol, patient time-line, and methods for recording and analysing patient data.

Chapter 5 reports the incidence of POCD and new MR lesions 6-8 weeks following surgery and tests the hypothesis that new MRI lesions are associated with a decline in cognition.

Chapter 6 presents our embolus detection and bubbles sizing results, alongside the results of Monte-Carlo simulations, to test whether the prevalence, size, or timing of emboli influences MRI or neurocognitive outcome.

Chapter 7 reflects on the key findings of this dissertation.

Chapter 8 concludes the main findings and purposes future work.

Chapter 3

3 Anatomy and Techniques

This study involved three main types of investigative technique: detection of cerebral ischaemic lesions using Magnetic Resonance Imaging (MRI) (sections 3.2 & 3.3), cognitive assessment (section 3.4), and detection of blood-flow and emboli moving through the Middle Cerebral Artery (MCA) using transcranial Doppler (TCD) ultrasound (section 3.5). This chapter briefly describes the anatomy of the cerebral arteries and provides a detailed description of MRI and neuropsychological tests used as part of our study to assess patient outcome. The final part of this chapter outlines the software and data analysis methods used to record and analyse embolic signals using transcranial Doppler ultrasound.

3.1 Basic anatomy of the cerebral vasculature

The brain is one of the most highly perfused organs in the body and the anatomy of the major cerebral arteries supplying blood to the brain is described in various textbooks (Lasjaunias, P, Brugge, K.G, 2006; Saladin, 2014). The brain receives blood from the heart via four main arteries; the left and right common carotid arteries and the left and right vertebral arteries. Each common carotid artery divides into internal and external carotid arteries. The internal carotid arteries principally supply the cerebrum, whereas the left and right vertebral arteries join to form the basilar artery which supplies blood to the brain stem and cerebellum. At the base of the brain, the two internal carotid arteries and the basilar artery are linked via communicating arteries to form a ring-like structure known as the ‘Circle of Willis’ (fig 3.1).

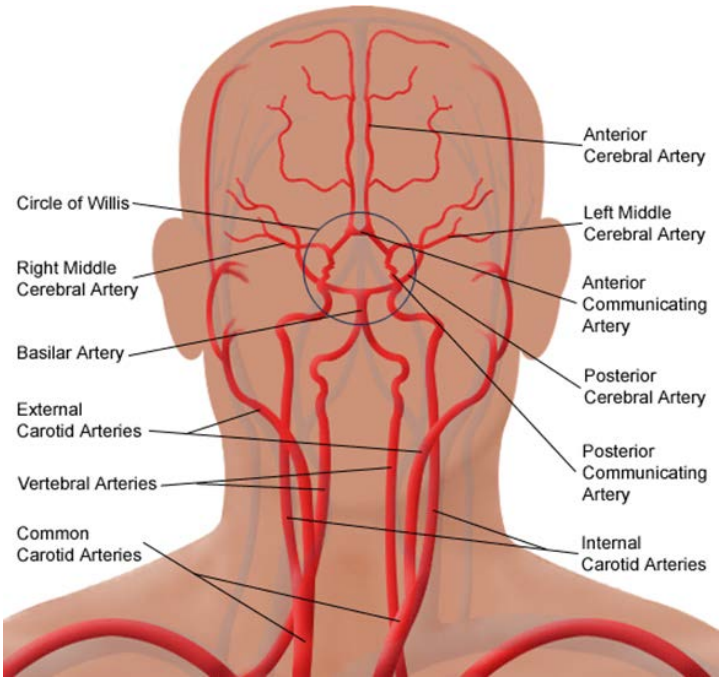


Figure 3.1 Arterial circulation of the brain showing the Circle of Willis (Yale Medical Group, USA)

The Circle of Willis gives rise to three main arteries supplying the brain, the Anterior Cerebral Artery (ACA), Middle Cerebral Artery (MCA) and Posterior Cerebral Artery (PCA). These branch into smaller arteries and arterioles that run along the surface of the brain, eventually penetrating the tissue to supply blood to the regions of the cerebral cortex. A schematic diagram of the cerebral arteries and associated perfusion territories is provided in figure 3.2 (David & Moore, 2008).

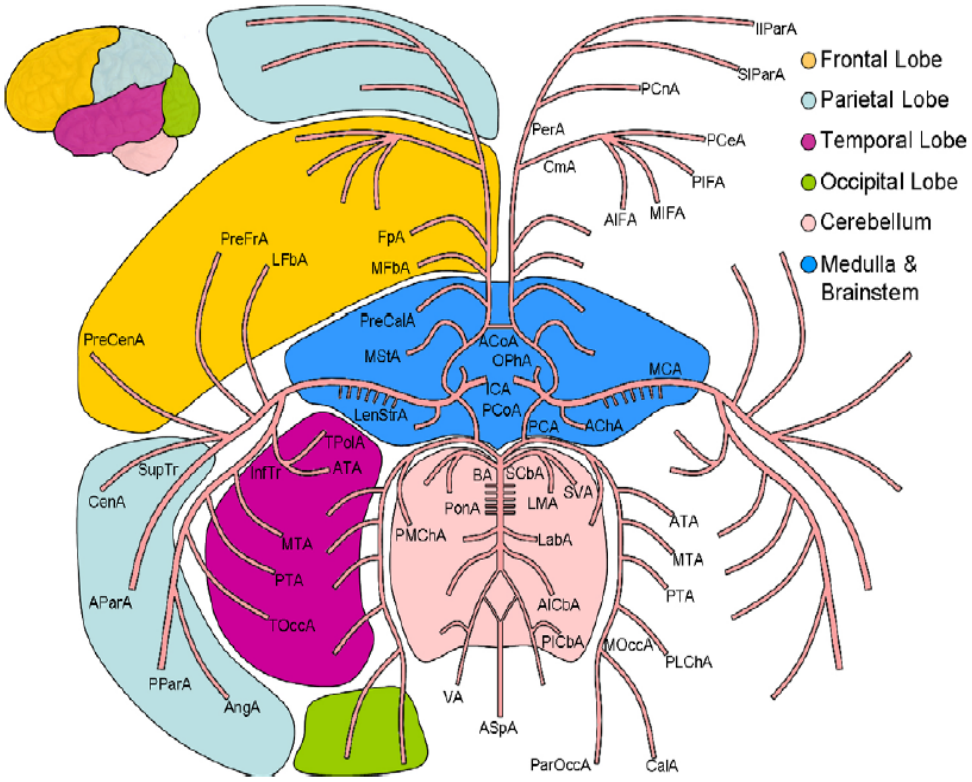


Figure 3.2 A schematic of the cerebral arteries, labelled by their abbreviations and illustrating the general regions of the brain which they supply with blood, **(David & Moore, 2008)**.

3.2 Imaging of the brain using MRI

3.2.1 Introduction to the basic principles of MRI

The Noble Prize in 1952 was awarded to Felix Bloch and Edward Purcell for their early research into nuclear magnetic resonance (NMR) phenomena. In 1971, Raymond Damadian discovered that healthy tissue and tumours exhibited differing NMR relaxation times, which encouraged scientists to consider harnessing MR for the detection of disease. In 1975, Richard Ernst proposed using phase and frequency encoding for Magnetic Resonance Imaging (MRI), which now forms the basis of modern MRI techniques (Rocchi *et al.*, 2015). Magnetic resonance imaging (MRI) is increasingly used for the identification of ischaemic lesions and is useful for detecting changes occurring in brain tissue following acute cerebral ischaemia.

MR images are generated by the detection of signals from protons contained mainly in tissue water and fat. Protons possess a magnetic moment that causes them to align with an externally applied magnetic field. MRI uses a sequence of radiofrequency electromagnetic pulses to align the magnetic moment of the protons. The moments then generate a decaying oscillating magnetic field before they relax back to their disordered equilibrium level. It is this oscillating magnetic field that is detected as a voltage induced in a receiver coil and which can be converted into images showing the distribution of protons (proton density). The relaxation rate of the excited tissue depends on tissue composition, and is characterised by the relaxation time constants, T_1 and T_2 (McRobbie, 2007). The contrast in the image results from different intensities of the emitted signals, which in turn result from different concentrations of protons and different T_1 and T_2 values in the various tissues of the body.

Interest in MRI as a technique for quantification of cerebral ischaemia lies in its capacity to detect early ischaemic lesions with high sensitivity, enabling researchers to identify their size and location. Typical MRI pulse sequences include: Diffusion-Weighted Imaging (DWI), Gradient-Recalled Echo (GRE), T_2-weighted, FLuid-Attenuated Inversion Recovery (FLAIR), and Perfusion-Weighted Imaging (PWI). MRI is capable of identifying hypo-perfused tissue that is at risk of infarction, as well as additional features of cerebrovascular pathology such as acute or chronic haemorrhage (McRobbie, 2007). Magnetic resonance angiography (MRA) can also be used to

investigate the anatomy of the Circle of Willis. In the next few sections, I describe each of the types of MRI scan performed as part of our study protocol and provide example scans from patient data.

3.2.2 Types of MR scan: T_1 and T_2 weighted images

T_1 weighting refers to a set of standard scans that show differences in the spin-lattice relaxation time of various tissues within the body. T_1 weighted images can be acquired using either spin-echo or gradient-echo sequences. T_1 weighted contrast can be increased with application of an inversion recovery RF pulse. Gradient-echo based T_1 weighted sequences can be acquired very rapidly because of the ability to use short inter-pulse repetition times (TR). In some applications, for example in oncology, T_1 weighted sequences are often collected before and after infusion of a T_1 shortening MRI contrast agent. In the brain, T_1 weighted scans provide acceptable contrast between grey and white matter and work well for differentiating fat from water, with water appearing darker and fat appearing brighter (McRobbie, 2007). Conversely, in a T_2 weighted scan, fat appears darker, while water appears lighter (fig. 3.3).

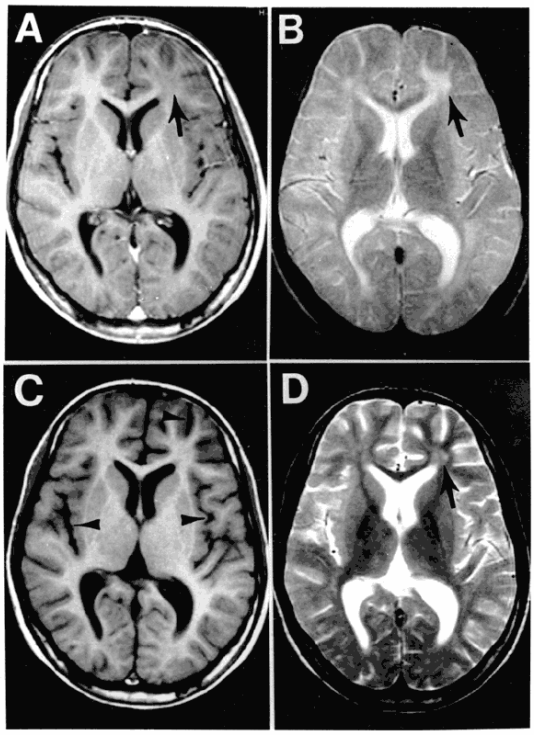


Figure 3.3 Brain MRI showing T_1 and T_2 weighted scans. Images A and C are T_1 weighted images; B and D are T_2 weighted images [http://physiology-physics.blogspot.co.uk/2010/07/relaxation-in-nuclear-microcosm.html, accessed on 15/04/2013]. Fluid appears dark on T_1-weighted images, but bright on T_2-weighted.

3.2.3 FLAIR Imaging

Fluid Attenuated Inversion Recovery (FLAIR) is an inversion recovery pulse sequence which uses a combination of T_1 and T_2 relaxation sequences to null the signal contributed by fluids. This can be used in brain imaging to suppress the appearance of cerebral spinal fluid and enhance visualisation of periventricular lesions. By carefully choosing the inversion time, TI (the time between the inversion and excitation pulses), the signal from any particular tissue can be suppressed. By including an additional Radio Frequency (RF) pulse, and manipulation of magnetic field gradients, a T_2 weighted sequence can be converted to a FLAIR sequence in which free water appears dark, but damaged tissue remains bright (fig 3.4). This sequence is currently one of the most sensitive ways to evaluate new ischaemic lesions (McRobbie, 2007).

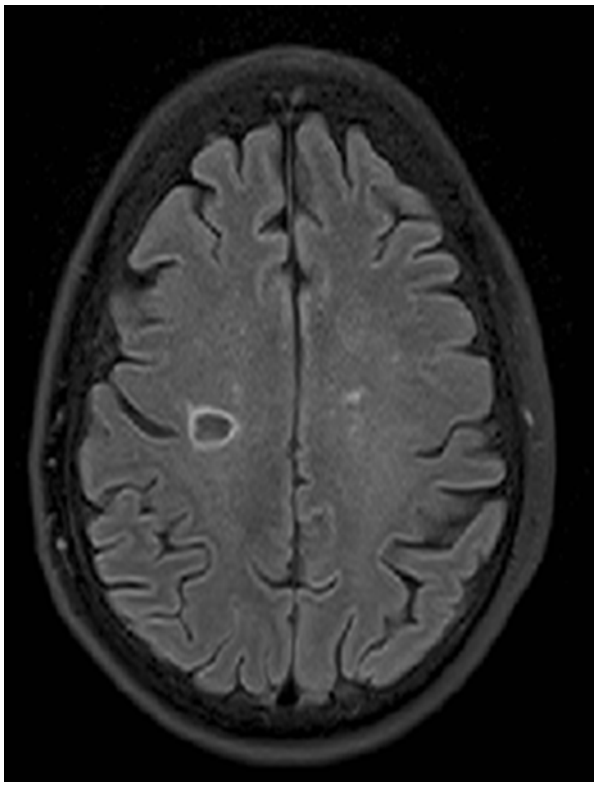


Figure 3.4 MRI FLAIR image showing a lacunar infarct in the right territory of the middle cerebral artery (patient 13).

3.2.4 Susceptibility weighted Imaging

Susceptibility weighted imaging (SWI), creates contrast in the image in a different way from traditional spin density, T_1, or T_2 imaging. SWI uses a fully flow-compensated gradient echo (GRE) scan to acquire images. This method exploits differences in magnetic susceptibility between tissues and uses the phase image to detect these differences. Magnitude and phase data are combined to produce an enhanced contrast magnitude image which is sensitive to venous blood and haemorrhage. The imaging of venous blood with SWI is sensitive to blood oxygen level and is occasionally still referred to as BOLD. Due to its sensitivity to venous blood, SWI is commonly used to investigate traumatic brain injuries and for high resolution brain venography (fig 3.5) (Lingegowda *et al.*, 2012).

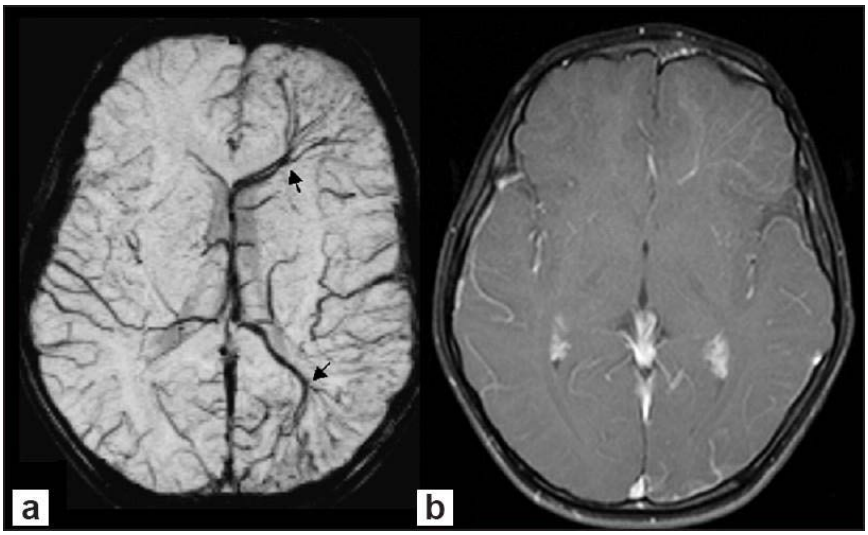


Figure 3.5 Example SWI scans: (a) shows cortical veins draining into enlarged transmedullary veins (black arrows), which are difficult to see on the contrast-enhanced T1-weighted axial image (b) [http://www.neurology.org/content/71/5/382/F1.expansion.html, accessed on 15/04/2013].

3.2.5 Diffusion-weighted Imaging

Diffusion weighted imaging (DWI) is useful for the diagnosis of acute ischaemic stroke and is the only brain imaging method demonstrated to reliably show ischaemic injury within the first minutes to hours after stroke onset (fig 3.6). Ischaemia-induced membrane dysfunction and cytotoxic oedema restrict the diffusion of water and lead to a decrease in the 'apparent diffusion coefficient' (ADC). The ADC provides a physiological measure of the rate of water movement through brain parenchyma (Warach *et al.*, 1992). The sensitivity of DWI for detection of acute ischaemia ranges from 73% (3 hours after the event) to 92% (>12 hours after the event). By contrast, the sensitivity of computed tomography (CT) at these times was 12% and 16%, respectively. The specificity of DWI MRI for stroke detection was 92% (at 3 hours) and 97% (>12 hours) (Chalela *et al.*, 2007). The sensitivity of DWI MRI was also higher than that of either CT (39-75%) or FLAIR (46%) (Lansberg *et al.*, 2000).

It is interesting to note that acute ischaemic lesions on DWI are dynamic: information from clinical trials and case series shows that DWI lesions initially grow with time and that the initial diffusion lesion volume tends to correlate well with final infarct volume and neurological and functional outcomes (Schwamm *et al.*, 1998). Stroke patients with multiple DWI lesions or large artery disease are more likely to experience additional

new lesions than stroke patients with single lesions on DWI (Kang *et al.*, 2003). This 'stroke-prone' state continues for up to 90 days, with the greatest risk occurring during the first month after the initial stroke (Kang *et al.*, 2004).

Differing lesion patterns are associated with specific stroke sub-types. Single cortico-subcortical lesions, multiple lesions in the anterior and posterior circulation, and multiple lesions in cerebral territories are thought to be associated with cardiac embolism (Baird *et al.*, 2000). Multiple lesions in the unilateral anterior circulation, and small scattered lesions in one vascular territory, particularly in a watershed distribution, are usually related to large artery atherosclerosis (Chaves *et al.*, 2000).

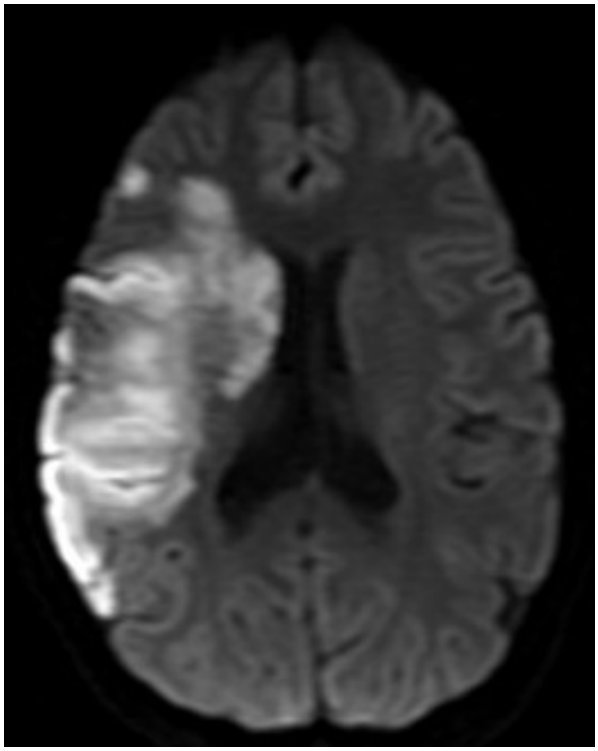


Figure 3.6 DWI: ischaemic infarct in the right middle cerebral artery identified using DWI imaging [http://www.neurology.org/content/74/24/1946/F2.expansion.html, accessed on 15/04/2013]

3.2.6 Time of flight MR angiography

Time-of-flight (TOF) MR angiography is based on the phenomenon of flow-related enhancement of spins entering into an imaging slice. As spins entering the image slice are unsaturated, these spins give a stronger signal than surrounding stationary spins.

With 2D TOF MRA, multiple thin imaging slices are acquired with a flow compensated gradient-echo sequence. These images can be combined using a reconstruction technique, such as maximum intensity projection (MIP) mapping, to obtain an image of the vessels in an analogous fashion as in conventional angiography (fig 3.7). With 3D TOF MRA, a number of images are obtained simultaneously by phase encoding in the slice select direction. An angiographic appearance can be generated using a MIP, as is done with 2D TOF. Several 3D TOF volumes can also be combined to visualise longer segments of vessels. 3D TOF angiography allows greater spatial resolution in the slice-select direction than 2D TOF MRA; however, with thick volumes and slow flowing blood, loss of signal can be seen with the 3D TOF method (Carr, 2012).

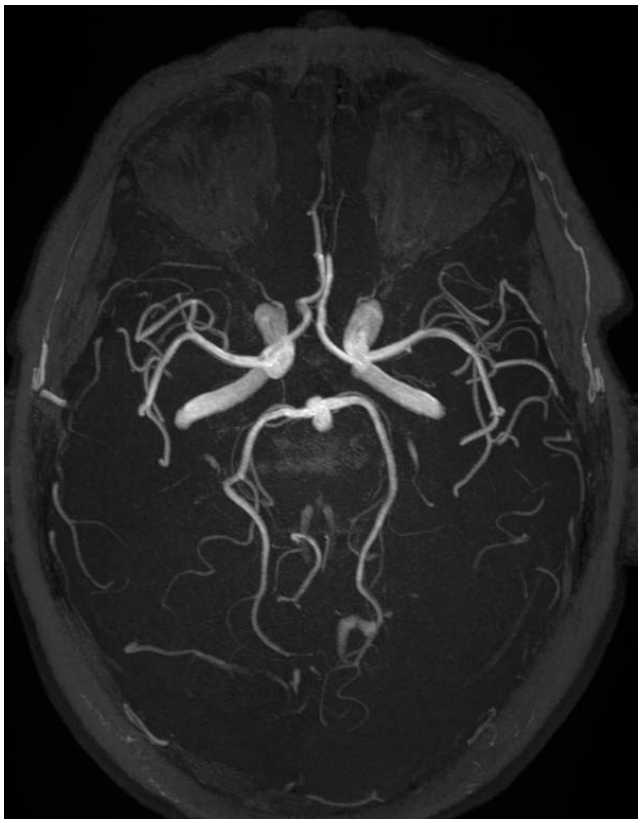


Figure 3.7 An example of a 3-D time-of-flight MR-angiography scan of patient 13.

3.3 'In house' MRI registration and subtraction software

In the current study pre- and post-operative MRI FLAIR images were registered and subtracted to aid in the detection of new lesions. This was performed using 'in house software' written by Dr Mark Horsfield. Registration involves creation of an average 'template' formed from both images. This 'reference image' is then kept fixed whilst the pre- and post-surgery source images are spatially transformed by translation and rotation until differences between the two images are minimised. Below is a schematic representation of the translation and transformation of the images (fig. 3.8).

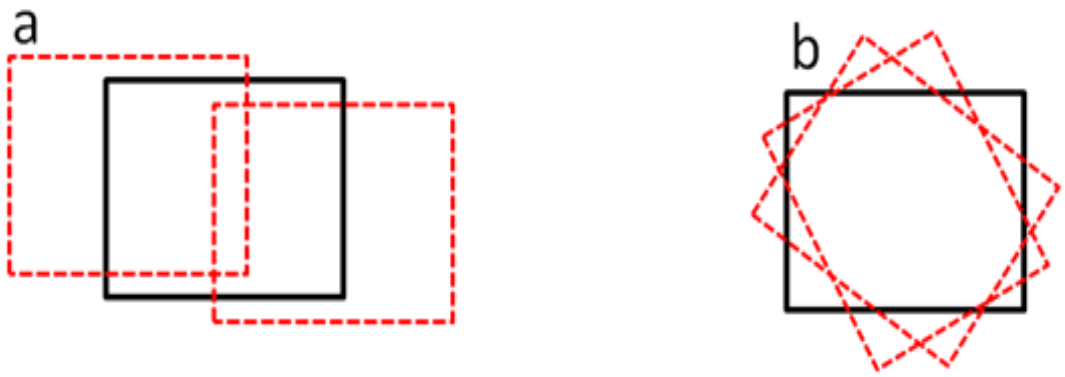


Figure 3.8 Registration is performed by allowing (a) translation, and (b) rotation, of the image.

The 'goodness of fit' of the source to the reference image is quantified by defining a *cost function* to describe differences between one image and another. Registration was optimised using a '*normalised cross-correlation'* method with a fixed reference image and translation and rotation of the source image in the *x*, *y*- and *z*- planes (6 degrees of freedom in total). Once the two images are aligned and matched within this common geometrical template they can be compared by digital subtraction to identify new lesions. Figure 3.9 shows example data from one of our patients, displayed using Dr Horsfield's software.

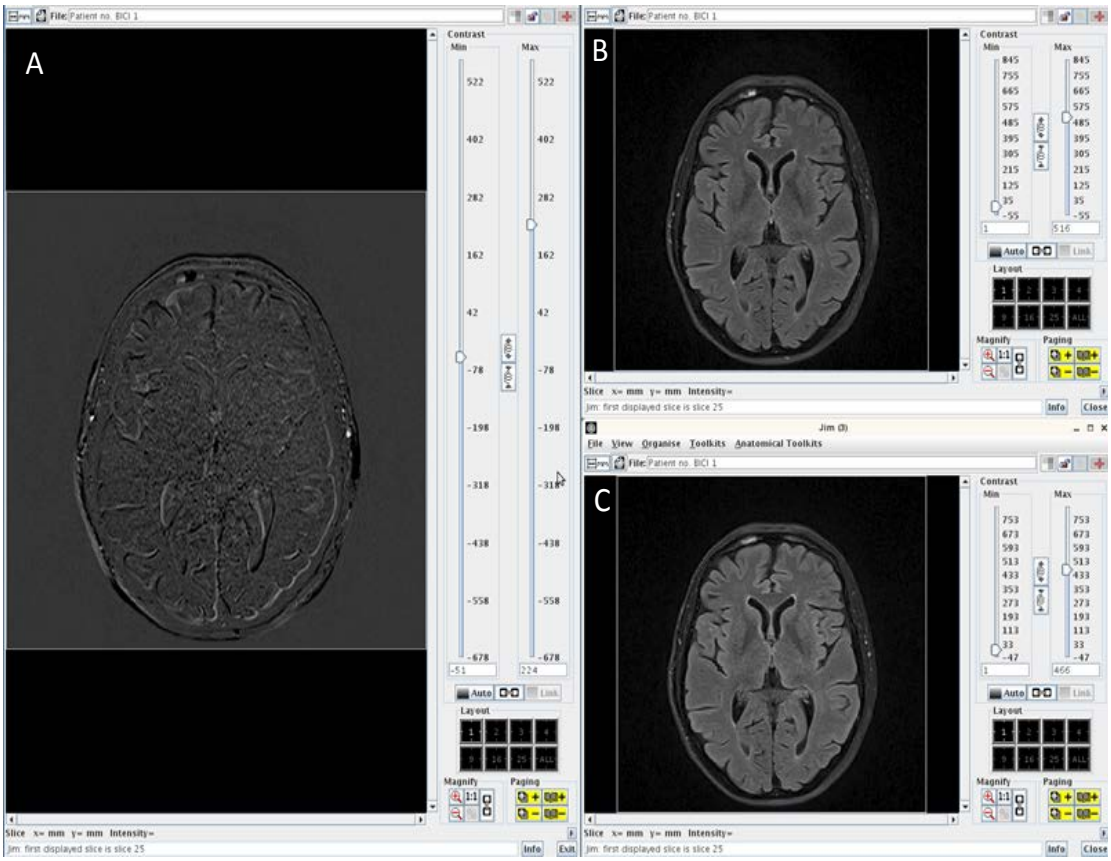


Figure 3.9 Example data subtraction analysis performed using in-house software for patient 76. (A) subtraction scan of the pre- and post-operative scan, (B) pre-operative scan, (C) post-operative scan.

The two images on the right hand side show 'before' and 'after' data, and the larger image on the left shows a 'difference' image following optimised registration and digital subtraction. In the difference image it becomes easier to identify new lesions, which show up as bright intensity regions. As similarities between before and after images are 'cancelled out', it also becomes easier to distinguish new lesions from pre-existing features such as old infarcts or small vessel disease.

3.3.1 Delineation of the number and volume of new and pre-existing lesions

To distinguish chronic lesions from acute ischaemic changes, the MR-FLAIR images were presented to a qualified neuroradiologist who was blinded to the results of neuropsychological assessments. Chronic ischaemic changes were then characterised through registration and subtraction of pre- and post-operative FLAIR images (fig. 3.10).

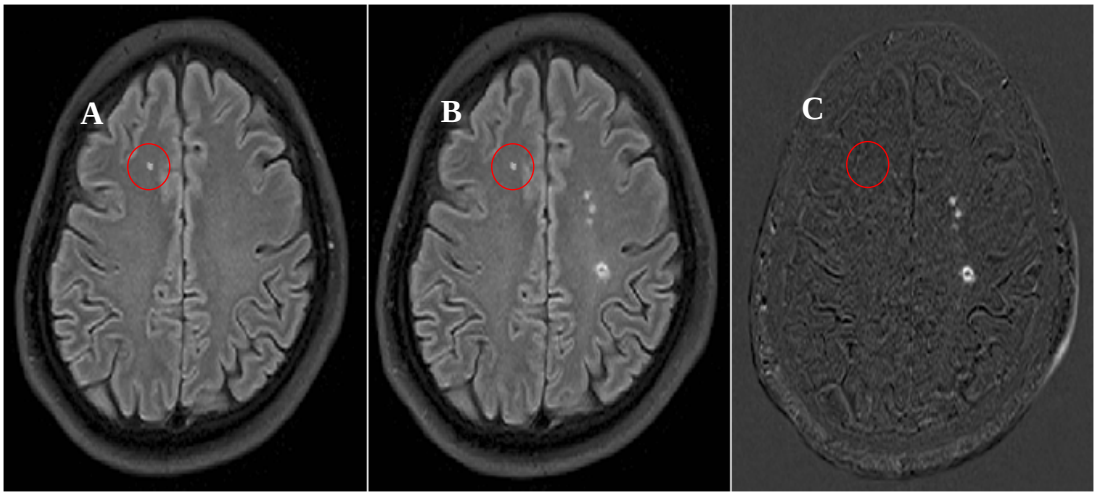


Figure 3.10 Images obtained for patient 76. (A) pre-operative scan; (B) post-operative scan; (C) difference image. Red circles show successful image subtraction of a pre-exiting lesion.

Images were analysed for the location and volume of pre-existing and new lesions, which were quantified using a semi-automated contouring technique (fig 3.11).

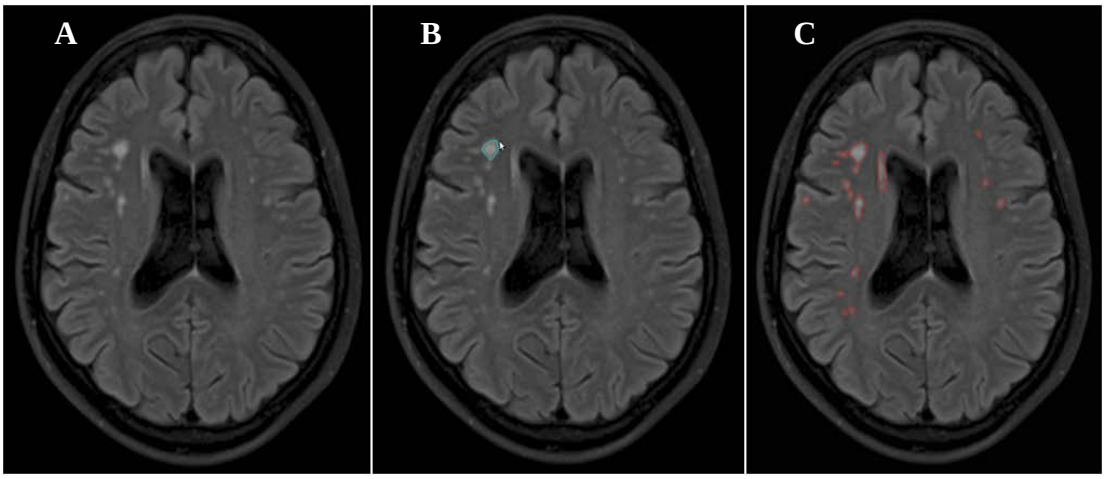


Figure 3.11 (A) image of patient 76 with pre-existing lesions; (B) using the semiautomatic contouring technique to hover over the selected lesion; (C) using the same principle to select all the lesions on that slice before moving to the next slice.

After selecting all lesions using the semi-automated contouring technique, the software outputs a report summarising the total number and volume of the lesions. Lesion volumes are reported in mm^3. In order to visualise the lesion distribution, post-operative FLAIR images were registered to a standard MRI brain atlas (Mazziotta *et al.*, 2001),

and lesions from all patients were segmented and displayed using the atlas as reference for the 3-D display.

3.4 Neuropsychological Assessment

Cognitive changes can be assessed by asking patients to complete a battery of neurocognitive tests. By comparing the results of cognitive tests conducted before and after surgery it becomes possible to determine whether patients have experienced a significant decline in function following surgery. Each test assesses different aspects of visual, verbal and co-coordinative functions of the human brain.

3.4.1 Pre- and post-operative neuropsychological tests

To examine the possible neuropsychological effects of cardiac surgery, all participants completed a battery of well-established neuropsychological assessments, lasting approximately 1.5 hours. Tests were conducted at the patient's bedside if necessary. These compromised the WASI test (which measures verbal and performance IQ via Block Design, Pattern Matrices, and Similarities and Vocabulary tests), parts A and B of the Trail-Making test (which measures attention), the WMS-III digit span task (which measures verbal and visual memory), the SCOLP test (measures the speed of information and language processing) and the Grooved Pegboard test (measuring attention and psychomotor speed). Cognitive domains corresponding to each neuropsychological test are listed in table 3.1.

Table 3.1 Neuropsychological domains tested and associated tasks.

Domains/tests	**Task**
Attention and psychomotor Trail making test A Grooved pegboard	 Connecting numbers on a test sheet Inserting identical pegs into grooves in a parallel order
Executive functioning Trail making test B WASI matrix reasoning	 Connecting number/letters alternately Connecting patterns by identifying missing shapes
Visual memory WMS-III pictorial memory (family pictures) Short-term learning WMS-III pictorial memory delayed learning	 Recognising family pictures within a variety of 4 different situations Recalling the family members and situations after 35 mins
Verbal memory WMS-III short-term learning WMS-III delayed learning	 Recalling a short story Recalling the story after 35 mins
Information processing SCOLP speed of comprehension	 Stating true or false for as many sentences possible within 2 mins
Verbal intelligence SCOLP spot-the-word WASI vocabulary and similarities exercise	 Identifying the correct and incorrect word Defining the word and the connection between the 2 words
Visual Constructive functions WASI block design	 Assembling square blocks to construct different designs

3.4.2 Standardisation and normative data for the neuropsychological tests

The statistical performance of a person's test score on a norm-referenced scale (raw scores) is of little significance by itself. A meaningful interpretation of the baseline test scores is obtained through comparison of the distribution of scores from a group of individuals of similar age, sex, and education level. All neuropsychological tests used in this study were standardised tests that were accompanied by normative data obtained from a large sample population to characterise the normal range of values expected.

For meaningful interpretation of test scores, the standardisation procedure takes into account two important factors:

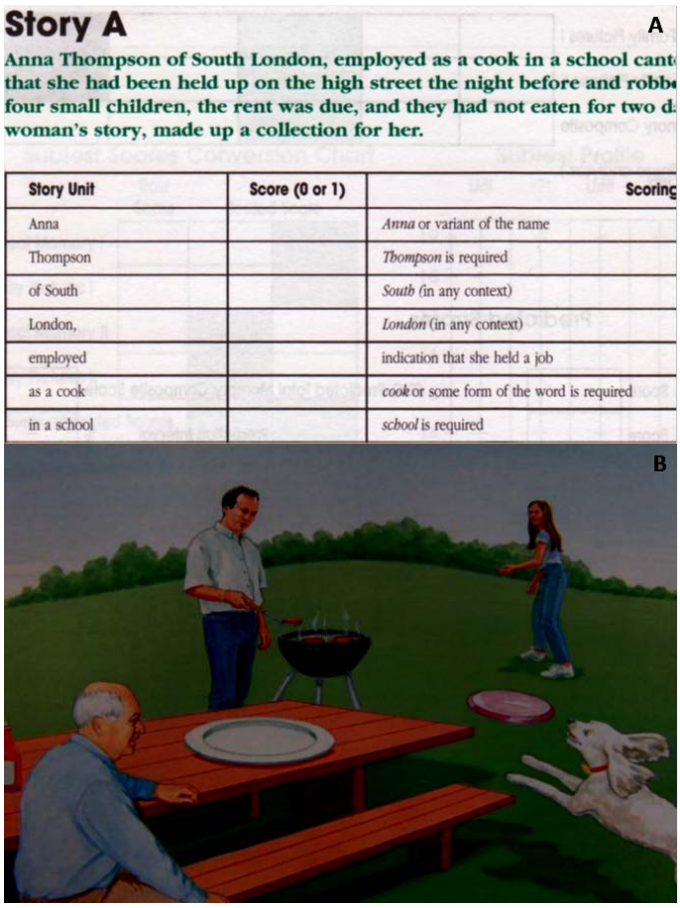
1. *Size of the standardisation sample*: the sample should be large enough to reduce the impact of individual variations in intelligence and personality.

2. *Representativeness of the sample*: the standardisation sample should be representative of the population for whom the test is intended.

3.4.3 The Wechsler Memory Scale-Third Edition Abbreviated (WMS-III) [Harcourt Assessment Company, London, UK].

WMS-III is a fast reliable, survey of auditory and visual memory abilities (fig 3.12), which is designed to provide clinicians with an estimate of general memory functioning when extended memory testing is not indicated or is not feasible.

The test is sensitive to memory impairments associated with a variety of clinical conditions including dementia, neurological, and neuropsychiatric conditions. The battery may be used as part of a standard psychological or neuropsychological evaluation. The WMS®-III was designed to monitor changes in memory performance through statistical analysis of serial assessments. This contains 4 subtests measuring auditory and visual, immediate, and delayed memory. This test is usually administered within 20-25 minutes.



Story A A

Anna Thompson of South London, employed as a cook in a school cant that she had been held up on the high street the night before and robb four small children, the rent was due, and they had not eaten for two d. woman's story, made up a collection for her.

Story Unit	Score (0 or 1)	Scoring
Anna		*Anna* or variant of the name
Thompson		*Thompson* is required
of South		*South* (in any context)
London,		*London* (in any context)
employed		indication that she held a job
as a cook		*cook* or some form of the word is required
in a school		*school* is required

B

Figure 3.12 (A) Verbal and (B) visual memory test

The standardisation sample for WMS-III is presented within the manual (Lo *et al.*, 2012) and is based on a national standardisation sample representative of a population of U.S. adults.

Age: For the WMS-III abbreviated standardisation sample, 1,250 adults were tested, aged 16-89 years. The sample was divided into 13 age bands: 16-17, 18-19, 20-24, 25-29, 30-34, 35-44, 45-55, 55-64, 65-69, 70-74, 75-79, 80-84, and 85-89. One-hundred participants were included in each age group, except the two oldest groups, which comprised of 75 participants each.

Sex: The sample consisted of an equal number of male and female participants in each group between ages 16-64. The older groups included more women than men, in proportions consistent with census data.

Race/ethnicity: For each group in the sample, the proportion of whites, African Americans, Hispanics, and other ethnic groups were based on the racial/ethnic

proportions of individuals within each age band in the U.S. population according to 1995 Census data.

Education: The samples were stratified according to the following 5 education levels based on the number of school years completed; ≤8 years, 9-11 years, 12 years, 13-15 years, ≥16 years.

3.4.4 Trail making exercise (Parts A and B) [GL Assessment, London, UK]

The first part of this test, Trails A, requires the subject to rapidly sequence numbers from 1 through to 25 (fig 3.13a). The second part, Trails B (fig 3.13b), is a more difficult cognitive flexibility task requiring the subject to sequence from 1 to 13 while switching between numbers and letters (i.e., 1-A-2-B, etc.). Scoring of trail-making tests A and B are reported as the number of seconds required to complete the task. Higher scores indicate greater impairment. Performance varies with age and education, and thus normative standards are used to classify patient performance. If a patient has not completed both parts after 5 minutes, it is unnecessary to continue the test. Parts A & B need to be completed together and in the correct order for test administration to be valid.

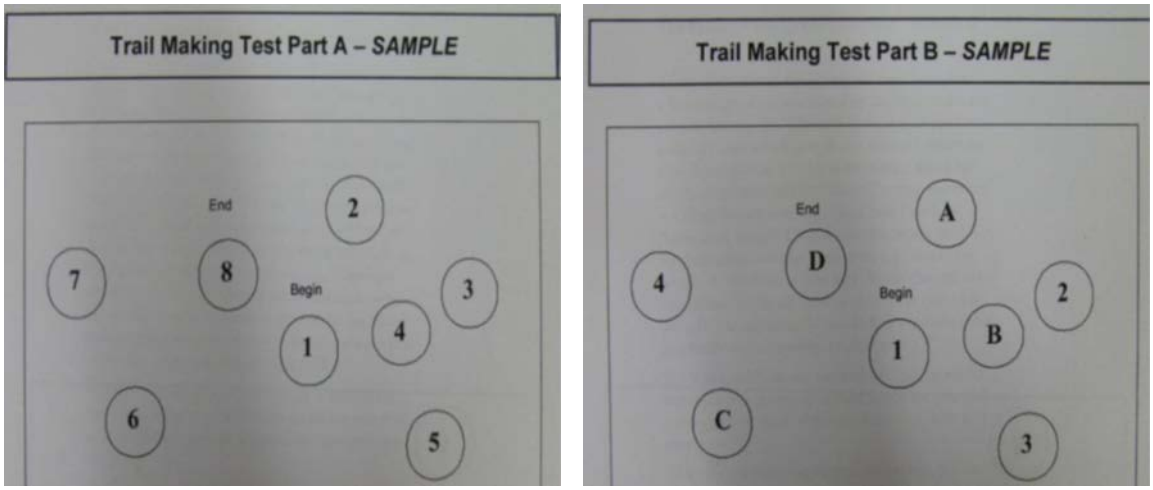


Figure 3.13 Trail making part A, Trail making part B

Normative data for the Trail Making Test was obtained from a trial published by N. Tombaugh in 2004 (Tombaugh, 2004). The sample was taken from community-dwelling individuals living in Canada.

Age: A total of 911 individuals were included in the sample, aged between 18-89 years. The norms were stratified for both age (11 groups) and education (2 levels). This article presents the most recent set of normative data for determining impaired performance in individuals of varying age and level of education.

Sex: The male to female ratio for this sample was 408 males to 503 females.

Education: The samples were stratified into two education levels based on the number of years of school completed; 0-12 and 12+ years.

3.4.5 The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) [Pearson Assessment, London, UK]

The *WASI* test gives an estimate of general intellectual ability based on 4 subtests, 'Vocabulary' (42 total items that require the subject to orally define 37 words presented both orally and visually), 'Matrix Reasoning' (35 incomplete grid patterns that require the participant to select the correct response from five possible choices), 'Similarities' (26 pairs of words which require the patient to give a word similar to the 2 words given), and 'Block making' (where the patient has to rearrange blocks to imitate an image) (fig 3.14). *WASI* provides a quick estimate of an individual's level of intellectual functioning, with higher scores indicating greater intellectual ability. This test can usually be administered within 20-25 minutes.

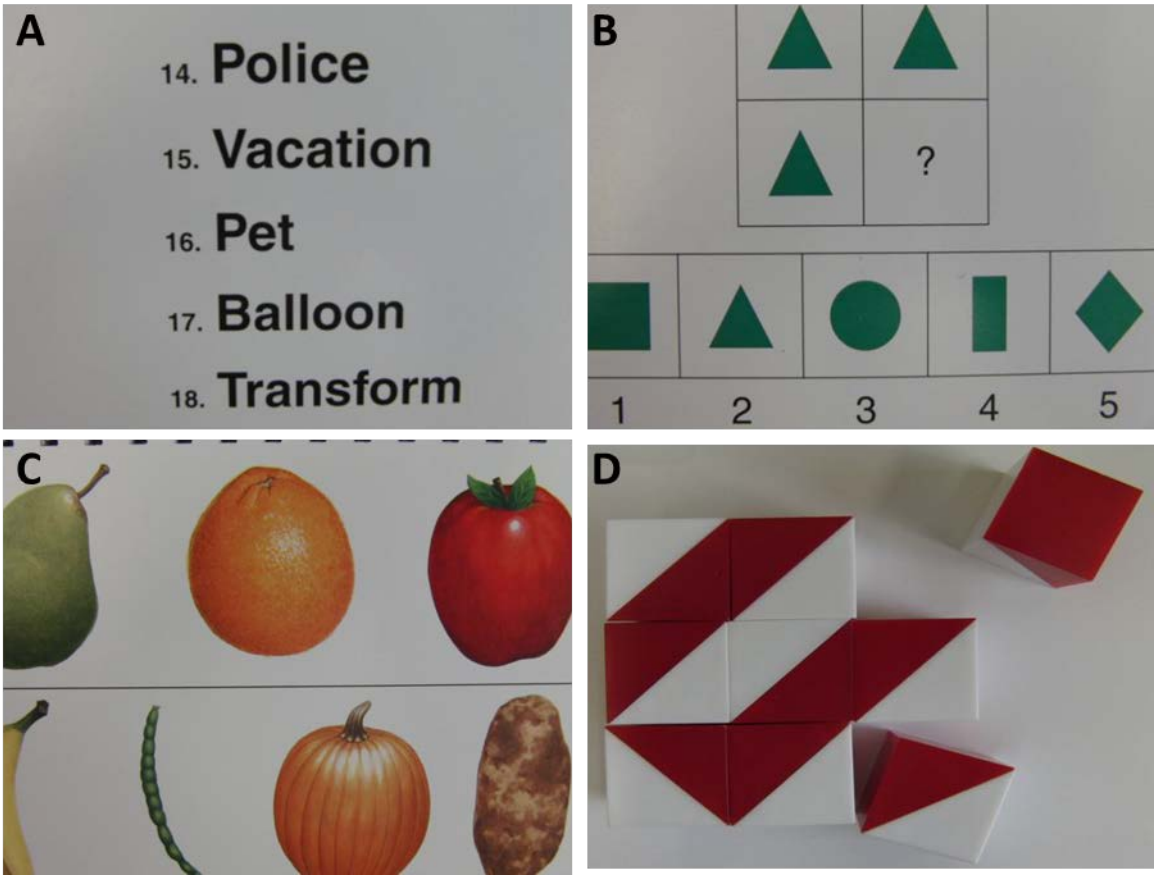


Figure 3.14 (A) vocabulary exercise; (B) matrix reasoning; (C) similarities exercise; (D) block making design.

Normative data for the WASI test is presented in a manual accompanying the test (Harman-Smith *et al.*, 2013) and is based on a national sample of the English-speaking U.S. population.

Age: A total of 2,245 participants were included in the standardisation sample of which 1,145 were adults aged 6-89 years. The standardisation sample was divided into 23 age groups spanning from 6-89 years, of which 12 groups were adult: 17-19, 20-24, 25-29, 30-34, 35-44, 35-44, 45-54, 55-64, 65-69, 70-74, 75-79. 80-84 and 85-89. One hundred participants were included in each group, except for the 75-79, and 80-84 age groups with 85 adults, and the 85-89 group with 75 adults.

Sex: The sample consisted of an equal number of male and female participants in each group from 6-64 years of age. The 3 oldest groups included more women than men, in proportions consistent with census data.

Race/ethnicity: For each group in the sample, the proportion of whites, African Americans, Hispanics, and other ethnic groups were based on the racial/ethnic proportions of individuals within each age band in the U.S. population according to 1997 Census data.

Education: The samples were stratified based on the number of school years completed; ≤8 years, 9-11 years, 12 years, 13-15 years, ≥16 years.

3.4.6 Grooved pegboard test. [Benefitsnow, Petersfield, UK]

This test is used to identify a decline in fine motor function, hand-eye coordination and sensory motor integration. The aim of the test is to orientate 25 identical pegs into the holes in the pegboard (fig 3.15). This process is repeated for both the dominant and non-dominant hand. The investigator records how long it takes to complete the task with both the left and right hand, and notes are made of any pegs that have been dropped. The total time (in seconds), plus the amount of drops, totalled with number of pegs correctly placed, gives the patient's overall score. A higher score in the post-operative test compared to the pre-operative test would indicate a decline in performance.

Figure 3.15 Grooved pegboard.

Normative data for the Grooved Pegboard Test was obtained from the manual (KLOVE, 1963). This sample was based on participants in the city of Waterloo, Canada.

Age: A total of 153 individuals aged between 9 and 89 years were included in the standardisation sample. Age ranges were divided into 12 groups: 9, 10, 11, 12, 13, 14, 15-19, 20-29, 30-39, 40-49, 50-59 and 60+.

Sex: Of the 153 participants, 47 were male, 39 right handed and 8 left handed. Of the 106 females, 97 were right handed and 9 were left handed.

Education: The sample was not stratified to level of education.

3.4.7 The Hospital Anxiety and Depression scale (HADS) [GL Assessment, London, UK]

This test is considered a reliable self-rating scale for assessing anxiety and depression in both hospital and community settings. The HADS score is not used to assess cognition, but to adjust for anxiety and/or depression as a confounding factor. The test comprises

of a brief one page questionnaire, with 14 questions; seven questions for anxiety and seven for depression, which can normally be answered within 2 – 5 minutes (fig 3.16).

Figure 3.16 Hospital Anxiety and Depression Scale

Scores are classified as 'normal', 'mild', 'moderate' and 'severe' (table 3.2).

Table 3.2 Interpretation of the HADS score

Score	Interpretation
0-7	Normal
8-10	Mild
11-14	Moderate
15-21	Severe

Validation has previously been performed through comparison with the four-point psychiatric rating scale for anxiety and depression for 100 medical outpatients (Zigmond & Snaith, 1983). Further validation has also been reported in psychiatric patients (Bramley *et al.*, 1988) and in a heterogeneous group of patients with physical illness (Aylard *et al.*, 1987).

3.5 Ultrasound embolus detection

3.5.1 Transcranial Doppler ultrasound embolus detection

Transcranial Doppler (TCD) was developed by Aaslid *et al*. in 1982 and uses 1-2.5 MHz ultrasound to measure cerebral blood flow velocity (CBFv). TCD is an important tool for measuring CBFv (Bishop et al., 1986), evaluating cerebral autoregulation (Aaslid *et al.*, 1991), and the detection of emboli (Ringelstein *et al.*, 1990; Mackinnon *et al.*, 2004). It is also important in the diagnosis of haemorrhage, stenosis and other problems related to CBF (Vora *et al.*, 1999; Markus, 2000).

3.5.2 Basic principles of Transcranial Doppler

Any sound wave with a frequency above that of the human hearing (approximately 20 KHz) is termed ultrasound. Sound waves behave in a similar way to light waves in the sense that energy is absorbed as the wave passes through a propagating media, and undergoes refraction, reflection and scattering at interfaces between media with differing acoustic impedances. The detection of reflected sound waves forms the basis of ultrasound imaging (Diagnostic Ultrasound: Physics and equipment, Hoskins *et al*, 2010).

Transcranial Doppler (TCD) ultrasound provides a method of estimating the velocities of scatterers moving through the arteries by harnessing a phenomenon called the Doppler effect. This was first described theoretically by Christian Doppler in 1842, and describes the change in the apparent frequency, or wavelength, of a wave caused by the relative motion of the source of the wave and an observer. For instance, if a wave source (sound emitter) is moving towards an observer, the frequency of the wave will appear higher than if the source was stationary (fig. 3.17).

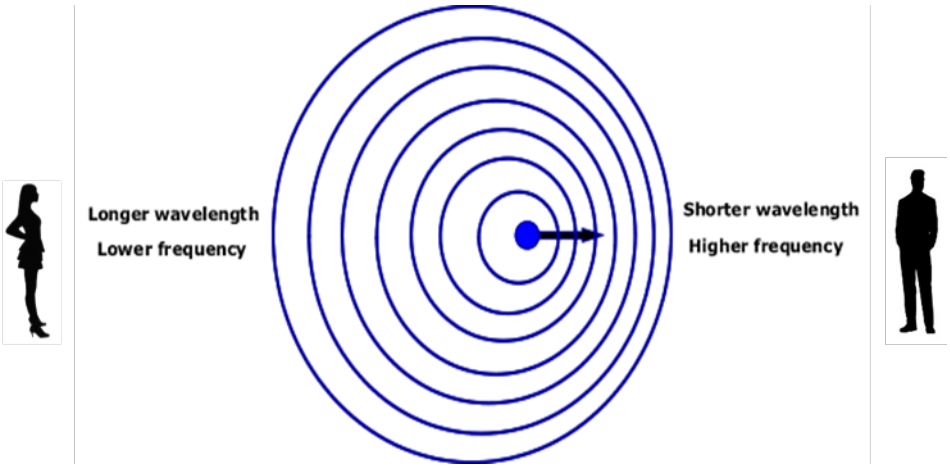


Figure 3.17 The Doppler effect describes the change in frequency observed when there is relative motion between the source and an observer. [http://www.einstein-online.info/spotlights/Doppler, accessed on 16/04/2013]

Doppler ultrasound was first applied to the measurement of blood flow in the cerebral circulation by Rune Aaslid in 1982 (Aaslid *et al.*, 1982). Transcranial Doppler applications make use of a technique called pulse-wave Doppler to sample velocity information from a specific sample depth. In this technique, pulses of ultrasound are emitted at regular intervals (the pulse repetition frequency) by a stationary transducer, which is angled so that the sample volume coincides with the position of the target vessel. If the scatterers are moving, the frequency of the scattered ultrasound returning to the transducer will be slightly shifted compared to that of the emitted ultrasound due to the Doppler effect. The difference between the transmitted and received frequencies ($f_t - f_r$) is known as the Doppler shift (f_D), and is related to the velocity of the scatterer via equation 3.1.

$$f_D = f_t - f_r = 2f_t \frac{v \cos\theta}{c} \qquad \text{Equation 3.1}$$

In this equation, v is the velocity of the scatterer (e.g. an embolus or red blood cell), θ is the angle between the ultrasound beam and the direction of the motion of the scatterer (also known as the Doppler angle), and c is the propagating velocity of ultrasound through the tissue (1540 m/s) (Hoskins, 1994). A typical TCD transducer emits

ultrasound with a central frequency of 2 MHz. Motion of the blood generates a Doppler shift of the order of 100-1000 Hz, which is in the range of normal human hearing. The Doppler shift will either be positive or negative depending on the Doppler angle between the direction of motion and the ultrasound probe. If the Doppler angle is known, then measurements of the Doppler shift can be used to calculate the velocity of the scatterer based on equation 3.1. In TCD applications, the Doppler angle is not usually known and a 0° Doppler angle is often assumed so that the y-axis can be displayed as a velocity rather than a frequency. In practice, the audio signal is made up of contributions of Doppler shift frequencies from an ensemble of scatterers. Most commercial ultrasound machines display this information visually by Fourier transformation of the audio signal as a Doppler frequency spectrum. A typical recording of MCA blood flow using TCD can be seen in fig 3.18. The top panel shows the Doppler spectrogram with velocity along the y-axis and time along the x-axis. The intensity colour scale of the sonogram indicates the backscattered power contributed by scatterers moving at each velocity. The bottom panel shows 'power M-mode' data where the y-axis indicates depth from the transducer in mm. Forward/reverse flows are coded red/blue with the intensity of the signal indicating backscatter signal intensity.

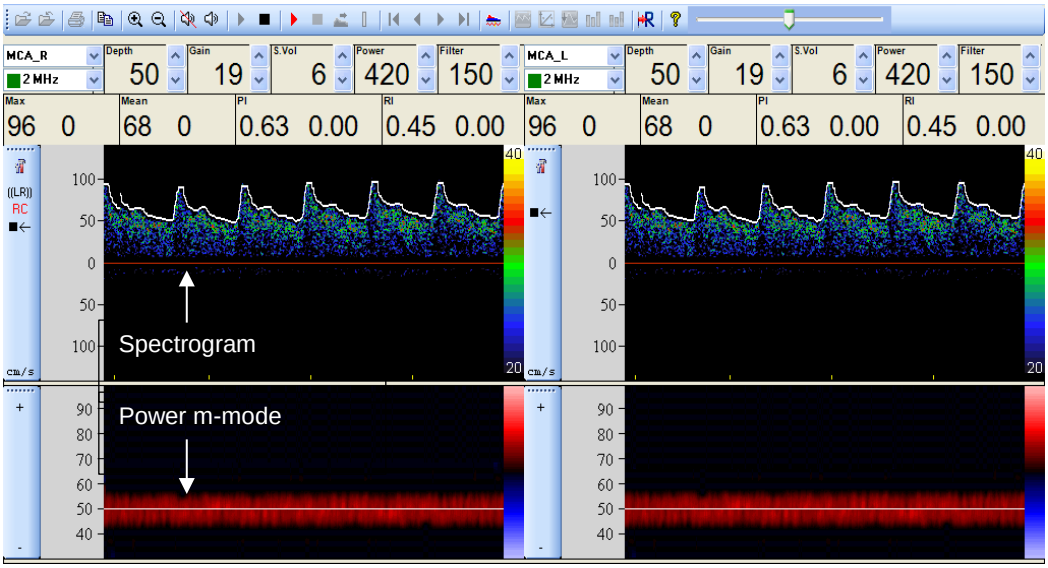


Figure 3.18 MCA Doppler spectrogram

3.5.3 Using TCD to measure cerebral blood flow

TCD measurements of the MCA provide a means of monitoring fluctuations in cerebral blood flow velocity and detecting emboli in real time during surgery. To obtain a TCD signal through the skull, a low frequency of ultrasound (~ 2 MHz) is used and the TCD probe must be positioned over the temporal bone window where the skull is relatively thin, fig 3.19. TCD signals can be obtained in around 90% of individuals (Sarkar *et al.*, 2007).

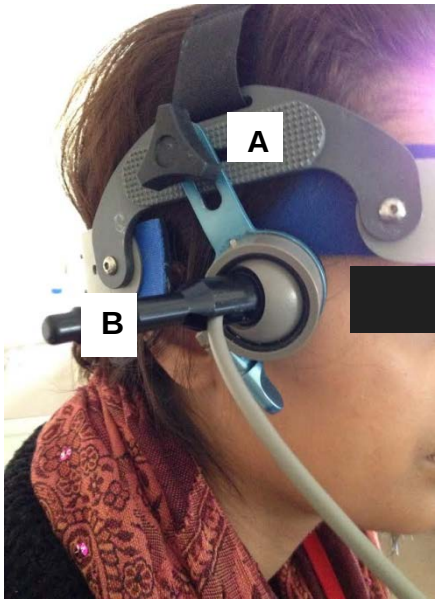


Figure 3.19 (A) headset is used to hold the TCD probe in position. (B) The beam is orientated through the temporal bone window towards the MCA.

Transmission of ultrasound is aided by using aqueous ultrasound gel. Typically, the probe is directed antero-superiorally from the temporal bone window using an initial sample depth of 50 mm. Minor adjustments can be made to angle the probe and increase or decrease the depth of insonation until a clear MCA signal is obtained.

There are various criteria for identification of the MCA in TCD monitoring, but the most important is that the blood flow in the MCA is towards the probe and persists over a wide range of sample depths, typically 30-60 mm. Although the MCA has potential to be confused with the PCA, which also generates flow towards the probe, the PCA signal is usually obtained at deeper sample depths (60-80 mm) with the probe angled downwards and slightly posteriorly.

TCD is a convenient method for monitoring the cerebral circulation; however, a thick temporal bone window precludes monitoring in some patients, and it is often difficult to locate the position of the MCA. The use of M-mode colour Doppler can help in identifying whether there is a window and locating the MCA. M-mode displays the Doppler signal as a function of depth, coloured red or blue depending on the direction of flow. M-mode facilitates rapid window location and alignment of the ultrasound beam, and makes it possible to view multiple vessels at different depths simultaneously (Moehring & Klepper, 1994).

3.5.4 Monitoring emboli using TCD

In addition to monitoring blood flow within the MCA, TCD can also be used to detect emboli (Ackerstaff *et al.*, 2004). As emboli travel swiftly through the ultrasound sample volume with a specific velocity give rise to a transient 'snap, chirp or moan' sound in the Doppler audio signal. The embolus appears in the Doppler spectrogram as a transient increase in backscatter intensity located at a discrete velocity within the blood flow profile. A typical Doppler sonogram illustrating the differing appearances of emboli and artefacts is shown in fig 3.20.

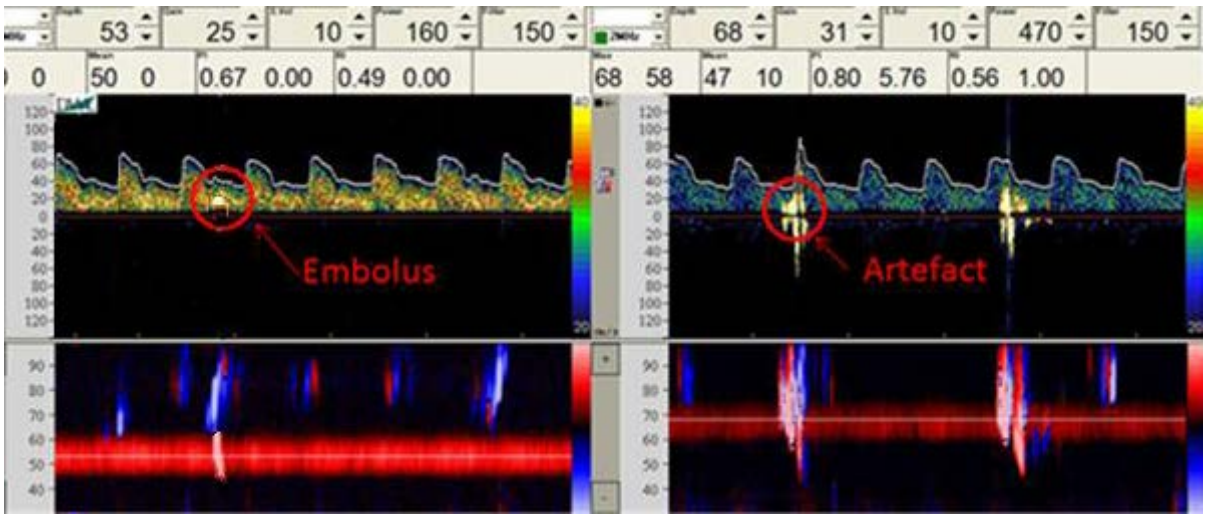


Figure 3.20 Doppler spectrogram showing the typical appearances of emboli and artefacts in the Doppler spectrum and Doppler M-mode display. This image is taken from a surgical recording of a patient recruited to our study.

3.5.5 Embolus detection criteria

Differences in criteria used for the identification of embolic signals previously led to formation of a consensus committee who recommended criteria for the identification of embolic signals. The Consensus Committee proposed that investigators should specify; the ultrasound frequency, gain settings, dynamic range and identification criteria for classifying microembolic signals. The Consensus Group recommended that; '*microembolic signals can be identified as a short duration (<0.01-0.03 s), unidirectional intensity increase*' (Ringelstein *et al.*, 1998).

Experts in the field of ultrasound discussed the limitations and problems involved with embolus detection and developed guidelines for its proper use in clinical practice and scientific investigations. Key parameters the authors suggested investigators report include: (1) ultrasound device, (2) transducer size and type, (3) insonated artery, (4) insonation depth, (5) algorithms for signal intensity measurements, (6) scale settings, (7) detection threshold, (8) sample volume, (9) transmitted ultrasound frequency and (10) recording time.

Emboli can be detected in numerous settings, such as in patients with atrial fibrillation (AF), acute stroke, decompression sickness, severe cardiac atheroma, and patients with mechanical heart valves (Grosset *et al.*, 1994). High numbers of cerebral emboli are also detected during cardiac surgery, catheter ablation as a treatment for AF, and during carotid surgery (Dagirmanjian *et al.*, 2000). During cardiac surgery, emboli are detected in virtually all patients regardless of the type of procedure or whether cardiopulmonary bypass (CPB) was used.

3.5.6 Embolic signal analysis

In the current study, Doppler signals were analysed using 'in house' software developed in MATLAB (The MathWorks Inc., Natick, MA) by Dr Caroline Banahan and Mr Clément Rousseau. The raw audio data from the Doppler recording was converted to bin files using the DWL QLS 2.10.3 software. Individual bin files are read into the 'in house' software (shown in fig 3.21) to analyse embolic signals.

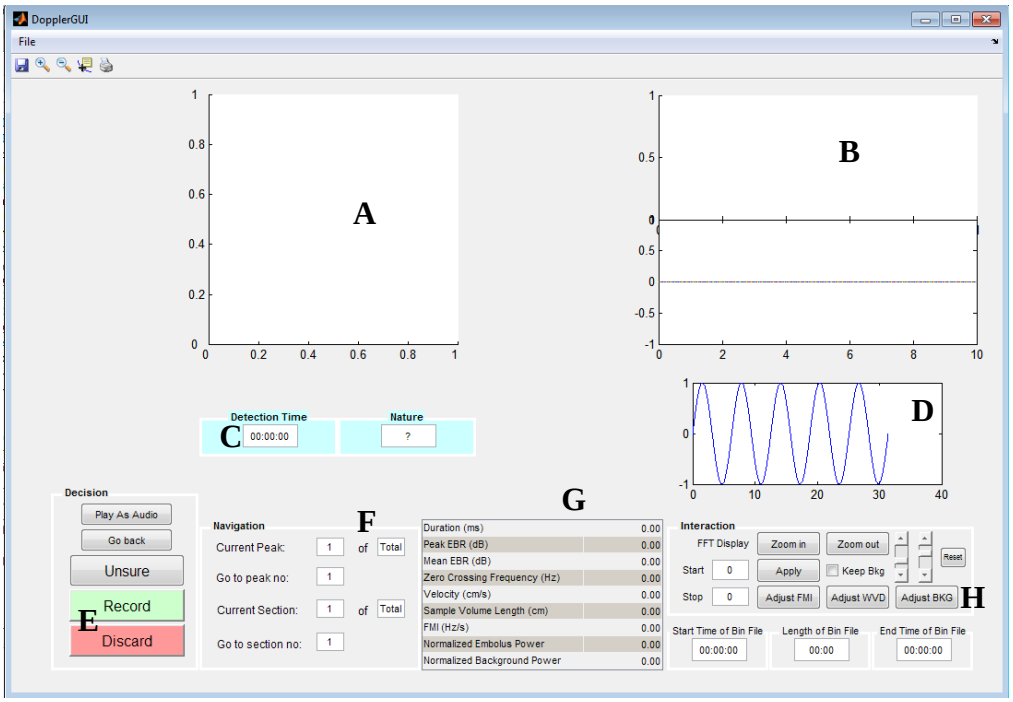


Figure 3.21 The 'in house' Doppler MATLAB GUI used to detect and analyse embolic signals. (A) detected current peak; (B) image of the current stage of the Doppler sonogram; (C) Time of detected peak during the surgery; (D) Frequency modulation index; (E) Decision to record as an embolus or discard as an artefact; (F) Navigation throughout the file to select a certain stage of the surgery, (G) Signal properties of the peak detected; (H) Adjustable functions to improve signal output (e.g. manually re-selecting the background, or the start and end points of the peak detected, along with the timing information of the current file).

Embolic signals were identified as peaks within the recording if they generated backscattered intensities >7 decibels (dB) above the average background intensity. An image of our 'in house' software in MATLAB showing an example embolic signal is shown in fig 3.22. Based on inspection of the sonogram and audio signal by a trained expert, signals were either accepted as emboli, or rejected as artefacts, based on internationally agreed consensus criteria (Ringelstein *et al.*, 1998).

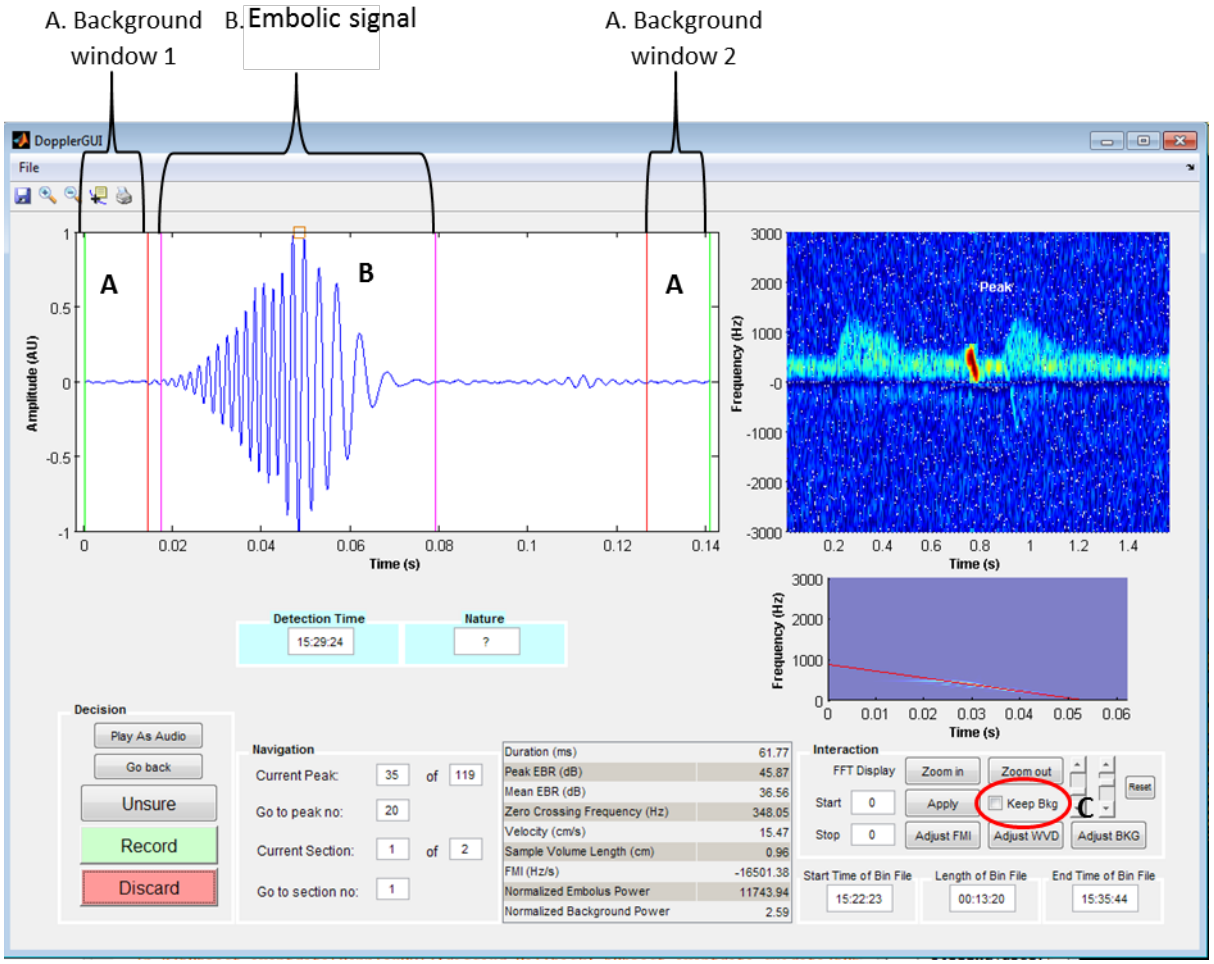


Figure 3.22 'In house' MATLAB software showing an embolic signal recorded during surgery. (A) Windows used to calculate the background value. (B) Window used to calculate the backscatter from the emboli. (C) During embolic showers, there is an option to retain the same background estimate for subsequent peaks by ticking the 'Keep Bkg' box.

The backscattered embolic signal intensities of accepted signals were then estimated relative to the scattering from the blood as a Measured Embolus-to-Blood Ratio (MEBR) in dB. To estimate MEBR, the intensities of the two background windows either side of the embolic signal are integrated and normalised with respect to time to estimate the mean scattering from blood flow. The Peak MEBR in dB is then calculated by taking the ratio of the maximum intensity of the embolic signal in blood (I_{E+B}) and average intensity of the background blood signal (I_B) using equation 3.2:

$$MEBR = 10log_{10}\left[\frac{I_{E+B}}{I_B}\right] \text{dB} \qquad \text{Equation 3.2}$$

During embolic showers (fig 3.23a) (>5 emboli/sec), it became difficult to confidently select a background signal on either side of the embolus. In this case, a background signal was selected prior to the shower and used in subsequent MEBR estimates. In the case of dense 'curtains' of emboli (fig 3.23b), it becomes impossible to distinguish individual emboli. In this case, only the duration of the curtain can be recorded.

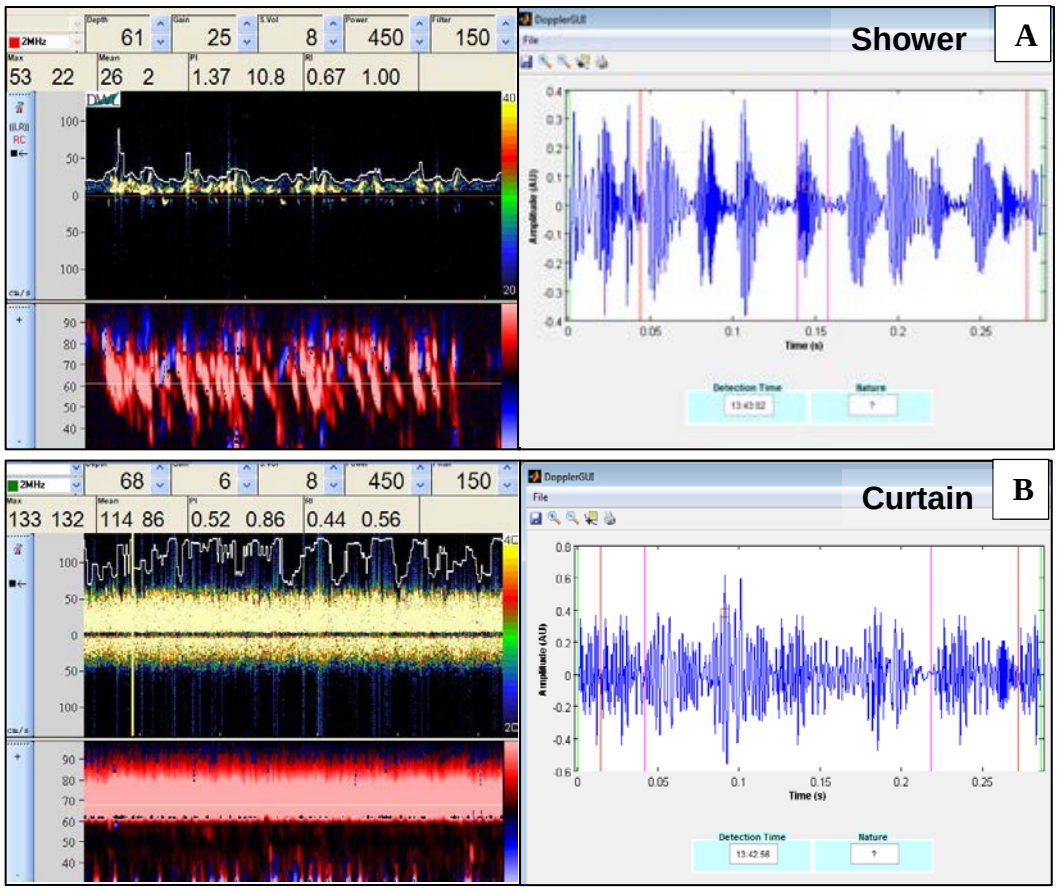


Figure 3.23 (A) Embolic shower, (B) curtain of emboli where it becomes impossible to distinguish between individual embolic signals.

3.5.7 Estimating bubble size and volume

Bubble sizes were estimated using an algorithm developed by Banahan *et al*. (Banahan *et al.*, 2012) based on a theoretical model describing backscattered ultrasound from a spherical embolus moving through a blood-filled vessel (Moehring & Klepper, 1994). Conversion of MEBR values from gaseous emboli to bubble diameters is illustrated in fig 3.24. In tests, 91% of 10,000 randomly generated simulated emboli were correctly

sized to within 10% of their true value (Banahan *et al.*, 2012). In general, embolic signals with MEBR >30.5 dB can be assumed to be gaseous, whereas weaker embolic signals could be attributable to either solid emboli or gas bubbles.

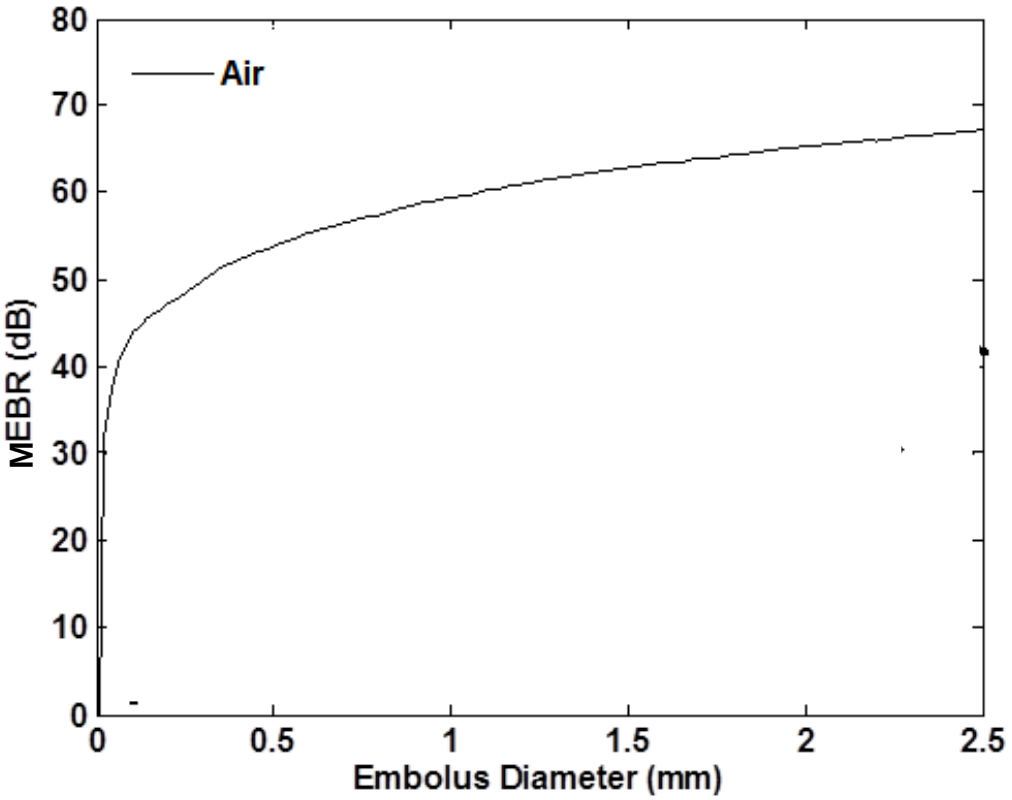


Figure 3.24 Measured Embolus-to-Blood ratio (MEBR) values for air emboli with diameters ranging from 1 μm to 2.5 mm using the model described in Moehring *et al*., 1994, assuming an average middle cerebral artery (MCA) diameter of 2.5 mm.

3.5.8 Estimating MCA diameters for accuracy of bubble sizing

Since uncertainty in MCA diameter can modify volume estimates by up to a factor of 3 for small bubbles, to improve the accuracy of our bubble sizing, patient specific measurements of MCA diameter were obtained for all patients by 3D reconstruction of the circle of Willis using time-of-flight magnetic resonance (MR) angiography (Magnetom Skyra, Siemens Medical, Erlangen, Germany). This analysis was carried out by Mr David Marshall who is a PhD student in the Department of Cardiovascular Sciences. The Vascular Modelling Toolkit (Antiga *et al.*, 2008) was used for analysis. Images were segmented using level sets at a constant threshold for all patients. Mean

diameter was calculated by averaging 5 cross sections separated by distances equal to the vessel radius, starting at two vessel radii from the internal carotid artery bifurcation (fig 3.25). Sections on poorly resolved areas were discarded. Diameter error was estimated based on the standard deviation of measurements of the vessel area.

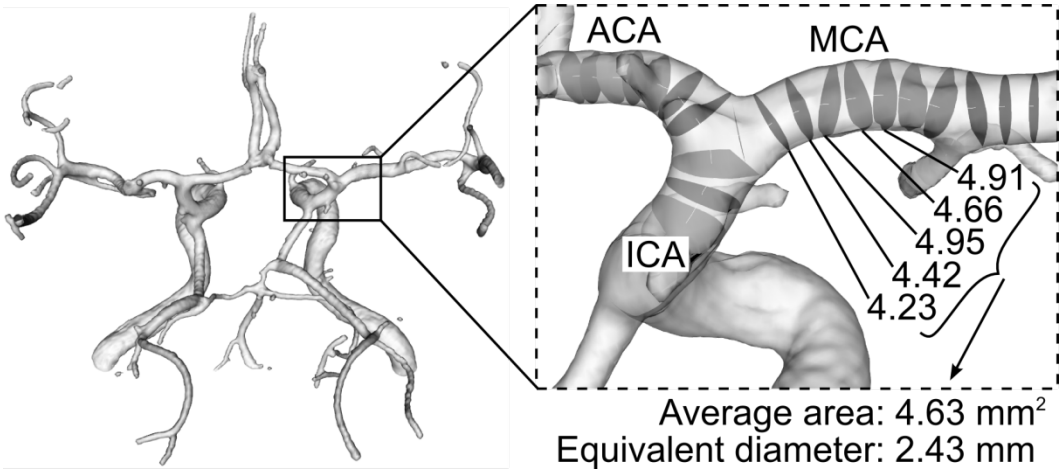


Figure 3.25 3D reconstruction of the circle of Willis of patient 47 with labelled MCA measurements used to estimate average diameters for both the left and right MCA.

3.5.9 Output of the bubble sizing algorithm and estimating volume of air

Each analysed bin file (fig 3.26a) outputs a text file containing the time a peak was detected, along with its signal properties. Signal properties are given a value of 0 if the signal was discarded as an artefact (fig 3.26b). Doppler recordings can be replayed during the analysis to help identify whether a signal is an embolus or an artefact. The user needs to manually note any periods of signal loss and the start and end of embolic curtains. Once all the bin files have been analysed, text files were collated into a single text file containing embolus data only (fig 3.26c). This text file was then used as an input for the bubble sizing algorithm.

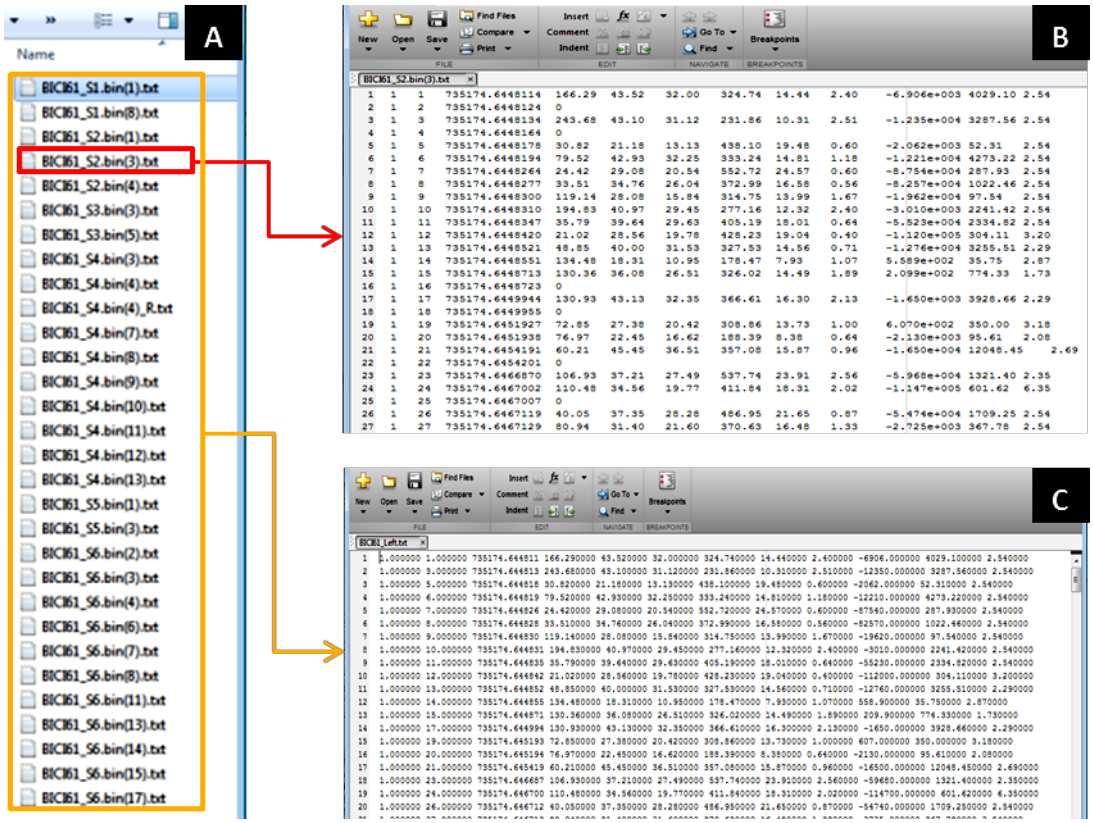


Figure 3.26 (A) the corresponding bin files for a patient's Doppler recording; (B) the output text file for individual bin files outlining signal properties for each recorded embolic signal. A '0' is given to peaks that had been discarded. (C) All text files combined for all the bin files in to a final text file only containing embolus data.

The collated text file is imported into the 'in house' sizing software algorithm (described below) along with haematocrit data taken from the perfusionist notes (time and percentage), start and end time of cardiopulmonary bypass, MCA diameters, and Doppler sample volume (fig. 3.27a). There is an option to only size emboli with Peak MEBR values greater than 30.5 dB (corresponding to gas bubbles ~18 µm), to facilitate simulations estimating the impact of bubbles on perfusion. The output of this text file was then stored in a separate folder for further analysis using Monte-Carlo simulations (as described in section 3.6). The full text file output with the tick box 'unchecked' was used as the output for the full embolic signal data analysis (fig. 3.27b). This process was repeated for all patients through detailed analysis of both the left and right MCA Doppler recordings.

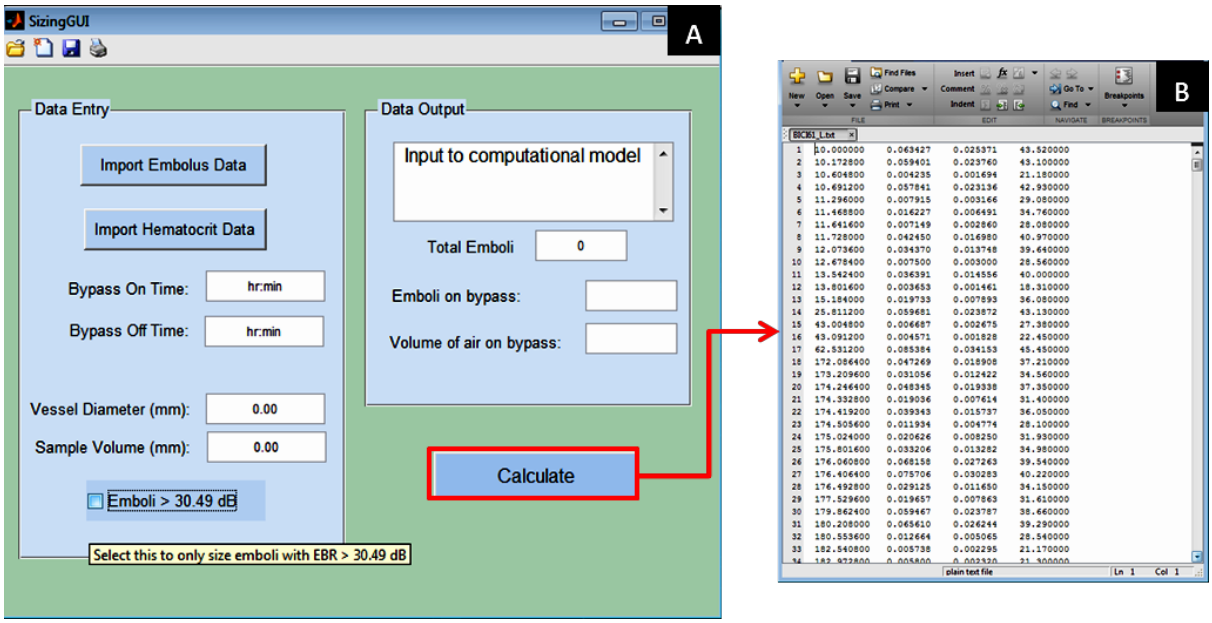


Figure 3.27 (A) option for the 'in house' sizing software; (B) text file output from the sizing software giving (from columns left to right) the time, bubble diameter, diameter error and volume of individual emboli which is reformatted in excel for the next stage.

The text file output from the sizing software (fig 3.27b) was reformatted in excel to give the time of each embolic signal, Peak EBR (dB), left or right sided recording, stage of surgery, embolus diameter (mm), error in the diameter estimate (mm), and the calculated volume (ml) for each embolus, which is then saved as a 'master text file' (fig. 3.28a). Bubble diameters were then converted to volume of air (V) by assuming a spherical bubble with bubble radius (r):

$$V = \frac{4}{3}\pi r^3$$

Equation 3.3

Conversion of bubble diameters to volume of air via equation 3.3 was used to estimate the total volume of air entering the MCA territories for each patient. The master file was then run through a final script in MATLAB to output the following data for each procedure/patient (fig. 3.28b):

1. The total number of emboli per side
2. Total estimated volume of air per side
3. Total number of emboli per side for each stage of the surgery (1-4)
    i. Stage 1: start of recording to aortic cross-clamp on

ii. Stage 2: 1 minute following aortic cross-clamp on

iii. Stage 3: 1 minute following aortic cross-clamp off

iv. Stage 4: Aortic cross-clamp off to end of recording.

4. Number of emboli < 40 microns
5. Number of emboli 40-99 microns
6. Number of emboli 100-999 microns
7. Number of emboli ≥ 1 mm

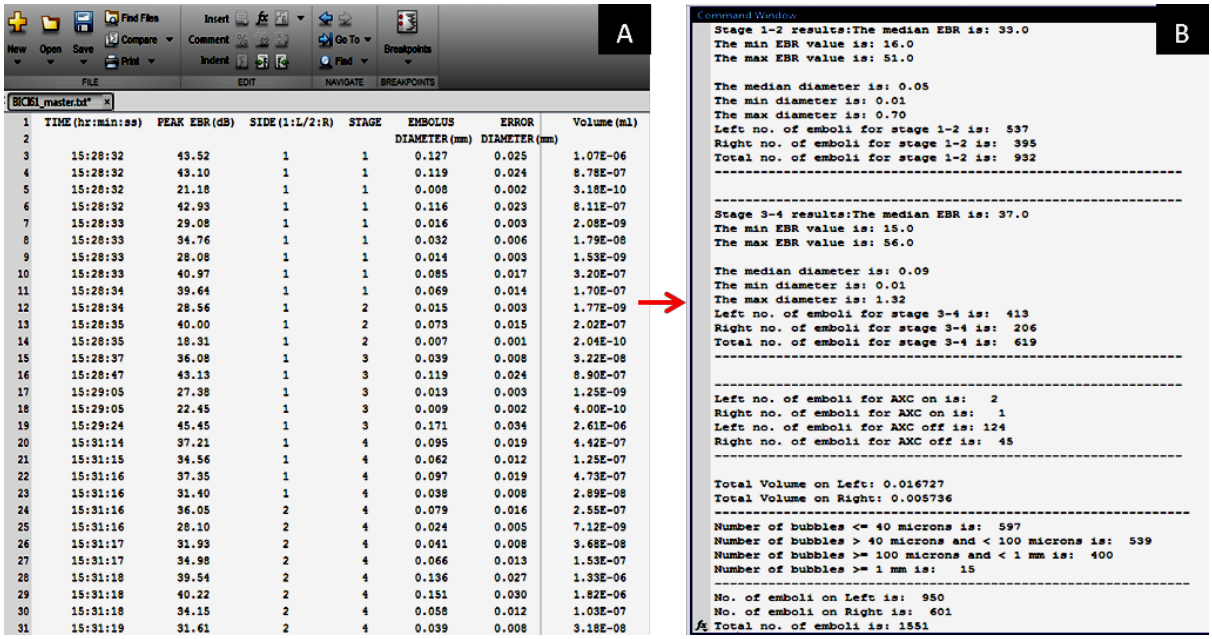


Figure 3.28 (A), the 'master text file' containing all the embolus data for both the left and right MCA recordings; (B) a final script in MATLAB that summarises the results of embolic signal analysis and bubble sizing for each patient.

3.6 Monte-Carlo simulations

Timing and sizing information (outlined in section 3.5.6) for the bubbles were used to model the accumulation and clearance of air bubbles within the vasculature during the surgery, using patient specific Monte-Carlo simulations featuring gaseous emboli which become lodged within a bifurcating arterial tree (Chung *et al.*, 2007; Hague *et al.*, 2013).

Previous simulations using theoretical emboli predict that solid emboli are responsible for focal persistent injuries, while fast clearing gas emboli produce diffuse transient blockages similar to global hypoperfusion. The model simulates the fundamental interactions between emboli and the geometry of the arterial tree. This model is based on a bifurcating fractal tree comprising over a million branches ranging between 1 mm and 12 microns in diameter. In this study, the model was adapted by Dr Jim Hague at the Open University for use with gaseous emboli to predict the duration of vascular occlusion and percentage of affected vasculature (fig 3.29). This provides a novel means of investigating the role of gaseous emboli in producing neurological injury. Further details of this Monte-Carlo simulation are described in previous publications (Chung *et al.*, 2007; Hague & Chung, 2009; Hague *et al.*, 2013).

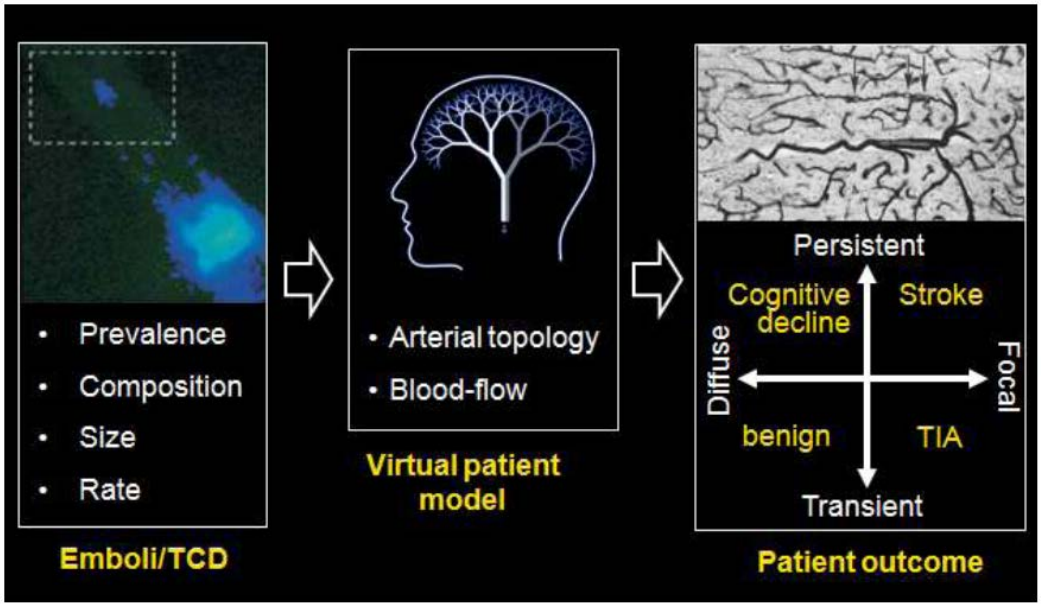


Figure 3.29 'virtual patient' computer simulations can be used to predict the impact of emboli on cerebral blood flow for comparison with patient outcome.

3.6.1 Model algorithm

The algorithm starts by calculating flows, pressures and resistances for an empty tree. All emboli are allowed to dissolve, leading to a reduction in radius during each time step. Completely dissolved emboli are removed from the simulation. If the reduction in radius generates a change in the blockage state of the tree, flows and pressures are recalculated.

The emboli in the bifurcating tree move according to the following rules:

(i) If the pressure behind the deformed embolus is insufficient to overcome 'static friction' it does not move (fig 3.30).

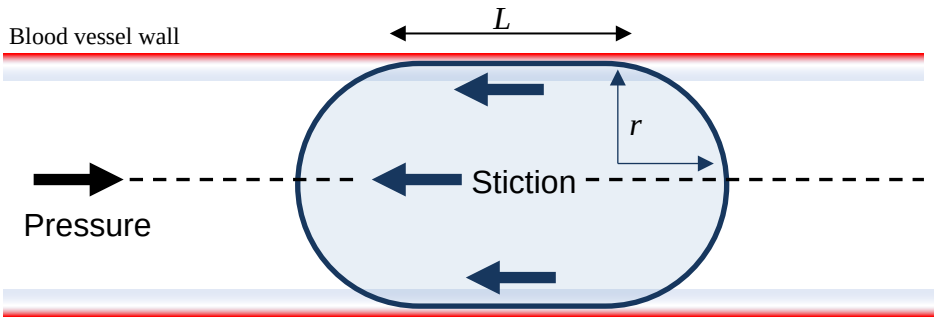


Figure 3.30 Schematic of a deformable bubble in a vessel, highlighting the forces required for the bubble to become lodged in an artery. Blood pressure leads to a force, which is opposed by 'stiction' (static friction). When the limiting stiction is larger than the force on the bubble from the blood, the artery becomes blocked (Image reconstructed from Hague *et al*, 2013).

(ii) If all arterioles downstream are blocked, the embolus may not move since there is no flow.

(iii) If the embolus radius becomes smaller than the current node and there is flow downstream then the embolus may move.

An air embolus encountering a bifurcation moves in direction A with a probability given by equation 3.4 where f_A and f_b designate flows in the A and B directions, w_a is related to the orientation of the branches with respect to gravity ($w_a = (1 + A_g \cos(\theta))/2$), A_g is a parameter that varies between 0 and 1. :

$$P_A = f_A w_A/(f_A w_A + f_B w_B) \qquad \text{Equation 3.4}$$

Otherwise, the embolus moves in direction B (fig 3.31).

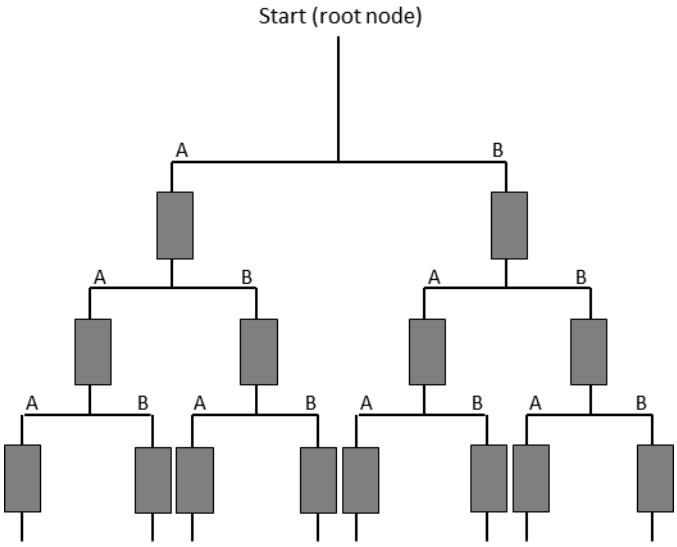


Figure 3.31 Pairs of parallel and serial resistances are repeatedly reduced to a single downstream resistance to facilitate calculation of pressures, flows and resistances at each level in the tree (Image reconstructed from Hague *et al.*, 2013).

If progress of an embolus generates a new blockage, then the pressures and flows are recalculated. At this stage numerical measurements of the state of the tree are repeated.

This simulation incorporates the effects of bubble deformation, buoyancy, blood pressure, and friction between the surface of the bubble and the vessel wall, as shown in fig 3.30. The simulations give additional time dependent estimates of the total embolic burden in the arterial tree over time. The root node of the tree was chosen to match the diameter of the MCA, with 20 layers of bifurcations representing the MCA microvasculature, terminating in ~500,000 terminal arterioles (~26 μm in diameter). Bubble radii and blood pressure were input to the model MCA vasculature as a function of time and each simulation run 30 times to determine the average number and duration of obstructed end arterioles during surgery.

Chapter 4

4 Clinical study protocol and statistical analysis

To investigate a potential link between brain injury following cardiac surgery and intra-operative cerebral emboli, we aimed to study approximately 100 patients undergoing cardiac surgery. In addition to their normal hospital care, patients were monitored intra-operatively using TCD and underwent MRI scanning and neuropsychological testing before and after their surgery.

4.1 Ethical approval

Ethical approval for the project entitled *'Causes of brain injury associated with cardiac interventions: A comparison of Doppler embolus detection and virtual patient predictions with post-surgical neurological outcomes quantified by MRI and neuropsychological testing'* was gained on the 18/05/2011 with an expected termination date of 31/12/2013 (UHL Ref: CLRN 51454, REC Ref: 10/H0401/78). My PhD studentship within the University of Leicester Department of Cardiovascular Sciences was funded by the Leicester Cardiovascular Biomedical Research Unit (BRU). All other costs associated with the project were funded by the British Heart Foundation. Patients provided written informed consent following a protocol approved by the University Hospitals of Leicester NHS Trust and Derbyshire Research Ethics Committee (REC reference:10/H0401/78). The study was sponsored by the University of Leicester.

It was mandatory for all investigators involved in patient recruitment to attain Good Clinical Practice (GCP) accreditation and patient consent training examined by the University Hospitals of Leicester Research & Development office (UHL R&D, Appendix 4.A and Ethical approval, Appendix 4.B). Once accreditation was achieved, I was added to the list of investigators (12/09/2011) and delegated to consent patients for this study, administrating neuropsychological tests, accompanying patients to MRI scans and carrying out intra-operative TCD monitoring during surgery.

4.2 Patient recruitment

4.2.1 Approaching the patients

We gained permission to approach potential cardiac surgery patients from 4 cardio-thoracic surgeons practicing at the Leicester Glenfield Hospital: Professor Tomasz Jerzy Spyt, Mr Mark St John Hickey, Mr Jacek Szostek and Mr Haitham Abunsara. Patients who were scheduled to have coronary artery bypass graft (CABG), aortic valve replacement/repair (AVR), mitral valve replacement/repair (MVR), or a combination of these procedures, and who were not recruited to other studies, were eligible to take part. Recruitment of patients took place at a pre-assessment clinic (Clinic C) on Tuesdays, Wednesdays, and Thursdays. Patients who were confirmed at their pre-assessment clinic to be undergoing cardiac surgery were approached with patient information materials and invited to participate. During this process the purpose of the study was explained to the patient and a study information sheet was provided for their consideration (Appendix 4.C). The patient and their family also had an opportunity to ask questions.

Patients were excluded if they were unable to have an MRI scan due to metal objects within the body. Patients were also excluded if their first language was not English as this would invalidate the neuropsychological tests. If the patient was willing to participate in the study, they were given a minimum of 24 hours to consider the study before being asked to provide written consent (Appendix 4.D). Patients who were interested in taking part in the study were asked to stay a further 2 hours after their next pre-operative appointment to allow us to obtain consent and carry out baseline MRI scans and neuropsychological tests. On the day of the patient's pre-operative assessment, approximately 2 weeks before surgery, myself, or another member of the research team approached the patient for written consent according to our standard protocol. A copy of the consent form, patient information sheet, and details of the study reference number in form of a sticker were added to the patient's medical notes. The original signed consent form was then retained within our project site file. On patient request, a covering letter and study information sheet was also sent to the patient's GP (Appendix 4.E). A typical timeline experienced by patients participating in our study is shown in fig 4.1.

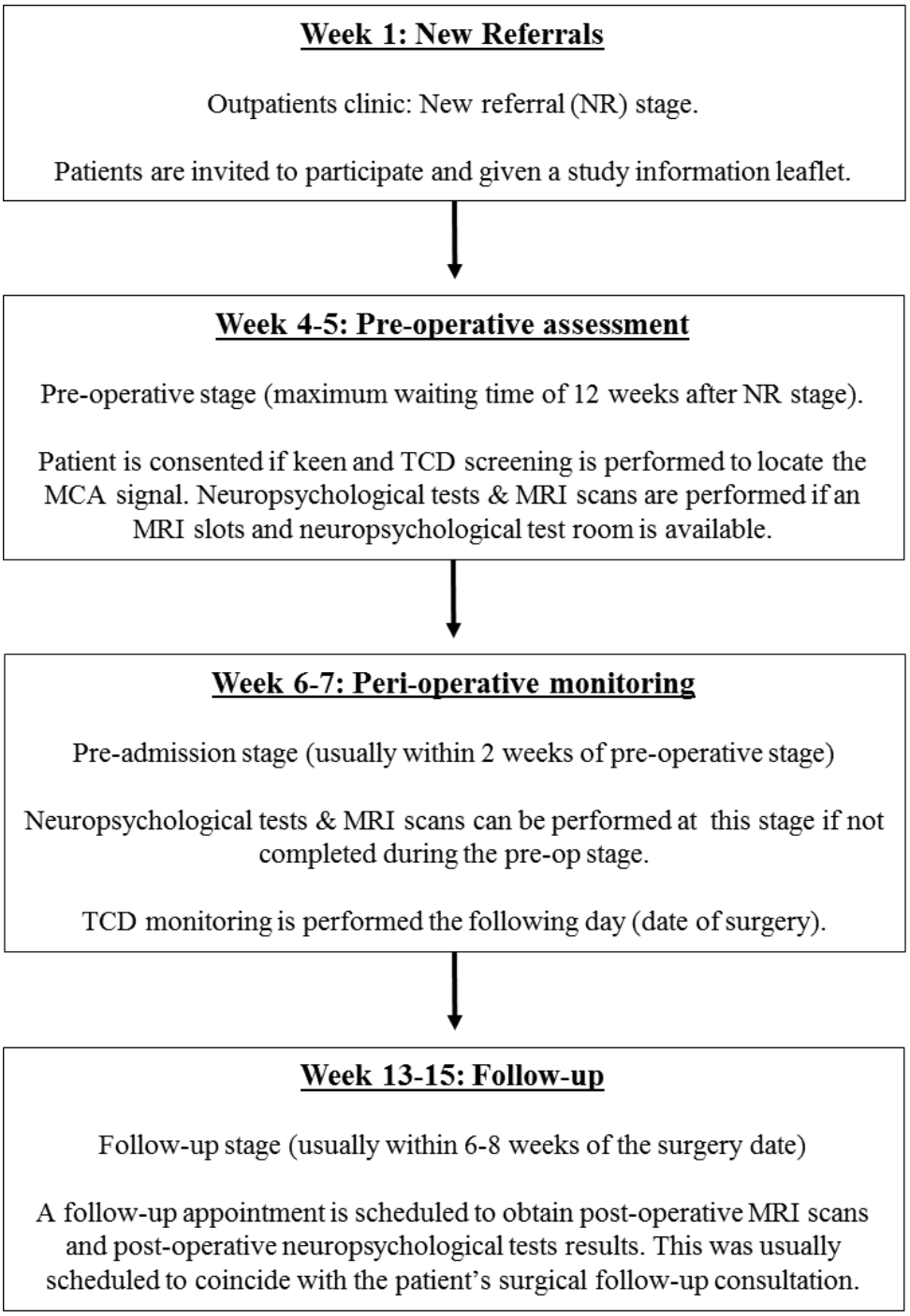


Figure 4.1 Typical timeline for patients approached and participating in this study.

Following informed consent, the TCD ultrasound machine was demonstrated to the patient and used to check for a suitable signal from MCA blood flow. If an MCA signal was found, the position of the probe, depth, angle and sample volume were recorded to facilitate accurate placement of the probe during surgery (Appendix 4.F). The TCD ultrasound setup used in the cardio-thoracic clinic is shown in fig 4.2.

Patient recruitment for the study began on the 31/08/2011 and was completed on 17/07/2013.

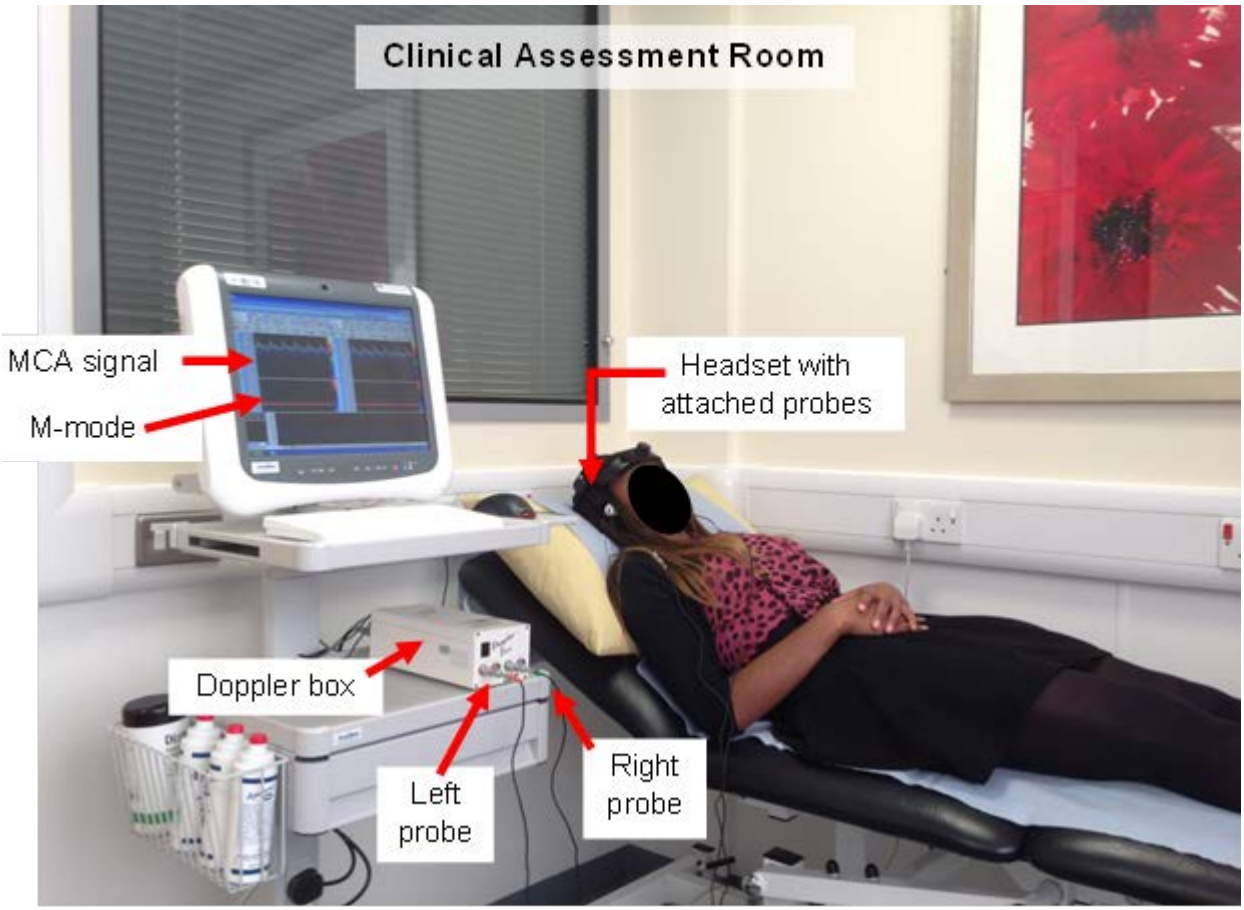


Figure 4.2 TCD ultrasound setup in the clinical assessment room available within the Leicester Cardiovascular BRU.

Where possible, patients were scheduled so that postoperative testing coincided with a routine 6-8 week follow-up appointment with their cardio-thoracic consultant. Patient appointment letters were sent out 2 weeks in advance with information containing the agreed time and location of both the MRI scan and the neuropsychological tests. Patients who were unable to complete the postoperative tests on this date were re-scheduled for the next available and convenient appointment.

4.3 Risk factor analysis

The patients' medical notes contain useful information regarding the surgical procedure (surgeon's surgical log) and data from the perfusionist's transcript, such as type of cardiopulmonary bypass machine used and blood pressure and haematocrit changes during the surgery. Patients' medical records were tracked by the University Hospitals of Leicester IT 'Track It' service. These medical records can also be used to identify whether the patient has any obvious neurological events following surgery (e.g. stroke or delirium). Medical notes were carefully examined to extract information regarding patient demographics and underlying risk factors for cardiovascular disease that had potential to be associated with adverse neurocognitive outcome (e.g. hypertension, diabetes, family history, smoking, and grade of cardiac atheroma). A full list of data recorded from the patient's medical notes is provided in Appendix 4.G.

4.4 Anaesthetic and surgical procedures

There were no specific alterations to standard surgical practice. Routine perioperative care was used in all patients, including direct arterial blood pressure monitoring using a radial cannula [Braun Medical Ltd]. Cold blood cardioplegia was used in all patients, and anaesthesia management usually consisted of a combination of isoflurane, propofol, midazolam and fentanyl. Body temperature was measured every 3 minutes with a nasal pharyngeal temperature probe. Non-pulsatile cardiopulmonary bypass (CPB) with a non-occlusive roller pump was used, along with adhering to perfusionist guidelines and a policy of keeping CPB perfusion pressure above 50 mmHg. The CPB circuit contained a membrane oxygenator and a 40 μm arterial line filter. Arterial blood pressure targets during surgery were based on usual clinical practice.

4.5 Magnetic Resonance Imaging

All patients who consented to participate in the study underwent MRI scans pre- and postoperatively. MRI scans were performed according to a detailed MRI protocol drafted by Professor Graham Cherryman. The pre-operative scan was obtained approximately 2 weeks prior to surgery, and the post-operative scan was conducted 6-8

weeks after surgery at the patient's next follow-up appointment. All scans were performed using the 3-Tesla NIHR-funded MRI whole body scanner (Magnetom Skyra, Siemens Medical, Erlangen, Germany) based at Leicester Glenfield Hospital by a qualified radiographer (Mrs. Joanne Wormleighton or Mr. Dean Mawby).

4.5.1 MRI scanning protocol

Scans were performed in the following order: 3-plane localiser; diffusion-weighted sequence; Time of Flight MR angiography; Susceptibility Weighted Imaging and Fluid-Attenuated Inversion Recovery (FLAIR) with a total imaging time of approximately 30 minutes (see Chapter 3.2). FLAIR images were obtained using a slice thickness of 3 mm with the number of slices set to cover the whole brain. Matrix size was 320×352, field of view was 240 mm, repetition time/echo time were 6770/108 ms, and inversion time was 2170 ms. MRI images were held on the Picture Archiving and Communication systems (PACS) and reviewed by a Senior Radiologist (Dr John Morlese) to identify incidental findings and confirm any changes in the pre- and post-operative scans. An example radiologist's report is included in Appendix 4.H All MRI scans were archived to a CD for further analysis.

4.6 Neuropsychological assessment

The neuropsychological tests were carried out in clinical rooms located at the Leicester Biomedical Research Unit at Leicester Glenfield Hospital. Where possible, neuropsychological tests were performed in accordance to the 'Statement of Consensus on Assessment of Neurobehavioral Outcomes After Cardiac Surgery', which recommends a battery of neuropsychological tests including the Rey auditory verbal learning test, Trail-making A, Trail-making B and the Grooved pegboard test (Murkin *et al.*, 1995). All tests were performed approximately 2 weeks before surgery and 6-10 weeks after surgery at the patient's next follow-up appointment. Neuropsychological tests included: immediate & delayed memory, verbal IQ, performance IQ, trail-making exercise A & B, and grooved pegboard tests. Further detail for individual tests can be found in Chapter 3.4. In all domains, parallel test forms were used postoperatively, and

variations in patients' test scores were minimised by ensuring '*the same suitably trained and qualified individual administers the test to minimise subjectivity in the tests and they are performed in a standardised manner*' (Murkin *et al.*, 1995). As assessment can also be negatively affected by mood (Funder *et al.*, 2010), levels of depression and anxiety were gauged using the Hospital Anxiety and Depression scale (HADS) to allow adjustment for mood (Rasmussen *et al.*, 2001).

4.6.1 Definition of neuropsychological decline

A variety of scoring methods can be used to quantify POCD which vary across studies. Criteria for decline can vary but are typically chosen to correspond to a ≥20% decline on 20% of the tests, or an absolute decline from baseline scores (e.g. of 1 or 2 SD) on one or more tests (Rudolph *et al.*, 2010). Such criteria do not discriminate between decline due to surgery and normal variability associated with repeated measures. As patients are expected to improve with repeated testing, these assessment techniques are thought to underestimate the incidence of cognitive decline.

The proportion of patients estimated to experience POCD appears to be dependent on a number of methodological factors. Nearly all previous studies report a decline in neurocognitive function in some patients. In assessing short-term POCD, other factors that potentially influence cognitive performance include the effects of anaesthetic drugs and painkillers (Silbert *et al.*, 2004; Wang *et al.*, 2007), acute pain, nausea, limited mobility and fatigue (Heyer *et al.*, 2000; Wang *et al.*, 2007). Therefore, it was considered best not to assess POCD until at least a week has elapsed following surgery (Murkin *et al.*, 1995; Blumenthal *et al.*, 1995; Mackensen & Gelb, 2004).

All of the neuropsychological tests were scored according to standard instructions provided with each test and the scores were recorded in an excel spread sheet. An example of the scoring sheet used to summarise scores for the full battery of tests is shown in fig 4.3.

Test (Patient 9)	Component	Before Score	After Score	Population mean	St.dv	z-score before	z-score after	z-score difference
HADS	Anxiety	6 (normal)	6 (normal)					
	Depression	3 (normal)	3 (normal)					
WMS-III	Logical Memory I (Raw|Scaled)	44	39					
	Family Pictures I (Raw|Scaled)	37	47					
	Logical Memory II (Raw|Scaled)	32	23					
	Family Pictures II (Raw|Scaled)	36	45					
	Immediate Memory (Scaled)	22	23					
	Delayed Memory (Scaled)	24	24					
	Total Memory (Scaled)	46	47					
	Immediate Memory Composite (95%CI)	105	107	101.8	13.6	0.24	0.38	0.15
	Delayed Memory Composite (95%CI)	112	112	105.1	13.2	0.52	0.52	0.00
	Total Memory Composite (95%CI)	108	109	102.8	13.4	0.39	0.46	0.07
WASI	Vocabulary (Raw|T-score)	65/58	65/58					
	Block Design (Raw|T-score)	50/61	52/62					
	Similarities (Raw|T-score)	38/57	35/53					
	Matrix Reasoning (Raw|T-score)	25/59	27/62					
	Verbal (T Score)	115	111	98.4	21.7	0.76	0.58	-0.18
	Performance (T Score)	120	124	98.0	19.8	1.11	1.31	0.20
Trail Making	Test A (seconds)	28	28	33.8	6.7	-0.87	-0.87	0.00
	Test B (seconds)	44	75	67.1	9.3	-2.48	0.85	**3.33**
Groove Pegboard Test	Dominant	100	109	82.7	18.7	0.93	1.41	0.48
	Non-dominant	121	130	88.0	26.2	1.26	1.60	0.34

Figure 4.3 Neuropsychological test scores for patient 9; test scores associated with a >1 S.D. decline in 'z-score difference' are highlighted in red.

4.6.2 Postoperative decline

For the purpose of this study, a decline of a calculated *z*-score of 1 SD was considered clinically significant (Murkin *et al.*, 1995). Individual neuropsychological test scores (x) were first converted to *z*-scores through comparison with published data describing the mean (X) and standard deviation (SD) of test scores measured from a population of healthy subjects (Equation 4.1):

$$z = \frac{x - X}{SD}$$

Equation 4.1

Post-operative *z*-scores were then subtracted from preoperative *z*-scores to calculate the pair-wise change in *z*-score; significant decline in cognition was assumed if there was a drop in *z*-score of more than 1 SD from baseline (figure 4.4).

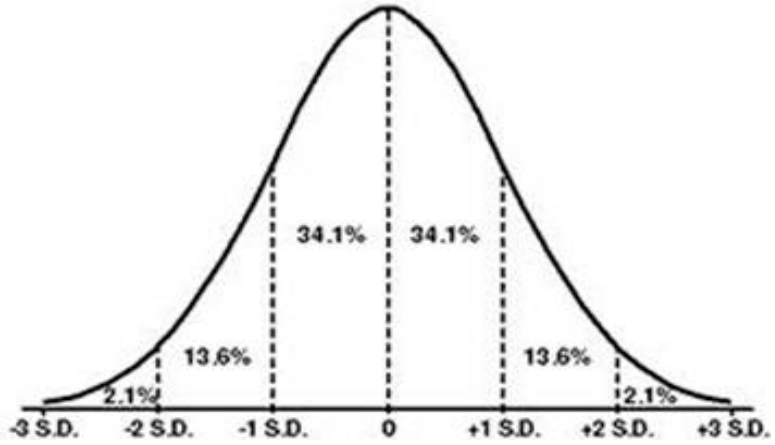


Figure 4.4 The normal distribution curve for *z*-score data showing standard deviation (SD) from the mean.

For timed tests (Trail Making A/B and Grooved Pegboard tests), the sign of the *z*-score was reversed so that improved performance corresponded to a positive *z*-score. In addition to calculating the *z*-score change for each individual test, *z*-scores were summed and averaged to estimate the overall cognitive performance of each patient as a 'composite' cognitive performance score.

4.6.3 Pre-existing decline

Pre-existing decline was assessed by calculating the baseline composite score for each patient. If the patient's composite score was ≤1 SD from the mean (0), the patient was considered to have pre-existing cognitive impairment. Individual cognitive test scores were also analysed along with their corresponding neuropsychological domains in an attempt to correlate the locations of lesions with decline in particular test functions. For individual test score analysis, a patient was considered to have experienced a deficit in a specific cognitive domain if the estimated z-score was ≤2 SD from the mean.

4.7 Intra-operative TCD monitoring and analysis of embolic signals

4.7.1 Transcranial Doppler sonography

Intra-operative TCD monitoring was performed bilaterally using a commercially available TCD system (DWL Doppler-Box^{TM}, Compumedics Germany GmbH, Germany) equipped with a pair of 2 MHz transducers. TCD probes were held firmly in place using an adjustable headset and settings were optimised to obtain a clear signal from MCA blood flow. A detailed transcript outlining the stages of surgery, fluctuations in blood pressure, and haematocrit values, were noted and cross-referenced with the perfusionist's notes to match the timing of embolic signals with surgical and perfusionist's interventions. An example transcript showing typical stages of the surgery is provided in Appendix 4.I.

4.7.2 Intra-operative data collection

TCD recordings were made throughout the surgical procedure and terminated roughly 30 minutes after the patient had been weaned from bypass. To correlate the timing of embolic showers with operative events, all actions of the surgeon, anaesthetist, and perfusionist were cross-referenced. Theatre staff were blinded to the results of embolus detection monitoring to avoid affecting clinical management. The main stages of the surgery included initiation of cardiopulmonary bypass, application of the aortic cross-clamp, cross-clamp removal, cardiac de-airing, weaning from bypass, and resumption of cardiac rhythm. During surgery, the blood was regularly sampled, and intravenous drugs, such as heparin and protamine, were introduced. Cardioplegia was also infused into the heart tissue during surgery via the aortic cannula to stop the heart from beating.

4.7.3 Obtaining the TCD data

Following surgery, recorded data files were compressed and transferred to a password protected external hard drive, which could be decompressed and analysed on another computer. The compressed TCD recordings were viewed offline using DWL QL 2.10.3 software to examine the recording and count the number of emboli, and were also

imported to MATLAB for detailed analysis and characterisation of embolic signals. Figure 4.5 shows examples of TCD data recorded from the left and right MCAs of patient 9 during de-airing of the heart.

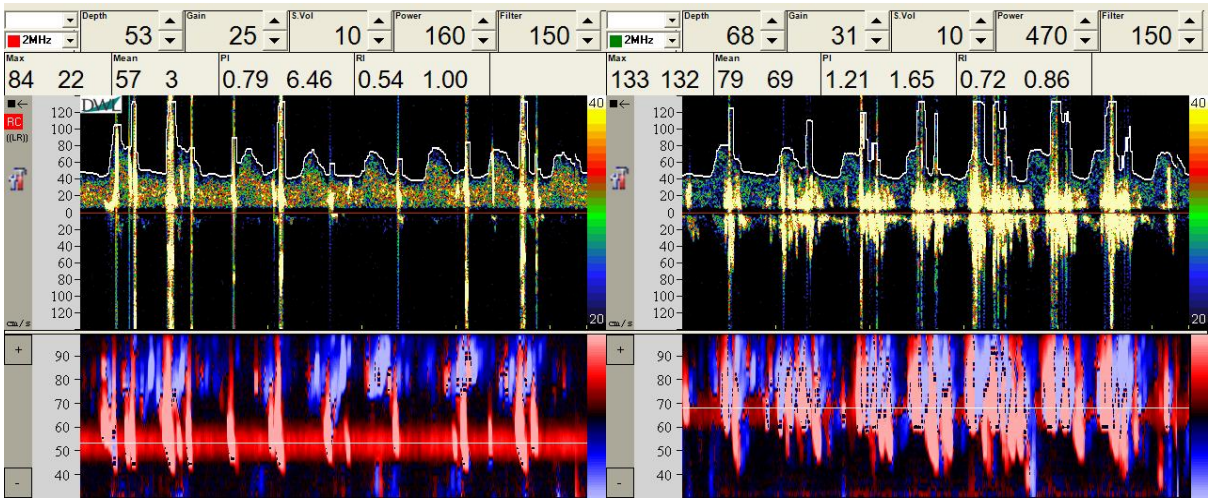


Figure 4.5 Example of a shower of emboli observed in the left and right MCAs of Patient 9 during de-airing of the heart.

As changes in haematocrit concentration can affect estimates of MEBR by up to 5 dB, backscattered intensities were adjusted for intra-operative haematocrit changes based on perfusionist blood sampling performed during bypass at 3 minute intervals. The Doppler sample length varied between 8 and 12 mm and the Doppler angle was assumed to be 30° to mimic a clinically realistic angle with respect to MCA geometry.

4.8 Statistical analysis

Statistical analyses were performed using a statistical software package (Statistical Product and Service Solutions, SPSS, version 20.0, SPSS Inc., IL, USA). Differences with a *p*-value of <0.05 were assumed to be statistically significant. Tests for normality were performed using the Kolmogorov-Smirnov test. Data are presented as mean ± SD unless stated otherwise. Comparisons of distributions were performed using either a Student's *t*-test or a Mann-Whitney U test, as appropriate.

An exploratory data analysis was performed to check for possible associations of neuropsychological and MRI outcome with baseline and surgical risk factors, such as: type of procedure, age, sex, smoking status, hypertension, hypercholesterolemia, ischaemic heart disease, aortic stenosis, and pre-existing cerebral white matter disease. Type of surgery was dichotomised into those undergoing extra-cardiac procedures (CABG) and intra-cardiac (valve/combined) procedures. Statistical tests applied to the analysis of neuropsychological tests results have been described previously (section 4.6.2).

The distribution of new MRI lesions between left and right were analysed using a binomial test assuming a null hypothesis that lesions were distributed equally between hemispheres. Differences in average dimensions of lesions between the left and right sides were assessed using Student's *t*-test. To assess whether new lesions were associated with poor cognition, differences in the characteristics of patients grouped by neurocognitive and MRI outcome were examined using Student's *t*-test for continuous measures, and Pearson's χ^2 statistic for categorical data (or Fisher's exact test if observed frequencies were less than 5). To assess whether surgical factors, timing of embolic events and size distribution of emboli were associated poor cognition and new MRI lesions, differences in characteristics of patients grouped by neurocognitive and MRI outcome were examined using a Mann-Whitney U test.

Chapter 5

5 Results – Part I: Cognitive and MRI outcome following cardiac surgery

5.1 Result of patient recruitment and demographics

5.1.1 Patient recruitment outcome

Patient recruitment for the study began on the 31/08/2011 and was completed on time in July 2013. During this study we approached a total of 362 patients and consented 114. Recruitment of patients and follow-up appointments were conducted over a period of 2 years. A total of 77 (68%) patients completed the MRI and neuropsychological test protocol. Full datasets (including additional TCD monitoring) were obtained for 71 (62%) patients. Of complete datasets obtained from 71 patients, 46 (40%) TCD recordings were suitable for detailed analysis of embolic signals. A full recruitment flow chart is provided in fig 5.1.

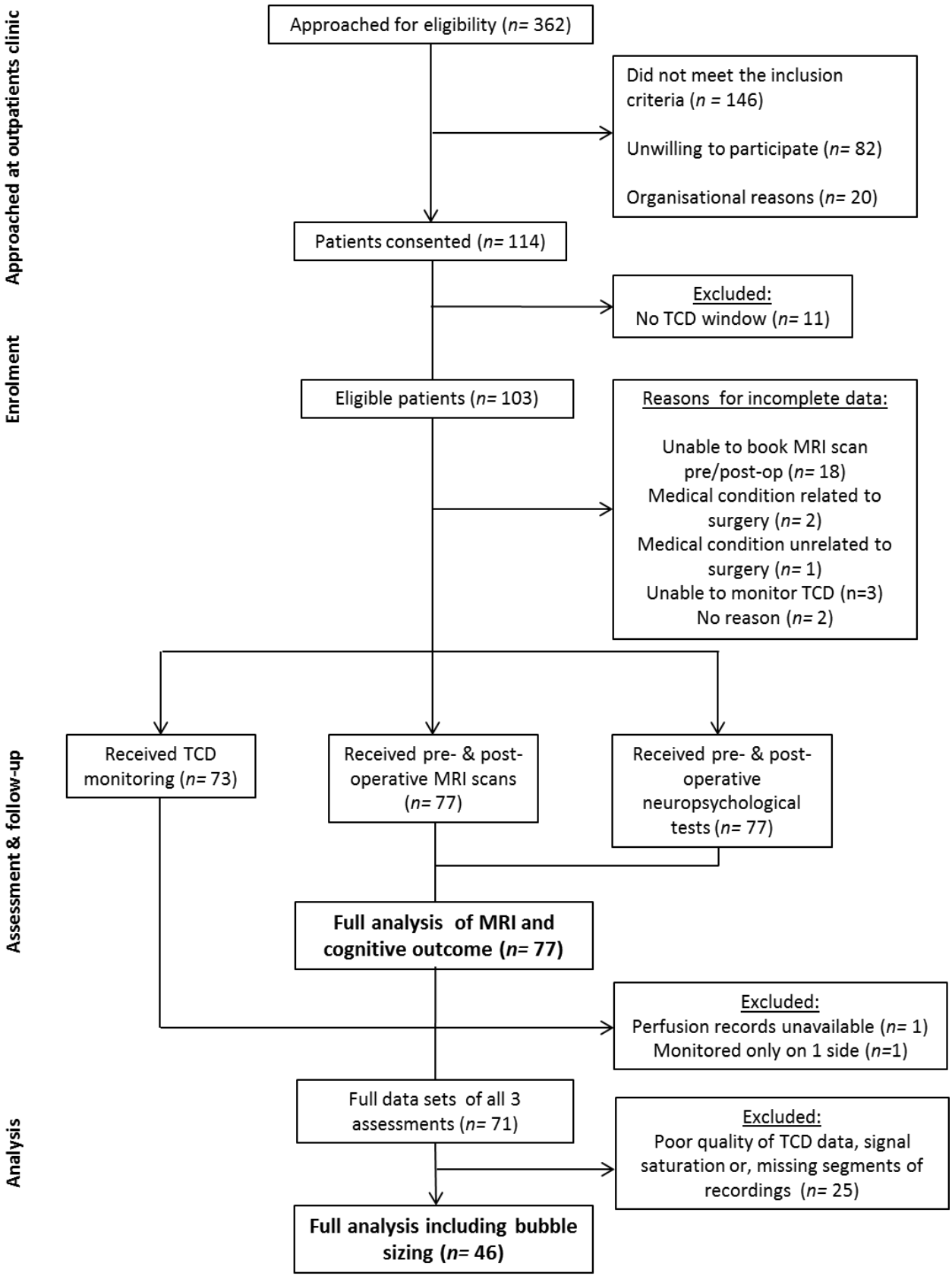


Figure 5.1 Diagram showing the flow of participants through each stage of the study.

5.1.2 Patient demographics

5.1.2.1 Age and sex

The mean age of the 77 patients was (age [SD]) 62.9 [10.3] years; range, 32 to 80 years, fig 5.2(a). The majority of patients were aged between 55 and 70 years (63 patients), with 13 patients below the age of 55 and only 1 patient above the age of 75. The majority of patients were male (72 males) with only 5 females Fig 5.2(b).

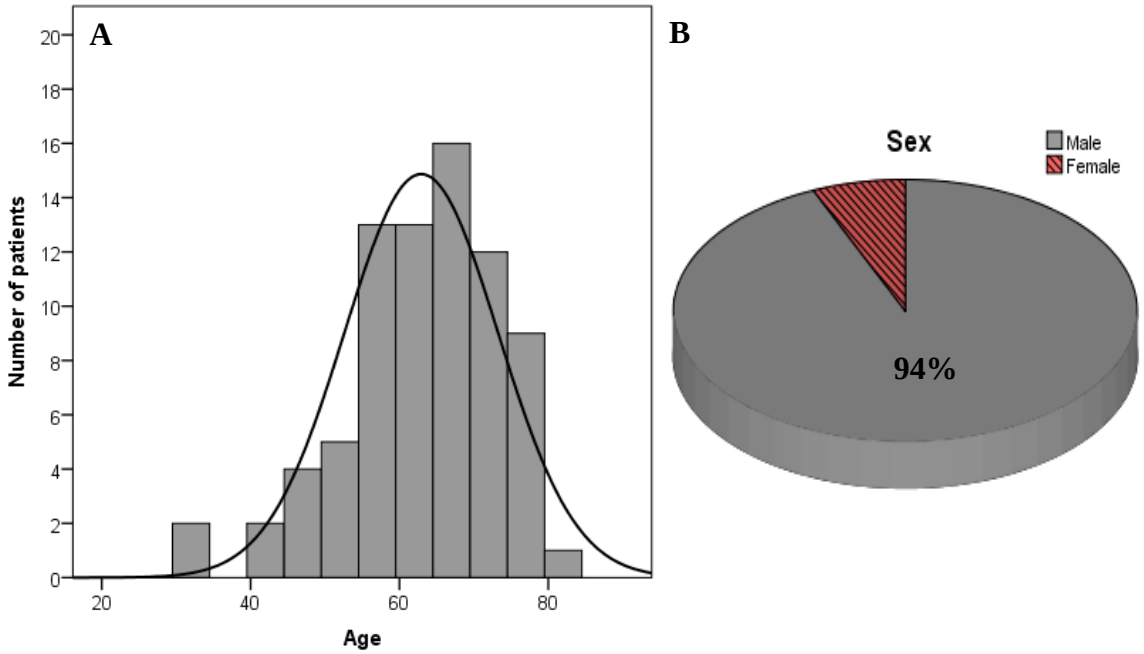


Figure 5.2 (A) distribution of the patient's ages and (B) sex

5.1.2.2 Associated risk factors

Associated risk factors for cardiovascular disease investigated as part of this study included smoking status, hypertension, hypercholesterolemia, family history of ischaemic heart disease, prevalence of aortic stenosis, left ventricle ejection fraction (LVEF). Figure 5.3 summarises the prevalence of associated risk factors within the study population.

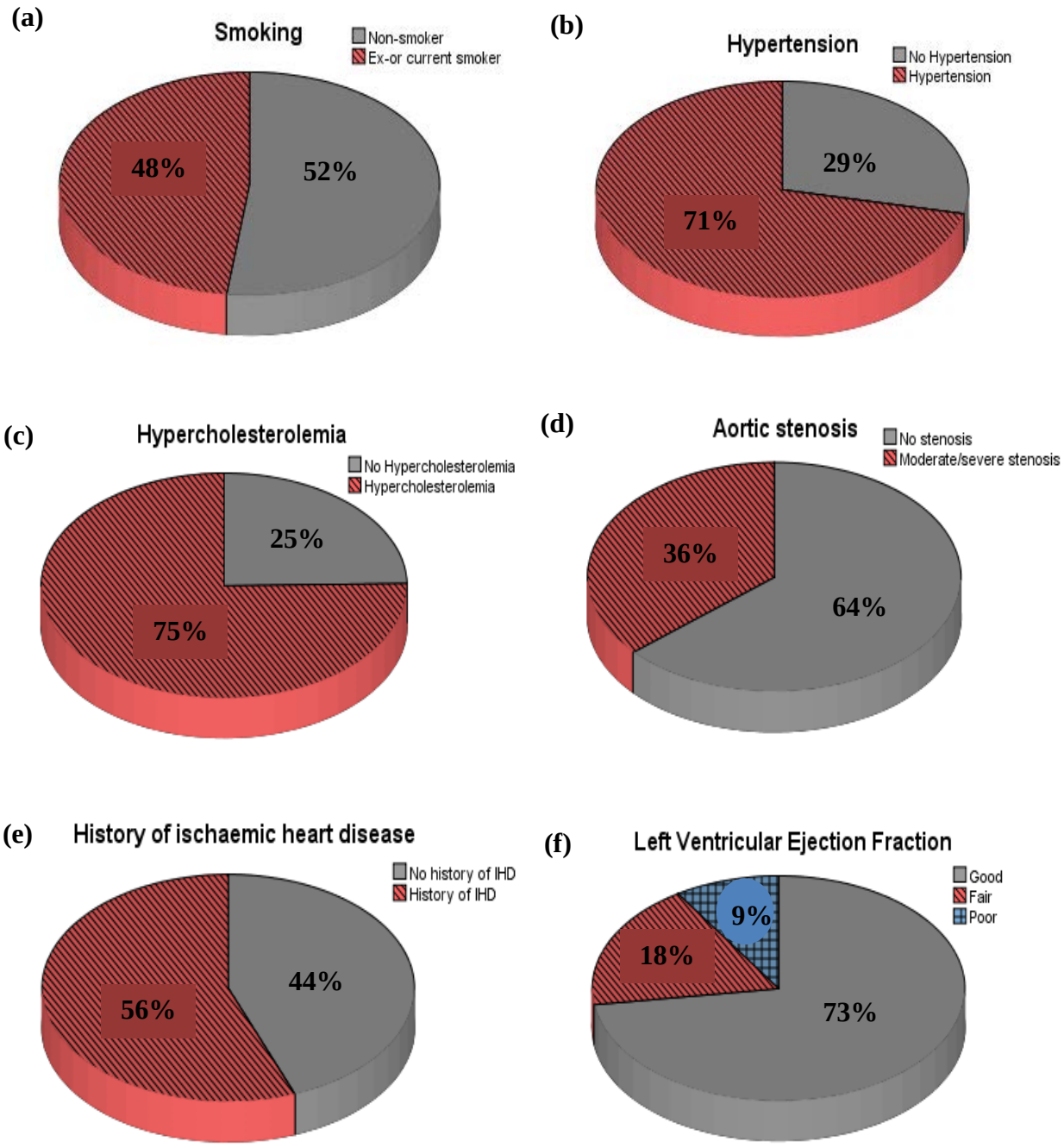


Figure 5.3 Proportion of patients with the following risk factors: (a) smoking, (b) hypertension, (c) hypercholesterolemia, (d) aortic stenosis, (e) history of ischaemic heart disease, (f) good, fair, or poor left ventricle ejection fraction.

5.2 Magnetic Resonance Imaging Results

One-hundred and three patients were eligible to undergo MR imaging however, 19 patients did not have a pre-operative MRI scan due to scheduling difficulties, 3 patients were unable to undergo the postoperative scan due to postoperative contraindications (i.e. pacemaker) and 4 patients decided to withdraw from the study. Outcome data from all 77 patients (72 males; 63±10 years) with complete pre-and post-operative MRI scans were analysed.

5.2.1 Pre-existing chronic ischaemic white matter disease

Using the FLAIR MRI digital registration and subtraction technique outlined in chapter 5, section 5.3.1, new and pre-existing lesions were identified through comparison of before and after MRI scans. Figure 5.4 shows an example of the spatial distribution of pre-existing ischaemic lesions for patient 47. This patient had 70 pre-existing lesions, estimated to occupy a total brain volume of 3516 mm^3.

Pre-existing lesions, identified radiologically as chronic ischaemic white matter disease, were noted in 64% (49) of patients pre-operatively. Of patients with pre-existing lesions, the average number of lesions was 30.5 (range: 1 - 100), and the average size was 2474 mm^3 (range: 186 - 27950 mm^3) per person. Assuming 1.50 L and 1.32 L as the average volumes of the male and female brain, respectively (Luders *et al.*, 2002), we estimate that pre-existing lesions in cardiac surgery typically affect up to 0.16% of total brain tissue.

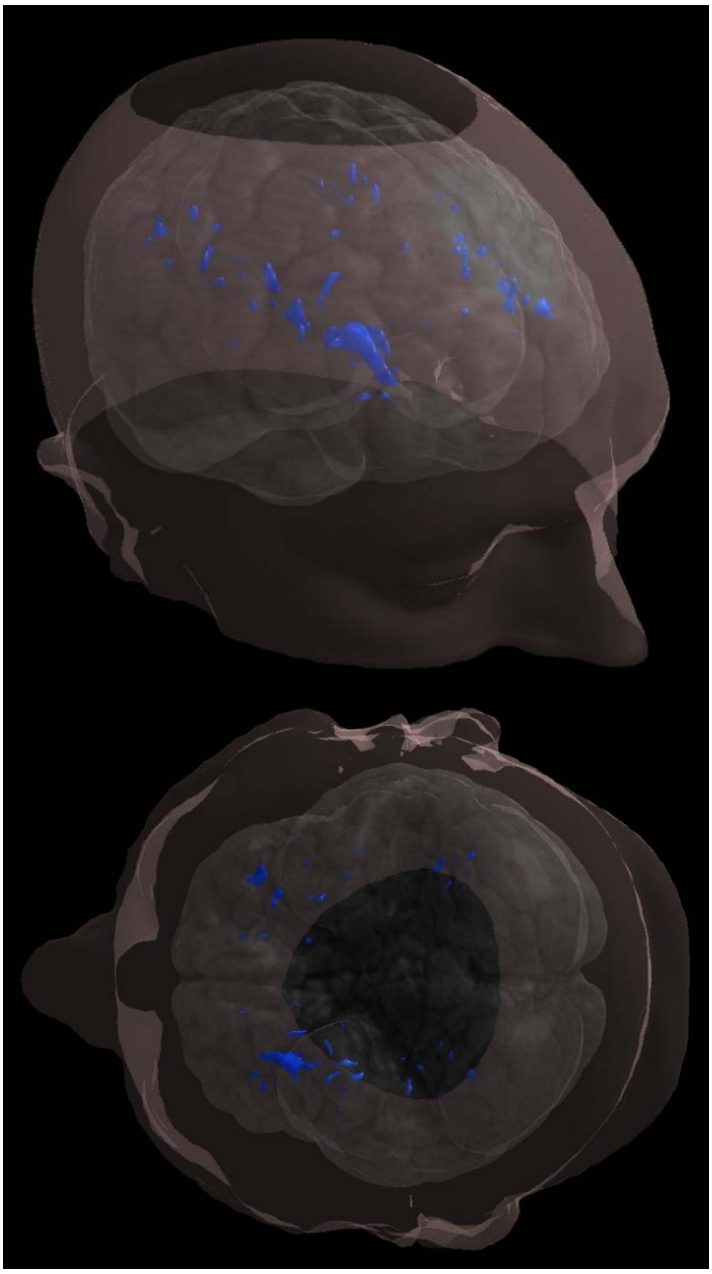


Figure 5.4 Example of the spatial distribution of pre-existing ischaemic lesions for patient 47. This patient had 70 pre-existing lesions estimated to occupy a total volume of 3516 mm^3. This image was obtained by the semiautomatic contouring technique outlined in chapter 3, section 3.3.

5.2.2 New ischaemic lesions

Following surgery, 5/77 patients (7%) had perioperative strokes confirmed by the Radiologist's MRI report: patients 13 and 62 had lacunar infarcts in the right corona radiata, patient 47 had a lacunar infarct in the left corona radiata, patient 63 had two small lacunar infarcts (one located in the right superior parietal lobule and one in the left

medial precentral gyrus), and patient 19 had a lacunar infarct in the right frontal lobe. Patient 19 was the only patient with perioperative stroke to also experience cognitive decline. 'Before' and 'after' MRI images for patients 13, 19 and 63 are shown along with the subtraction images in fig 5.5.

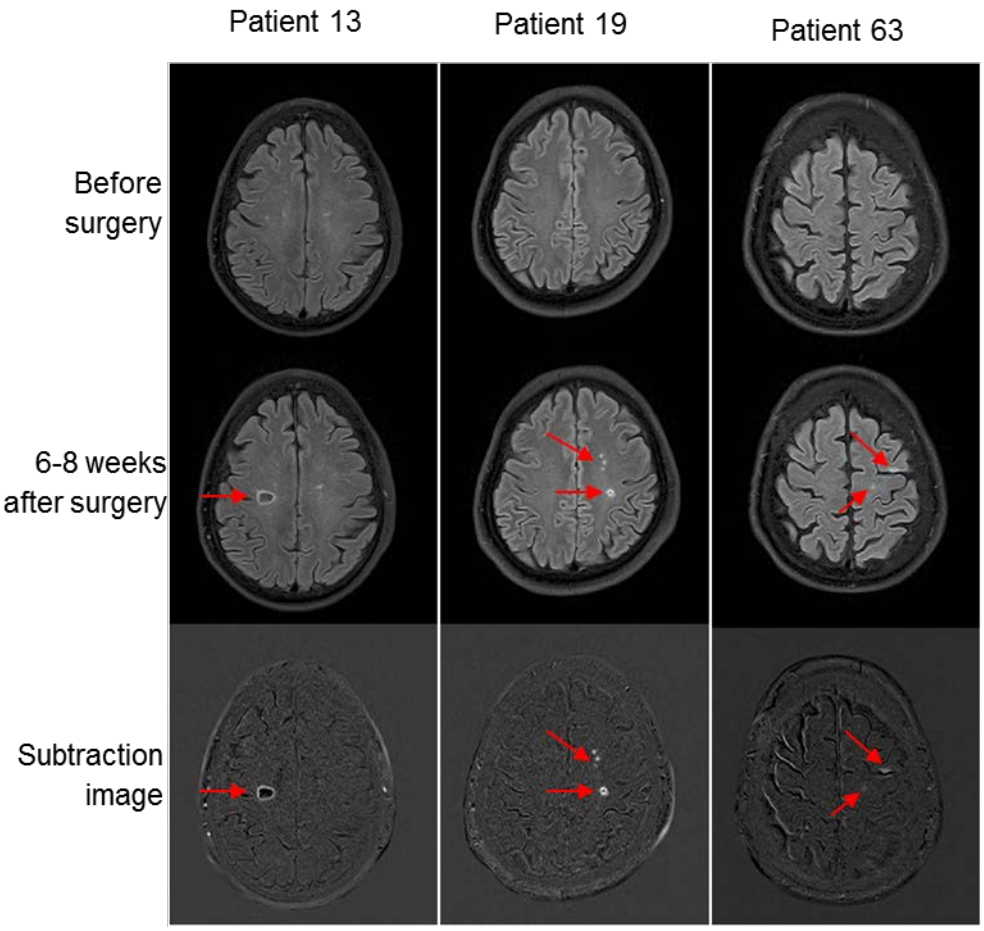


Figure 5.5 Comparison of FLAIR MR images obtained 1-2 weeks before and 6-8 weeks after cardiac surgery. Registration and subtraction of MRI data were performed using 'in house' software to confidently distinguish new ischaemic lesions from pre-existing infarcts and provide an estimate of the position and volume of new lesions.

Nearly a third of patients, 31% (24/77), had new chronic lesions observed using FLAIR MRI. Nine patients (12%) exhibited multiple MRI lesions (up to a maximum of 5). Three patients had lesions located in more than one vascular territory. Of the 9 patients with multiple lesions, 7 possessed lesions that were larger than 100 mm^3. New lesions with estimated volume greater than 100 mm^3 were observed in 10 patients. The largest observed lesion had an estimated volume of 1383 mm^3 located in the right frontal lobe

of patient 13, fig 5.5. The 10 patients with the largest lesions included 4 out of the 5 patients with perioperative stroke symptoms.

A 3-dimensional representation of the overall distribution of new MRI lesions, created by superimposing data from all 24 patients, is presented in fig. 5.6.

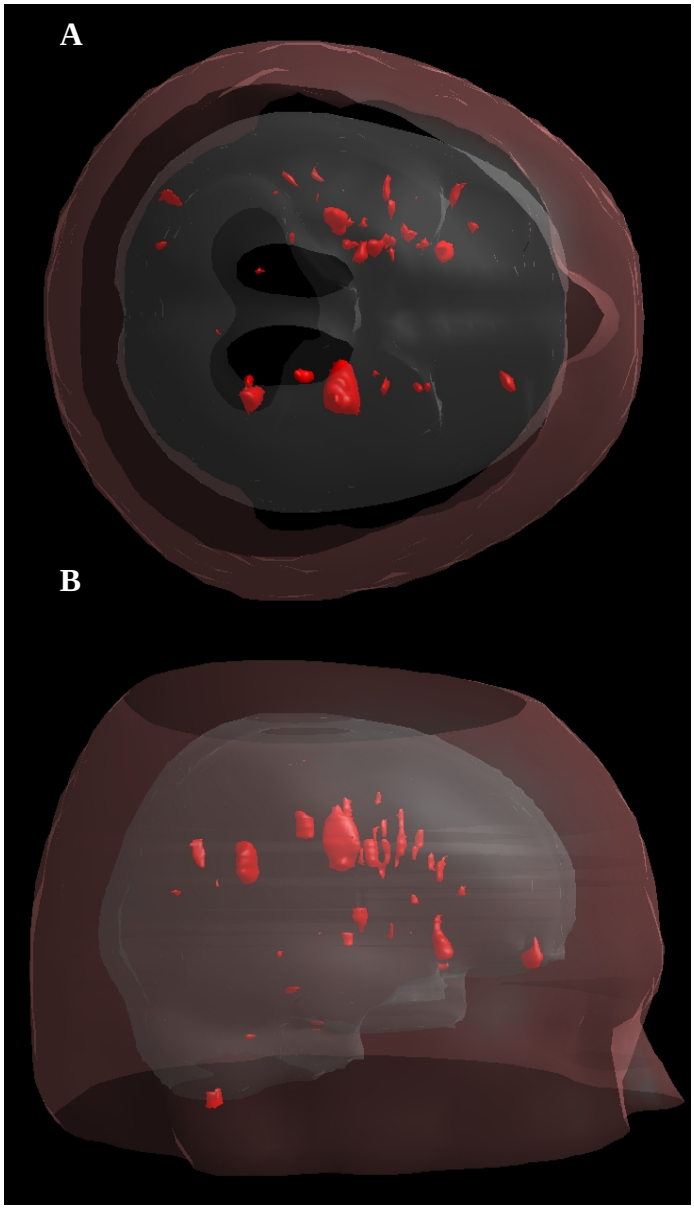


Figure 5.6 (A) superior view, (B) lateral view of new ischaemic lesions, compiled from the combined data of all 24 patients who received new lesions following surgery. The size and position of new lesions are consistent with a cardio-embolic pathogenesis. Lesions are highlighted in red against the background of a standard atlas image.

On average, right hemisphere lesions were three times larger (mean volume=264 ± 412 mm^3) than left hemisphere lesions (mean volume=87 ± 95 mm^3), *t*-test: p=0.034, fig. 5.7(a). However, the left hemisphere was the site of 74% of all new lesions compared to only 26% in the right hemisphere (χ^2=9.3: p=0.002), fig 5.7(b).

Overall, most new MRI lesions were found in the middle cerebral artery (MCA) territory (64%), followed by the anterior cerebral artery (ACA) territory (13%), posterior cerebral artery (PCA) territory (13%), superior cerebellar artery (SCA) territory (5%), and lateral lenticulostriate artery (LLA) territory (5%), fig. 5.7(b).

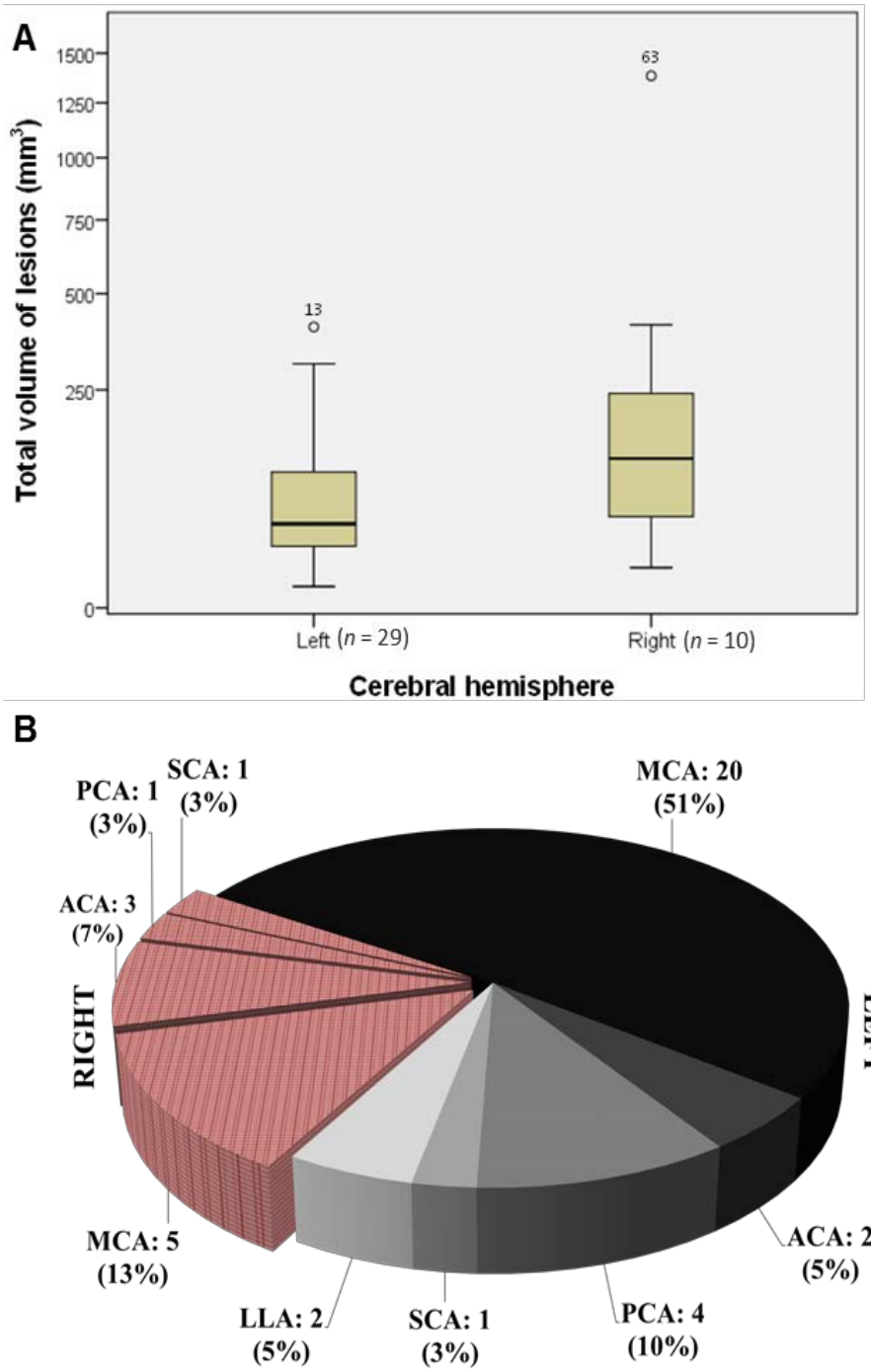


Figure 5.7 (A) Lesions observed in the left hemisphere tended to be smaller than those on the right (*n*= number of lesions). (B) The majority (74%) of new lesions were located in the left hemisphere (χ^2 test: p=0.002). Lesions appeared in multiple territories, but particularly favoured regions supplied by the middle cerebral artery (MCA). ACA= anterior cerebral artery, PCA=posterior cerebral artery, SCA=superior cerebellar artery, LLA=lateral lentistriate artery.

A detailed table summarising all data relating to the MRI results is provided in Appendix 5.A.

5.2.3 Comparison of old and new ischaemic lesions

Of the 64% (49) of patients with pre-existing lesions, 45% (22), went on to develop new lesions post-operatively compared to only 7% (2/28) of patients without pre-existing lesions (i.e. 92% (22/24) of patients with new lesions had pre-existing lesions). An example showing the location and volume of new (red) and pre-existing lesions (blue) in patient 47 is provided in fig. 5.8.

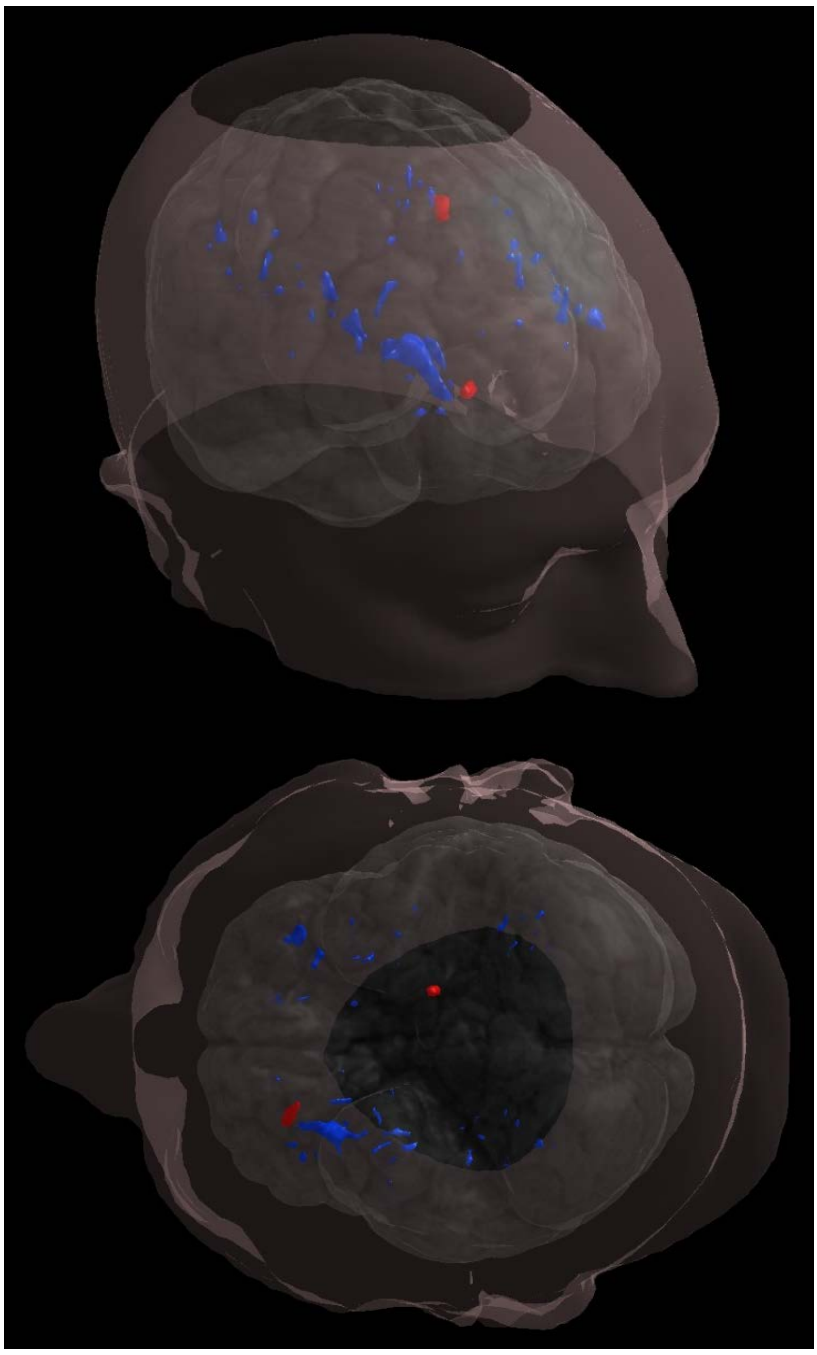


Figure 5.8 Spatial distribution of new ischaemic lesions (red), and pre-existing lesions (blue) for patient 47.

Comparison of the contribution from new and pre-existing lesions suggests that the accumulation of new lesions following surgery is relatively minor in comparison with the pre-existing burden due to chronic cerebrovascular disease. Figure 5.9(a) compares the volume of pre-existing and new lesions for the patients with new lesions. Figure 5.9(b) summarises the volume of pre-existing lesions for the patients without new lesions.

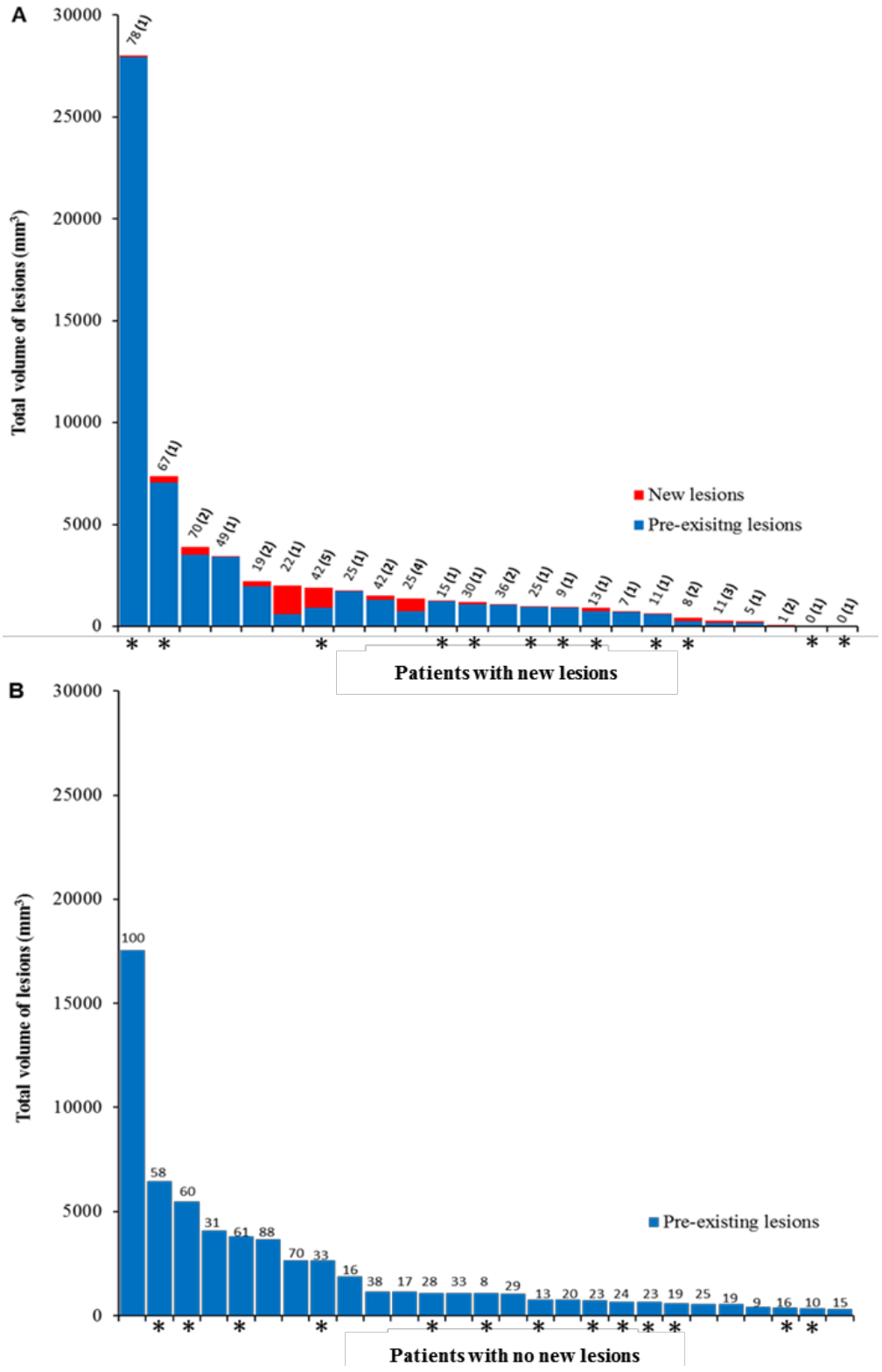


Figure 5.9 (A) Comparison of the total volume of pre-existing and new lesions in patients who received new lesions following cardiac surgery. Patients are ranked in order of the total volume of lesions and the number of pre-existing (and new) lesions is shown above each bar. (B) Volume and number of pre-existing lesions in patients who received no new lesions following surgery. * denotes patients who exhibited cognitive decline.

5.3 Neuropsychological Test Results

One-hundred and three patients were eligible to undergo neuropsychological assessment. Patients who were unable to undergo MRI were not asked to complete the neuropsychological tests. Data from all 77 patients (72 males; 63±10 years) with complete pre-and post-operative neuropsychological data were analysed.

5.3.1 Baseline cognitive scores

To investigate post-operative outcome, patient's baseline test scores were used as their own controls. Figures 5.10 and 5.11 summarise the distribution of baseline test scores for immediate memory, delayed memory, verbal IQ, performance IQ, trial making A & B, grooved pegboard dominant and non-dominant hand respectively. Pre-operative test performances were similar to the general population in all tests apart from the grooved pegboard test where our cohort of patients exhibited a moderate pre-existing decline. Performance IQ was slightly better than the general population, which probably reflects the higher IQ of patients willing to participate in our research.

Overall, 22% of patients were estimated to have cognitive impairment in at least 1 test at baseline and 46% of patients experienced cognitive decline following surgery. A detailed breakdown of the results of neuropsychological testing is provided in the next few pages.

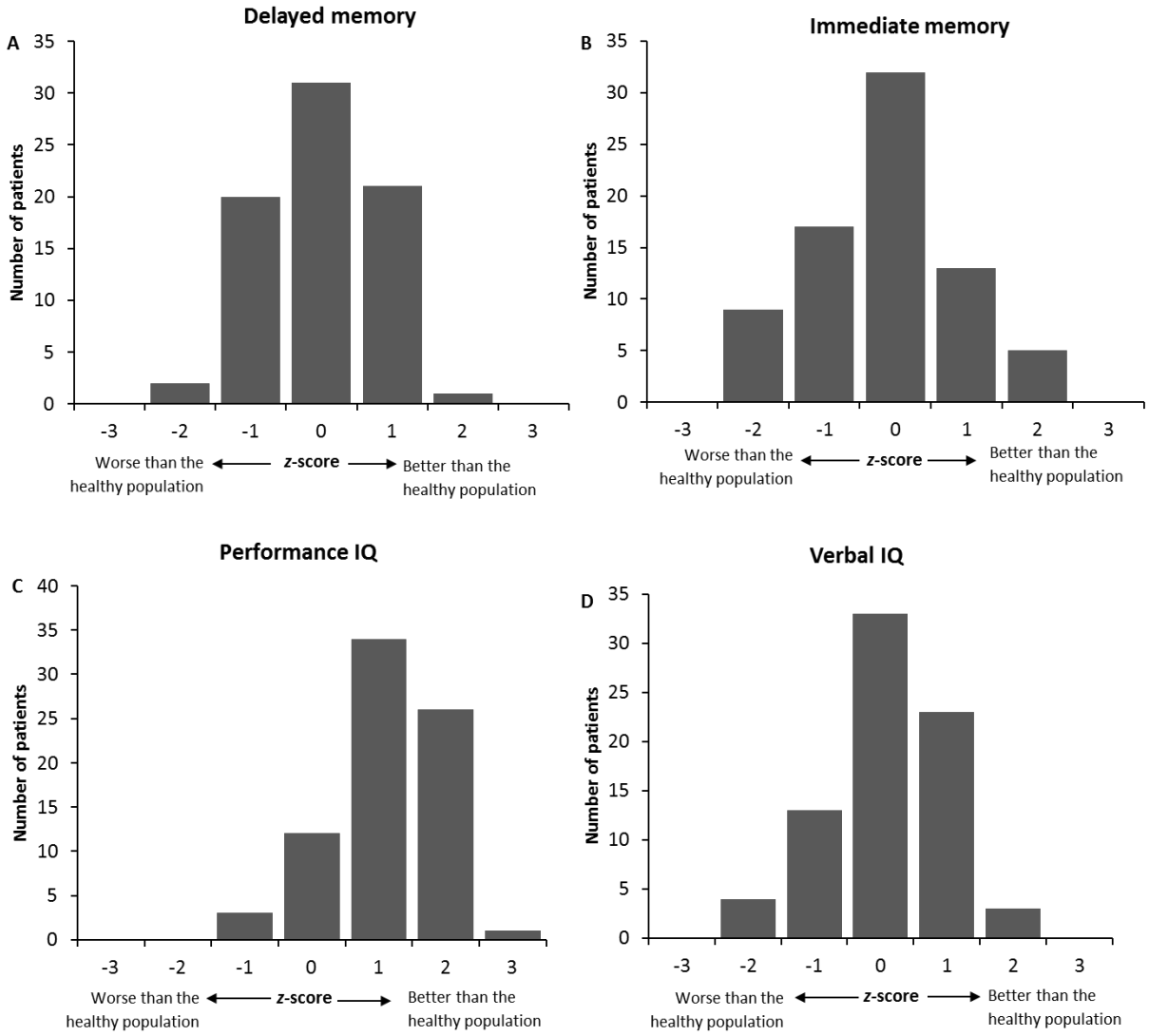


Figure 5.10 Baseline z-scores for (A) immediate memory, (B) delayed memory, (C) verbal IQ and (D) performance IQ. z-scores < 0 resulted in scores below the normal healthy population average and > 0 above average.

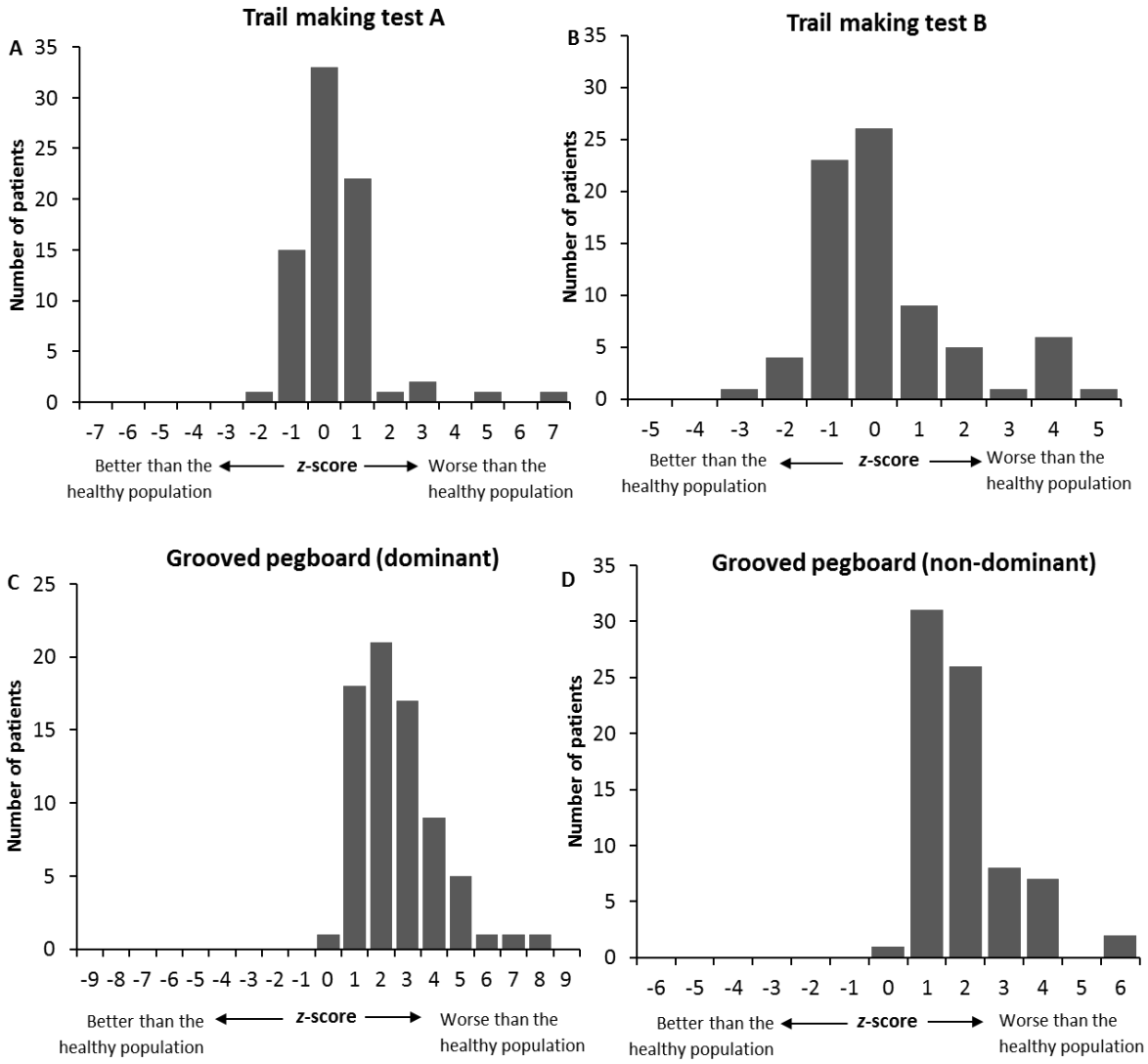


Figure 5.11 Baseline z-scores for (A) Trail making A, (B) Trail making B, (C) Grooved pegboard (dominant) and (D) Grooved pegboard (non-dominant). *z*-scores > 0 resulted in scores below the normal healthy population average and < 0 above average.

5.3.2 Pre-existing cognitive impairment

Pre-existing cognitive impairment at baseline was noted in 17 (22%) of 77 patients, as defined by a 'composite *z*-score' >1 SD below the normative population average. The most commonly affected tests were the Grooved pegboard exercise (dominant hand: 46% (36) and non-dominant hand: 23% (18)). More patients showed pre-existing impairment in the immediate memory exercise (12% (9)) than the delayed memory exercise (3% (2)). Likewise, a higher proportion of patients exhibited pre-existing

impairment in the Trail making-B test (10% (8)) than the Trail making-A (4% (3)). Five percent of the patients (4) had low scores in the verbal IQ tests. No patients had impaired performance IQ, fig 5.12. However, this may reflect selection bias as more highly educated individuals were more likely to agree to participate in our research.

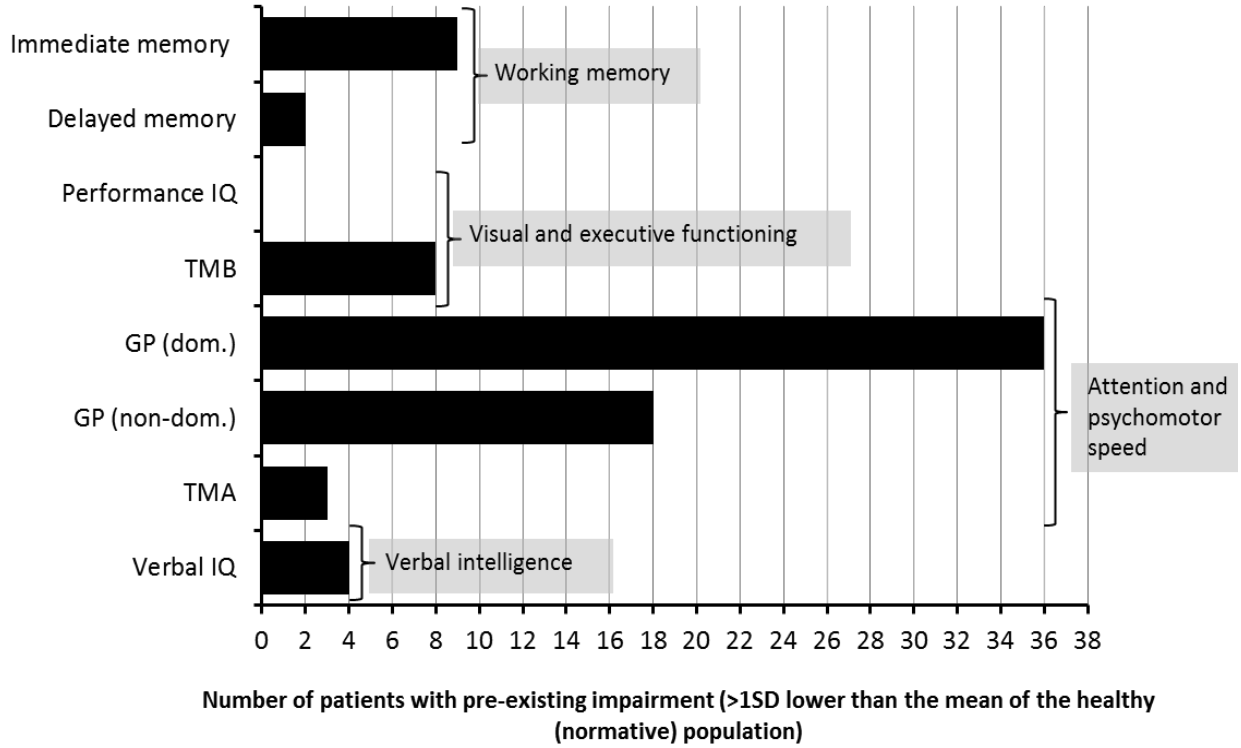


Figure 5.12 Numbers of patients showing pre-existing decline in individual tests by >2 SD. TMA; Trail making-A, TMB; Trail making-B, GP; Grooved pegboard.

5.3.3 Postoperative cognitive decline

The mean raw and *z*-scores for the entire cohort were grouped by test and examined as a group to see if there were any significant differences overall between the baseline and postoperative scores. We found no evidence to suggest a statistically significant difference between the scores of our cohort before and after surgery in any of the 4 domains assessed, table 5.1.

Table 5.1 Mean raw and *z*-scores for baseline and postoperative test scores for each type of test performed. The S.D. refers to the raw scores.

Cognitive function (n=77)		Baseline		6-8 weeks		
		Mean (z-score)	**SD**	**Mean (z-score)**	**SD**	***t*-test**
Working memory	*Immediate memory*	92.4 (-0.69)	14.1	95.7 (-0.45)	14.4	0.161
	Delayed memory	98.6 (-0.49)	13.1	102.2 (-0.24)	15.3	0.126
Visual and executive functioning	*Performance test*	110.9 (0.63)	15.5	110.4 (0.67)	18.2	0.830
	Trail making B	67.4 (-0.59)	25.1	64.8 (-0.27)	25.4	0.530
Attention and psychomotor speed	*Trail Making A*	32.5 (-0.18)	11.2	30.3 (-0.38)	9.40	0.182
	Grooved pegboard (dom)	109.6 (2.44)	23.0	107.4 (2.22)	23.7	0.565
	Grooved pegboard (non-dom)	110.1 (1.59)	17.8	114.1 (1.76)	25.4	0.245
Verbal intelligence	*Verbal test*	90.4 (-0.43)	18.3	91.3 (-0.39)	17.2	0.762

Analysing data from individual patients where each patient acts as their own control, revealed a >1 SD decline in neuropsychological performance in at least one test for 35 (46%) of the 77 patients studied. Five patients (6%) declined in two or more tests. The most commonly affected domains were attention and psychomotor speed, affecting 23% (18) of patients (TMT-A: 5% and Grooved pegboard: 18%). Visual & executive domains were affected in 17% (13) of patients (performance: 4% and TMT-B: 13%), immediate memory was affected in 8% (6) of patients, while delayed memory was affected in 4% (3) of patients. Only one patient declined in the verbal intelligence test (1%). The magnitude of decline quantified as a *z*-score change for all patients who experienced cognitive decline are summarised in fig. 5.13. This figure shows the individual patient's pre-operative *z*-score (●) and post-operative *z*-score (■).

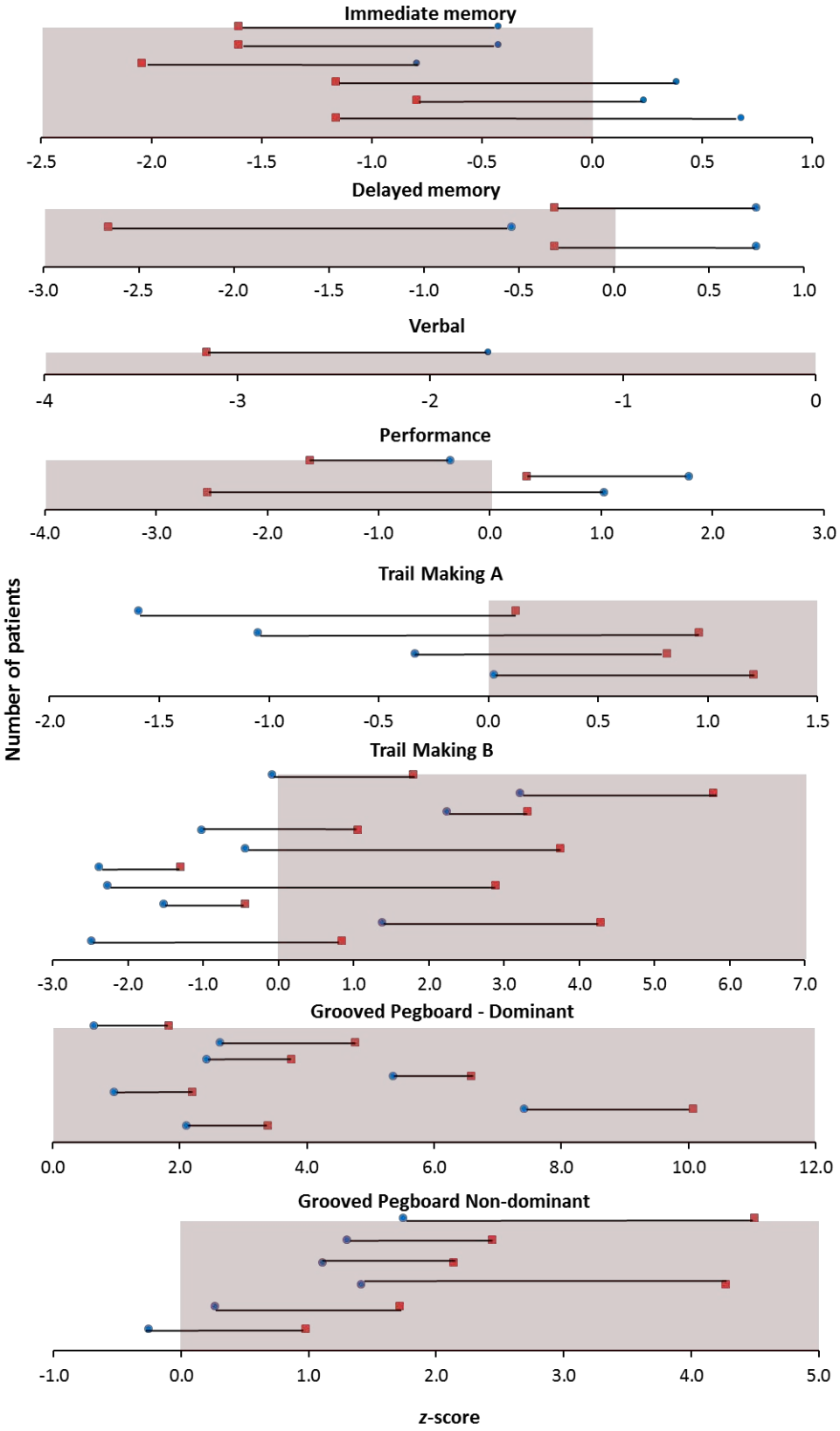


Figure 5.13 Magnitude of *z*-score change for patients that declined postoperatively. ● denotes the pre-operative *z*-score and ■ denotes postoperative *z*-score. Shaded areas (in pink) within each graph indicate *z*-scores below the general population (normative) average.

Overall, more patients improved in their postoperative test scores than declined, however, only 2 patients showed an improvement in mean 'composite' *z*-score greater than 1 SD. The most commonly improved performances were in the Trail making-B test (18% (14)), delayed memory test (17% (13)) and the immediate memory test (16% (12)). Twelve percent of the 77 patients showed an improvement in the Trail making-A tests (9) and 7% (5) in both verbal IQ and the Grooved pegboard (dominant) tests. Five percent (4) showed an improvement in the Grooved pegboard (non-dominant) test and only 3% (2) showed an improvement in performance IQ. A comparison of the number of patients that declined and improved in each specific test is shown in fig 5.14.

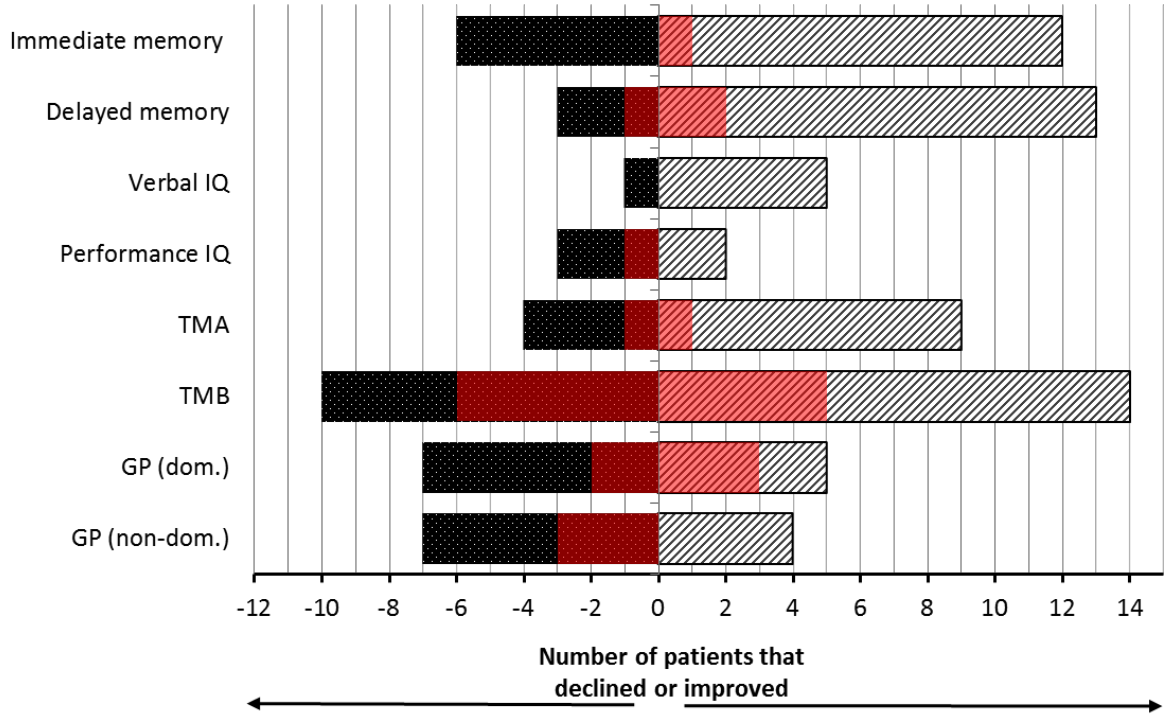


Figure 5.14 Comparison of the patients that declined and improved within specific tests. Bars shaded red indicate the number of patients that improved or declined by ≥2 SD in their respective cognitive tests

The majority of the patients had normal levels of depression and mild levels of anxiety on HADS at pre-operative assessment (anxiety: 6.3±3.8; depression: 3.3±2.7). The level of anxiety had dropped in some, but not all, patients after surgery (anxiety: 3.9±3.1; depression: 2.9±3.2). Depression levels were stable compared with baseline scores.

HADS assessment suggests that any decline in neuropsychological test scores was not due to an increase in anxiety or depression.

The incidence of cognitive decline in our study population was 46%, which was independent of the presence of new lesions, and irrespective of whether new lesions were large or multiple. We found no association between declining *z*-score and the presence of new MRI lesions (denoted ⭘) (filled circles ● denote no new MRI lesions) (fig. 5.15 and 5.16). Similarly, as previously shown in fig 5.9, there was no association between the volume of new MRI lesions and >1 SD cognitive decline.

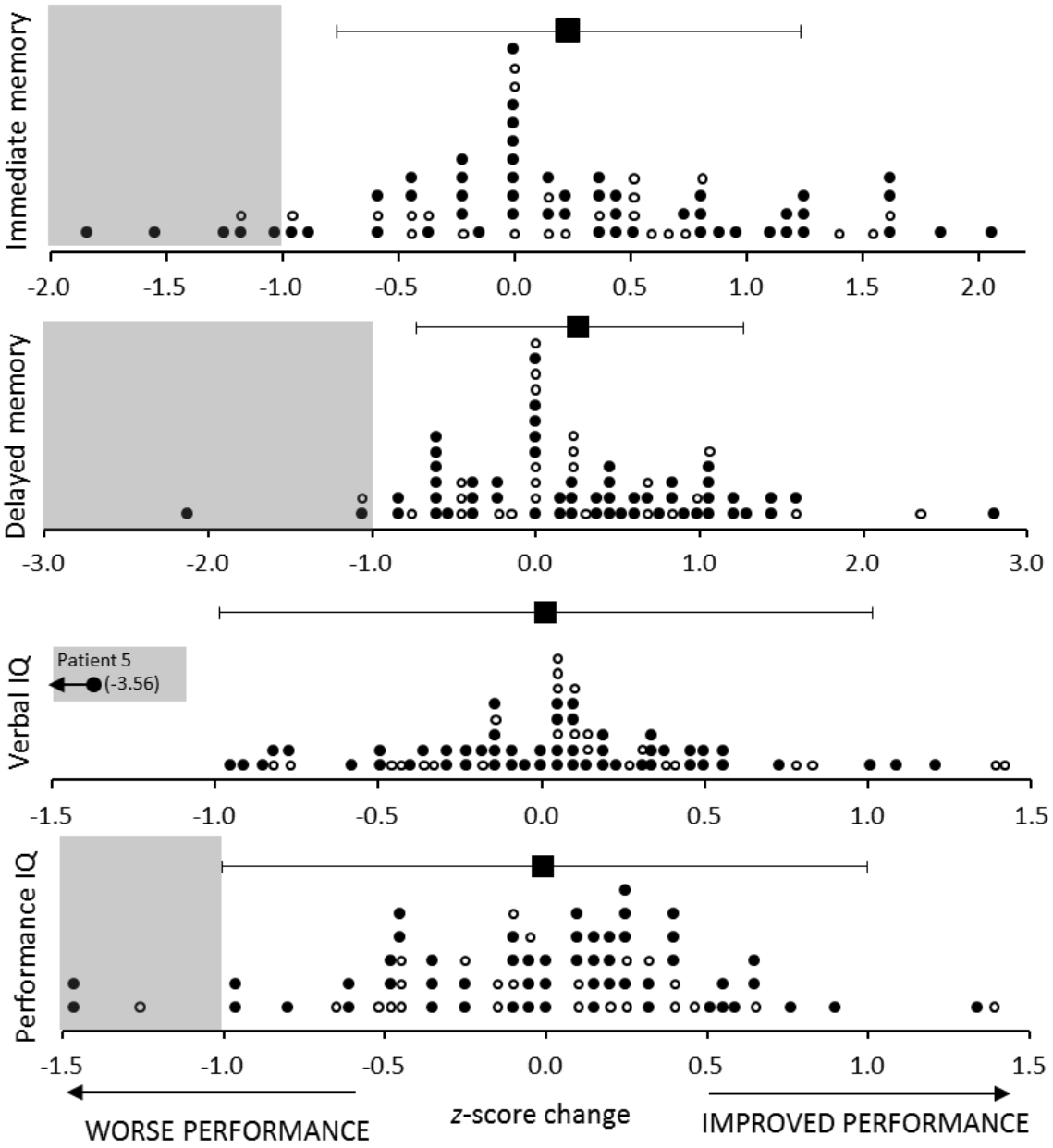


Figure 5.15 Summary of changes in neuropsychological test performance (*z*-score change) for 77 patients taking non-timed cognitive tests. Overall, test performance tended to improve slightly on retesting, indicated by a positive mean *z*-score change (mean: ■, 1 SD). Patients who had a drop in *z*-score of more than 1 SD (shaded) were assumed to have significantly declined in at least 1 test (indicated by the shaded grey regions). Visual inspection suggests no obvious correlation between *z*-score decline and the presence of new MRI lesions (denoted **O**).

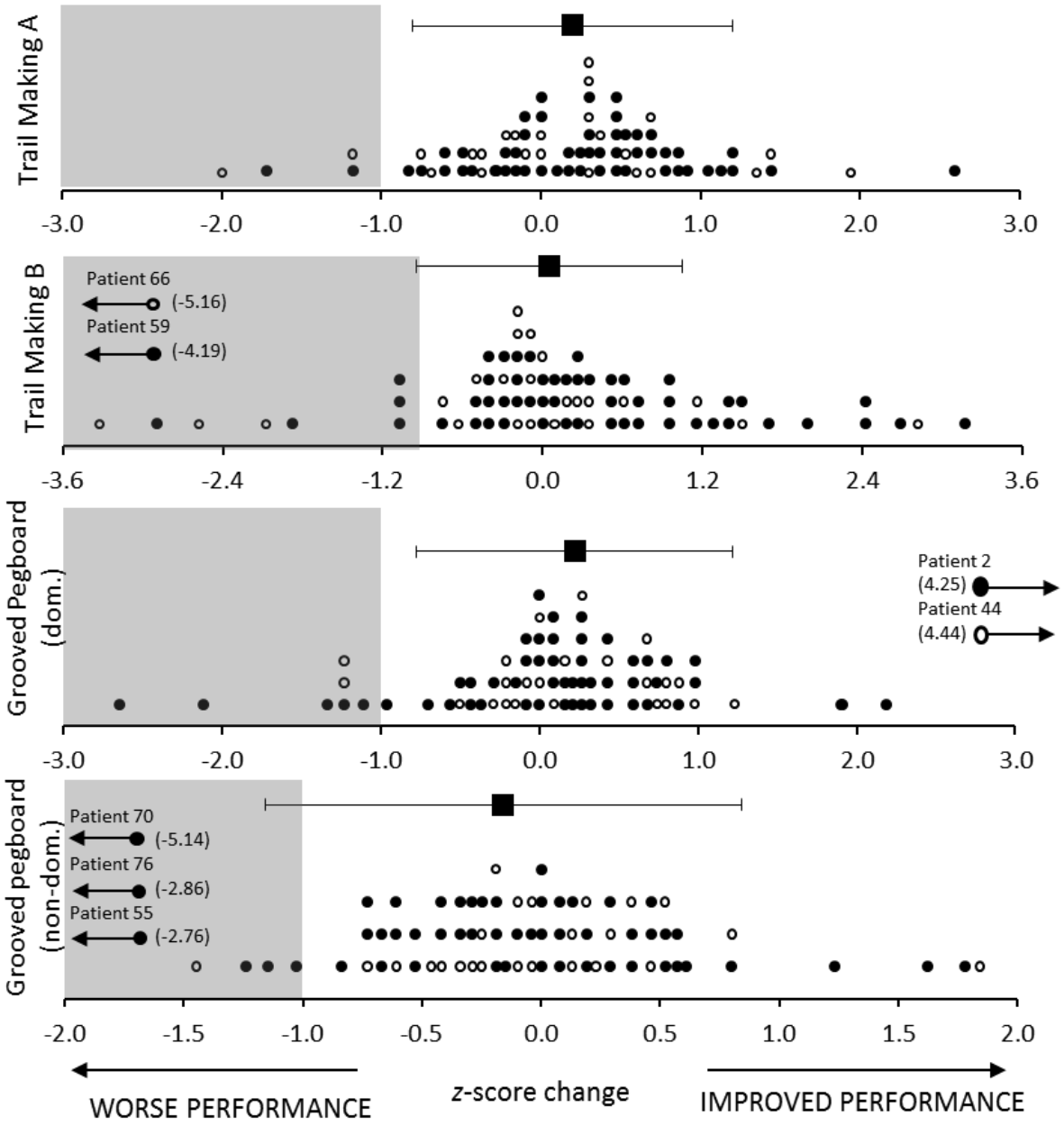


Figure 5.16 Summary of changes in neuropsychological test performance (*z*-score change) for 77 patients taking timed cognitive tests. Overall test performance tended to improve slightly on retesting, indicated by a positive mean *z*-score change (mean: ■, 1 SD) apart from the Grooved pegboard (non-dom.) which showed a small decline. Patients with a drop in *z*-score of more than 1 SD (shaded) were defined as having significantly declined. Visual inspection suggests no obvious correlation between *z*-score decline and the presence or characteristics of new MRI lesions (denoted ○).

Grouping patients by neuropsychological outcome showed similar demographic and surgical factors between groups with the exception of age (*t*-test, $p= 0.022$) and aortic stenosis (χ^2 test, $p= 0.042$), table 5.2.

Table 5.2 Comparison of potential risk factors grouped by cognitive outcome.

	Cognitive decline *N*=35	**No cognitive decline *N*=42**	***p*-value**
Male: female	33:2	39:3	1.000*
Age, years ± SD	66±7	60±12	0.022†
CABG: intra-cardiac procedures	12:23	15:27	0.896‡
Smoking, *n* (%)	14 (40)	23 (55)	0.254‡
Hypertension, *n* (%)	23 (66)	32 (76)	0.311‡
Hypercholesterolemia, *n* (%)	27 (77)	31 (74)	0.735‡
Ischaemic heart disease, *n* (%)	23 (66)	20 (48)	0.111‡
Aortic stenosis (mild/severe), *n* (%)	24 (69)	18 (43)	0.042‡
Pre-existing white matter disease, *n* (%)	23 (66)	26 (62)	0.727‡
New FLAIR MRI lesions, *n* (%)	11 (31)	13 (31)	0.964‡

*Fisher's exact test, †*t*-test, ‡Chi-squared test; CABG=Coronary Artery Bypass Graft, FLAIR=Fluid Attenuated Inversion Recovery. Significant risk factors are highlighted.

There were no significant differences between the characteristics of patients with and without new lesions other than an association between new and pre-existing lesions. Ninety-two percent (22/24) of patients with new lesions had pre-existing lesions, compared to only 51% (27/53) of patients with no new lesions (χ^2 test: p=0.001), see table 5.3

Table 5.3 Comparison of potential risk factors grouped by FLAIR MRI outcome.

	New lesions (*N*=24)	**No new lesions (*N*=53)**	***p*-value**
Male: female	21:3	51:2	0.172*
Age, years (SD)	64±10	63±11	0.606†
CABG: intra-cardiac procedures	6:18	21:32	0.213‡
Smoking, *n* (%)	9 (38)	28 (53)	0.212‡
Hypertension, *n* (%)	15 (63)	40 (75)	0.243‡
Hypercholesterolemia, *n* (%)	17 (71)	41 (77)	0.538‡
Ischaemic heart disease, *n* (%)	12 (50)	31 (59)	0.487‡
Aortic stenosis (mild/severe), *n* (%)	16 (67)	26 (49)	0.151‡
Pre-existing lesions, *n* (%)	22 (92)	27 (51)	0.001‡
Neuropsychological decline, *n* (%)	11 (46)	24 (45)	0.964‡

*Fisher's exact test, †*t* test, ‡Chi squared test. CABG=Coronary Artery Bypass Graft, FLAIR=Fluid Attenuated Inversion Recovery. Significant risk factors are highlighted.

5.4 Summary

In summary, the results of this chapter confirm that neurological injury is common in patients undergoing cardiac surgery; 7% of patients suffered a perioperative stroke, 31% had new MRI lesions, and 46% exhibited signs of neuropsychological impairment at 6-8 weeks postoperatively. Older patients and patients with aortic stenosis were confirmed to be most likely to experience cognitive decline. Patients with pre-existing lesions were most likely to receive new lesions following surgery. Pre-existing lesions, affecting up to 0.16% of total brain volume, were observed in 64% of patients and were associated with a high risk of receiving new lesions following surgery.

We found no evidence to support a link between new lesions on MRI and cognitive decline. Of those patients who experienced neuropsychological decline, 69% (24/35) had no new postoperative MRI lesions. Similarly, over half (54%) of the 24 patients with new MRI lesions (13/24) did not experience any discernable neuropsychological decline. No association between the magnitude of cognitive decline and the size or number of new lesions was found. On average, patients with new MRI lesions did not experience a greater magnitude of decline than patients without new MRI lesions (mean composite *z*-score change, 0.07 versus 0.11, respectively; *t*-test, p=0.7) and there was no association between having multiple new lesions and larger decline in composite *z*-score (*t*-test, p=0.6).

Chapter 6

6 Results – Part II: Intra-operative risk factors and detailed embolic signal analysis

6.1 Patient recruitment outcome

Of the 77 patients with complete sets of outcome measures, 73 received bilateral intra-operative transcranial Doppler (TCD). Of these recordings, data from 46 patients (43 males; mean age [range] 64 [41-80]) were of a sufficiently high quality to be used for detailed embolic signal analysis. Data were excluded from analysis for the following reasons: (i) Signal saturation (i.e. the dynamic range of the recording was insufficient for estimation of embolic signal intensity) (24), (ii) unilateral monitoring only (1), (iii) perfusionist records absent (1), (iv) poor quality recording (1).

6.2 Intra-operative exploratory data analysis

Intra-operative data collected as part of this study for all 77 patients included the type of surgery, duration of cardiopulmonary bypass, and duration of aortic cross-clamp application. Intra-operative blood pressure, haematocrit levels, temperature, rate of re-warming, and carbon dioxide levels are also reported for the 46 patients whose Doppler data were analysed.

6.2.1 Type of surgery

All patients underwent one of the following procedures; coronary artery bypass graft (CABG), valve procedure, or a combination of both. The number of patients within each surgical group is summarised in table 6.1.

Surgical procedure	No. of patients with complete MRI and cognitive tests	No. of patients with complete TCD data
CABG (x1 graft)	18	12
CABG (x2 graft)	6	5
CABG (x3 graft)	3	1
Total CABG	**27 (35%)**	**18 (39%)**
Aortic valve	29	14
Mitral valve	7	5
CABG & aortic valve	9	4
CABG & mitral valve	3	3
Mitral & tricuspid valve	1	1
CABG & mitral/tricuspid valve	1	1
Total Intra-cardiac	**50 (65%)**	**28 (61%)**
Total patients	**77**	**46**

Table 6.1 Number of patients undergoing each type of surgical procedure.

6.2.2 Cardiopulmonary bypass and aortic cross-clamp

The start and end of cardiopulmonary bypass (CPB) were noted and later cross-referenced with the perfusionist's records. CPB duration for CABG ranged between 35 and 122 minutes (mean [SD] 71 [22]), fig 6.1(a) and aortic cross-clamp times ranged between 13 and 58 minutes (41[12]) fig 6.1(b). CPB duration for intra-cardiac surgery ranged from between 44 and 271 minutes (103 [57]), fig 6.1(c), and aortic cross-clamp times ranged from 34 to 234 minutes (72[48]) fig 6.1(d).

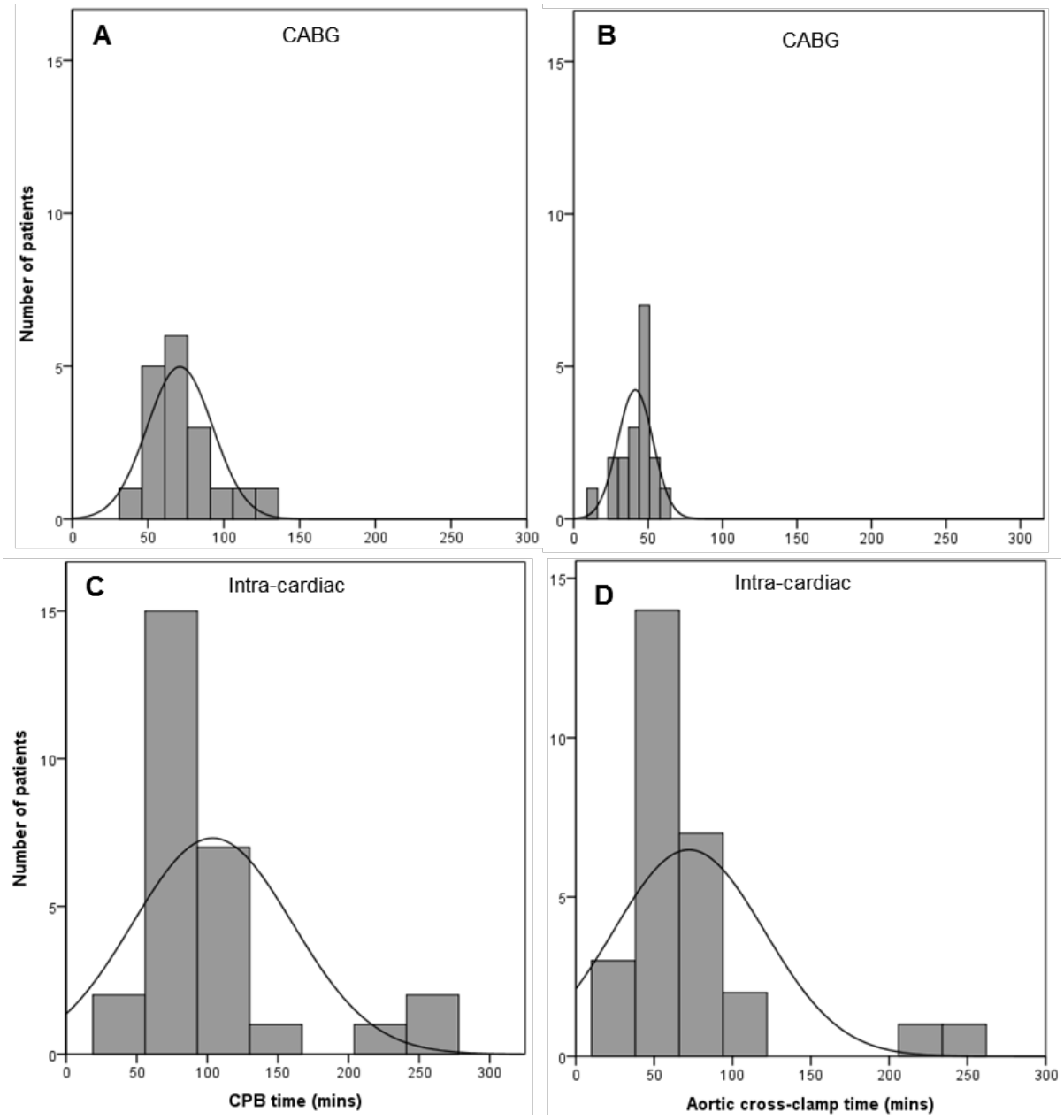


Figure 6.1 (A) CPB time for CABG, (mean [SD]) 71 [22]), (B) aortic cross-clamp time for CABG, (41[12]), (C) CPB time for intra-cardiac (103 [57]), and (D) aortic cross-clamp for intra-cardiac (72[48]) (n=77).

6.2.3 Blood pressure and haematocrit levels during CPB

Blood pressure

Arterial blood pressure targets during surgery were based on usual clinical practice. Blood pressure readings were taken every 5 minutes by the perfusionist during CPB,

and the mean blood pressure during CPB for each patient was estimated. Blood pressure typically varied by 5-10 mmHg between recordings. Mean blood pressure varied considerably between patients, ranging from 45 to 85 mmHg with a mean of 62 mmHg, fig 6.2(a).

Haematocrit

Haemodilutional anaemia is inevitable during CPB and has potential to generate ischaemic organ injury. Normal haematocrit values are usually lower in adult females (38-46%) than adult males (42-54%). Haematocrit values can vary during CPB, but the majority of studies suggest that haematocrit less than 22% increases the risk of morbidity and neurological injury (Murphy *et al.*, 2009). Percentage haematocrit was recorded every 3 minutes during CPB and varied between 22% and 38% with a mean value of 29%, fig 6.2(b).

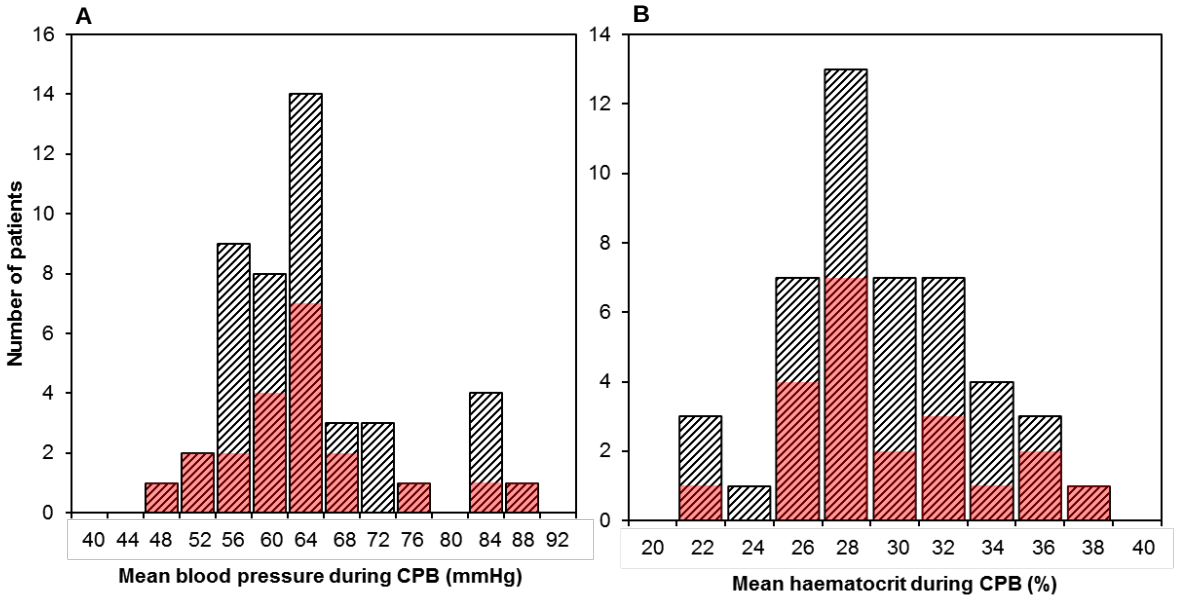


Figure 6.2 Mean blood pressure during CPB (mean [SD]) 62.4 [8.8] (n=46)), (B) mean haematocrit levels during CPB (mean [SD]) 29.0 [3.8] (n=46). Areas shaded red highlight patients experiencing cognitive decline.

6.2.4 Carbon dioxide levels during CPB

Respiratory carbon dioxide (CO_2) measurements provide instantaneous information during surgery about how effectively CO_2 is being eliminated by the pulmonary system

(via ventilation), and how effectively CO_2 is being transported through the vascular system (perfusion). The level of respiratory CO_2 in kilopascals (KPa) was measured every 3 minutes during CPB and varied between 4.3 and 6.4 KPa with a mean CO_2 level of 5.2 KPa, fig 6.3.

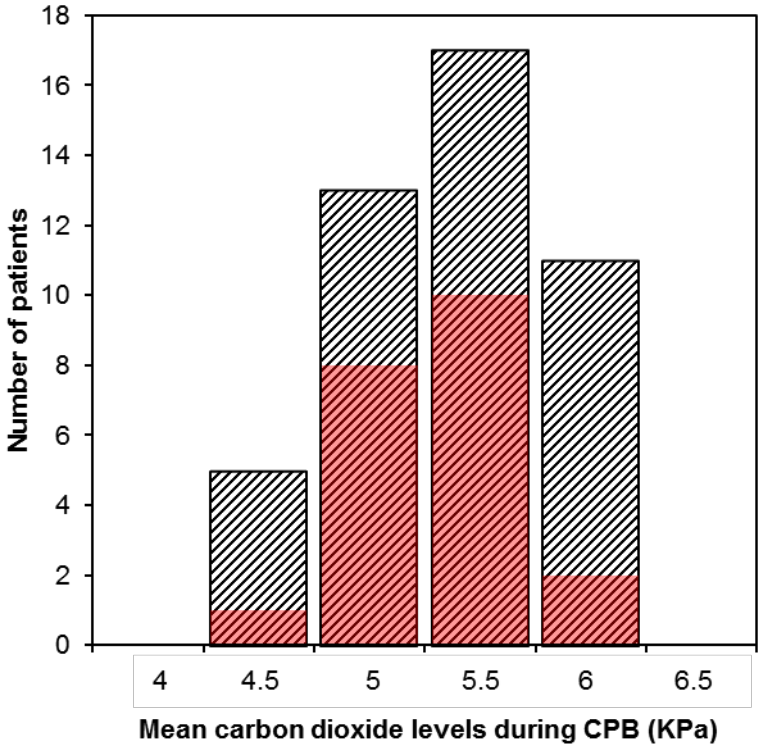


Figure 6.3 Mean carbon dioxide levels during CPB (mean [SD]) 5.2 [0.5] (n=46). Areas shaded red highlight patients experiencing cognitive decline. The normal range of CO_2 levels during CPB are 4.6 – 6.0 KPa outlined in The Society of Clinical Perfusion guidelines (Department of Health, [http://www.scps.org.uk/pdfs/GuidetoGoodPractice.pdf: accessed on 25/08/2014]).

6.2.5 Body temperature and the rate of re-warming during CPB

Temperature

Mild hypothermia is thought to be protective for the brain during surgery by reducing metabolic demand. Body temperature was measured every 3 minutes with a nasal pharyngeal temperature probe. The majority of our patients were operated on under mild hypothermia, during which the average body temperature during CPB was lowered

to between 30°C and 34°C with a mean temperature of 32°C. Seven patients were not cooled, fig 6.4(a).

Rate of re-warming

The average rate of re-warming was calculated by subtracted the first reading after the commencement of re-warming from the last reading of the temperature before re-warming. The distribution of re-warming rates is summarised in fig 6.4(b). Patients under '0' on the histogram were not cooled during their surgery.

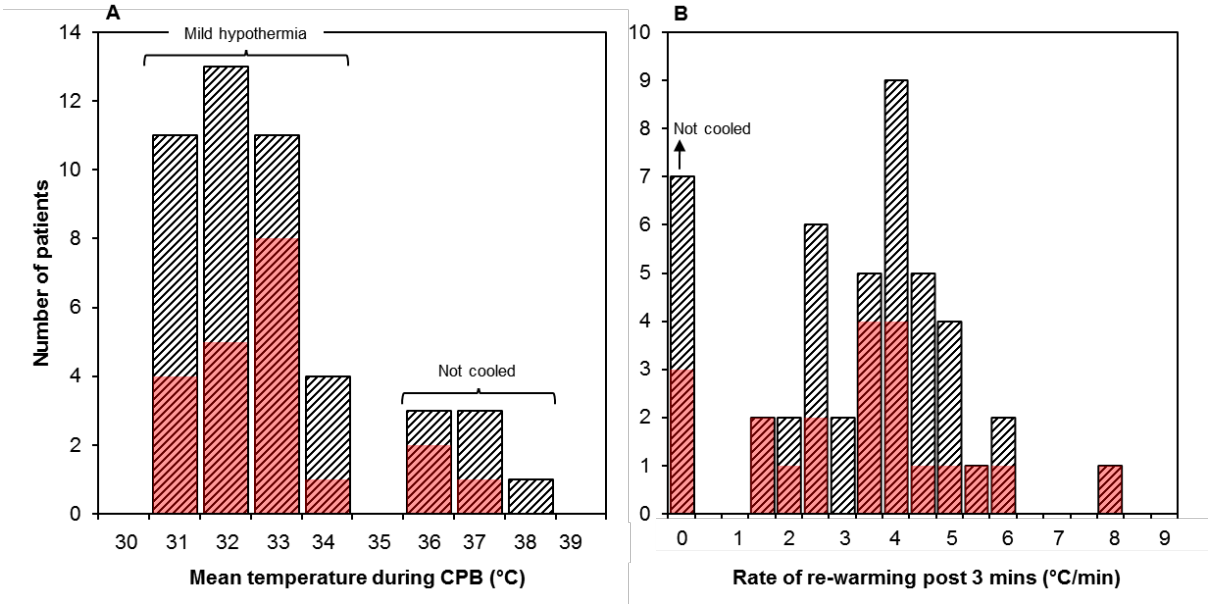


Figure 6.4 (A) Average body temperature during CPB (mean [SD]) 32 [1.7] (n=46), (B) average rate of re-warming during surgery (mean [SD]) 5.2±0.5 (n=46). Areas shaded red highlight patients experiencing cognitive decline.

Blood pressure, haematocrit, carbon dioxide and temperature readings were similar between procedure types (table 6.2) in patients with and without new MRI lesions (table 6.3), and in patients with and without cognitive decline (table 6.4), with the exception of patient age which was significantly higher in patients experiencing cognitive decline (*t*-test: p=0.022). The rate of rewarming was significantly higher during intra-cardiac procedures (*t*-test: p=0.039).

Table 6.2 Comparison of age, blood pressure, haematocrit, CO_2 levels, temperature and re-warming (post 3 mins) during CPB with type of procedure. All values describe median and IQR.

	CABG *n* =18		**Intra-cardiac** *n* =28		***p*-value**
Age (years)	67	61-73	64	56-71	0.150*
Blood pressure	62	56-70	60	55-64	0.213*
Haematocrit	29	26-32	28	27-31	0.935*
Carbon dioxide levels	5	4-5	5	5-6	0.233*
Temperature	32	31-34	32	31-33	0.695*
†Re-warm temp.	3	2-4	4	3-5	0.039*

IQR; Interquartile Range (25^{th} – 75^{th} percentile) AxC; Aortic cross-clamp, CPB; cardiopulmonary bypass, **t*-test, significant factors are highlighted, †7 patients were not cooled, CABG: 15 patients, Intra-cardiac: 24 patients.

Table 6.3 Comparison of age, blood pressure, haematocrit, CO_2 levels, temperature and re-warming (post 3 mins) during CPB in patients with and without new MRI lesions. All values describe median and IQR.

	No new MRI lesions *n* =28		**New MRI lesions** *n* =18		***p*-value**
Age (years)	64	56-72	66	61-71	0.568*
Blood pressure	61	56-63	62	59-65	0.828*
Haematocrit	29	27-31	28	26-31	0.571*
Carbon dioxide levels	5	5-6	5	5-6	0.426*
Temperature	31	31-33	32	31-36	0.151*
†Re-warm temp.	4	3-5	4	3-4	0.887*

IQR; Interquartile Range (25^{th} – 75^{th} percentile), AxC; Aortic cross-clamp, CPB; cardiopulmonary bypass, **t*-test, †7 patients were not cooled, No new lesions: 26 patients, New MRI lesions: 13 patients.

Table 6.4 Comparison of age, blood pressure, haematocrit, CO_2 levels, temperature and re-warming (post 3 mins) during CPB in patients with and without cognitive decline. All values describe median and IQR.

	No cognitive decline *n* =25		**Cognitive decline** *n* =21		***p*-value**
Age (years)	62	56-70	68	63-72	0.022*
Blood pressure	61	59-67	61	59-64	0.695*
Haematocrit	29	26-31	28	27-31	0.642*
Carbon dioxide levels	5	5-6	5	5-5	0.445*
Temperature (during CPB)	32	31-33	32	31-33	0.792*
†Re-warm temp.	4	3-4	4	3-5	0.588*

IQR; Interquartile Range (25^{th} – 75^{th} percentile), AxC; Aortic cross-clamp, CPB; cardiopulmonary bypass. **t*-test, significant factors are highlighted, †7 patients were not cooled, No cognitive decline: 21 patients, Cognitive decline: 18 patients.

6.3 Timing of emboli during cardiac surgery

By manually analysing data from the entire procedure, and comparing the timing of the emboli showers with detailed intraoperative transcripts, we were able to identify sources of embolic showers during surgery. This was used to determine the number and estimated sizes of bubbles using the embolus analysis software and bubble sizing algorithm previously described in Chapter 3.5.6. Examples of detailed plots for specific patients, illustrating the timing and estimated sizes of individual air bubbles, and estimated total accumulated volume of air, are presented in figs 6.5-6.8. Each marker in the upper panel represents an individual embolic event. The y-axis and marker width indicates estimated bubble diameter and the x-axis displays the time during surgery.

Showers of emboli typically occurred in the left and right MCA simultaneously and included bubbles with a broad distribution of sizes. Showers typically coincided with the introduction and removal of cannulas, preparing and stitching the grafts, and injections. Dense showers, and curtains of emboli containing particularly large bubbles were consistently observed while restarting the heart following removal of the aortic cross-clamp.

To estimate the dynamic impact associated with accumulation and clearance of air bubbles within the vasculature over time, the diameters and timing of the bubbles were used as inputs for a Monte-Carlo simulation (see Chapter 3.6). Patient specific estimates for the instantaneous percentage of obstructed end arterioles in our model are plotted as the solid line in the lower panels of figures 6.5 to 6.8. Where possible, examples of patients have been selected to include patients undergoing differing procedures and with differing cognitive and MRI outcome.

Patient 39: AVR/CABG, POCD, no new MRI lesions

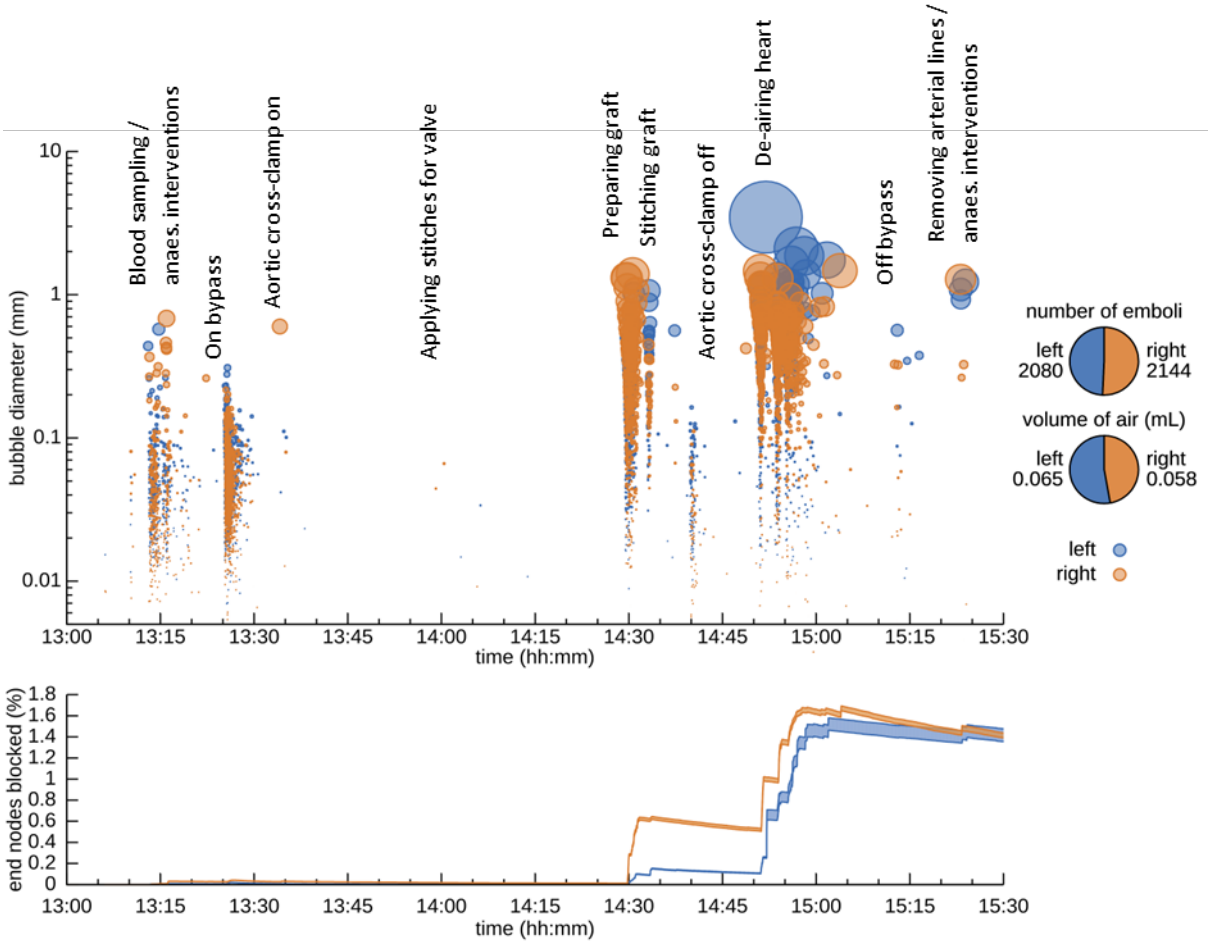


Figure 6.5 Bubble diameters estimated for patient 39 undergoing AVR/CABG. Each marker denotes an individual embolic event (blue: left MCA events, orange: right MCA events). The y-axis and marker size indicates estimated bubble diameter displayed on a log scale. The lower panel displays the predicted number of blocked arterioles obtained by Monte-Carlo simulation. The inset on the right-hand side summarises estimated total number of emboli and volume of air.

Figure 6.5 shows data from a 55 year old male with POCD (2/8 tests: delayed memory, *z*-score change: -2.12/grooved pegboard (non-dom.) *z*-score change: -5.14) with no new MRI lesions. This patient received a total of 4224 emboli with a total estimated volume of air of 0.12 ml. He had a CPB time of 102 mins (aortic cross-clamp time: 71 mins) with no major complications reported in the surgical transcript. Showers can be seen during blood sampling and anaesthetic interventions, initiation and weaning from bypass, stitching of grafts, release of the aortic cross-clamp and de-airing of the heart. The largest bubbles were seen after the release of the aortic cross-clamp, estimated to be

up to ~3.48 mm in diameter (approximately the diameter of the MCA). Monte-Carlo simulations predicted <2% obstruction in both the left and right MCAs. The highest percentage of blocked end nodes appeared to be following the release of the aortic cross-clamp during de-airing (~1.8%).

Patient 20: AVR, POCD, 1 new MRI lesion

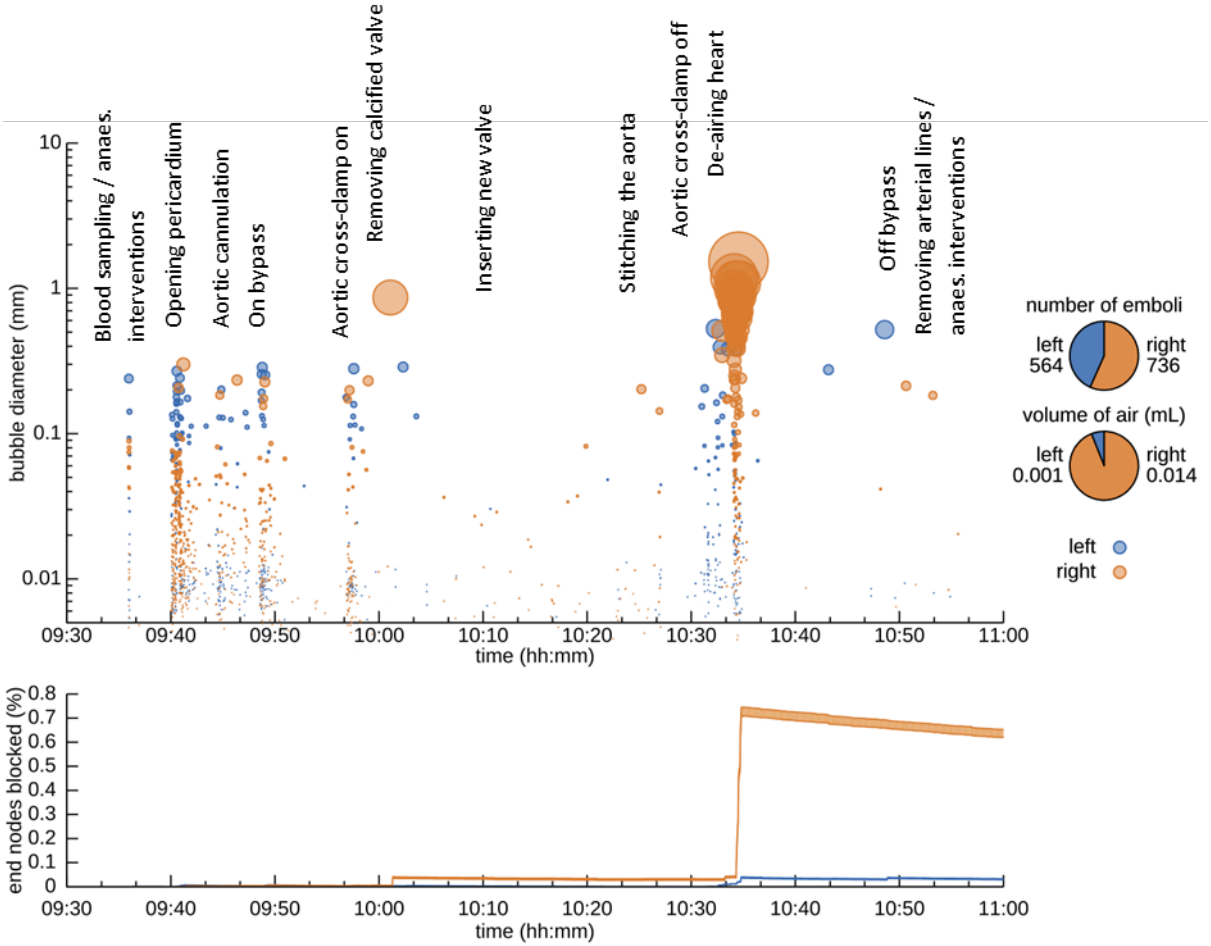


Figure 6.6 Bubble diameters estimated for patient 20 undergoing AVR. Markers denote individual embolic events (blue: left MCA events, orange: right MCA events) where the y-axis and marker size indicate estimated bubble diameter. The lower panel displays the predicted number of blocked arterioles obtained by Monte-Carlo simulation. The inset on the right summarises estimated total number of emboli and volume of air.

Figure 6.6 presents data from a 71 year old female with POCD (1/8 tests: grooved pegboard (dom.) *z*-score change: -1.23) and one new MRI lesion (309 mm^3 in the left-lateral lenticulostriate territory). This patient received a total of 1300 emboli with a total estimated volume of air of 0.02 ml. She had a CPB time of 66 mins (aortic cross-clamp time: 45 mins) with no major manoeuvres reported in the surgical transcript. Showers

were observed during surgical interventions (aortic cannulation and the opening of the pericardium). Large bubbles were observed in the right MCA during de-airing with the largest bubble estimated to be ~1.7 mm. Monte-Carlo simulations predicted <1% obstruction of the model vasculature in the right MCA, following the release of the aortic cross-clamp (~0.7%).

Patient 4: CABG, no POCD, 1 new MRI lesion

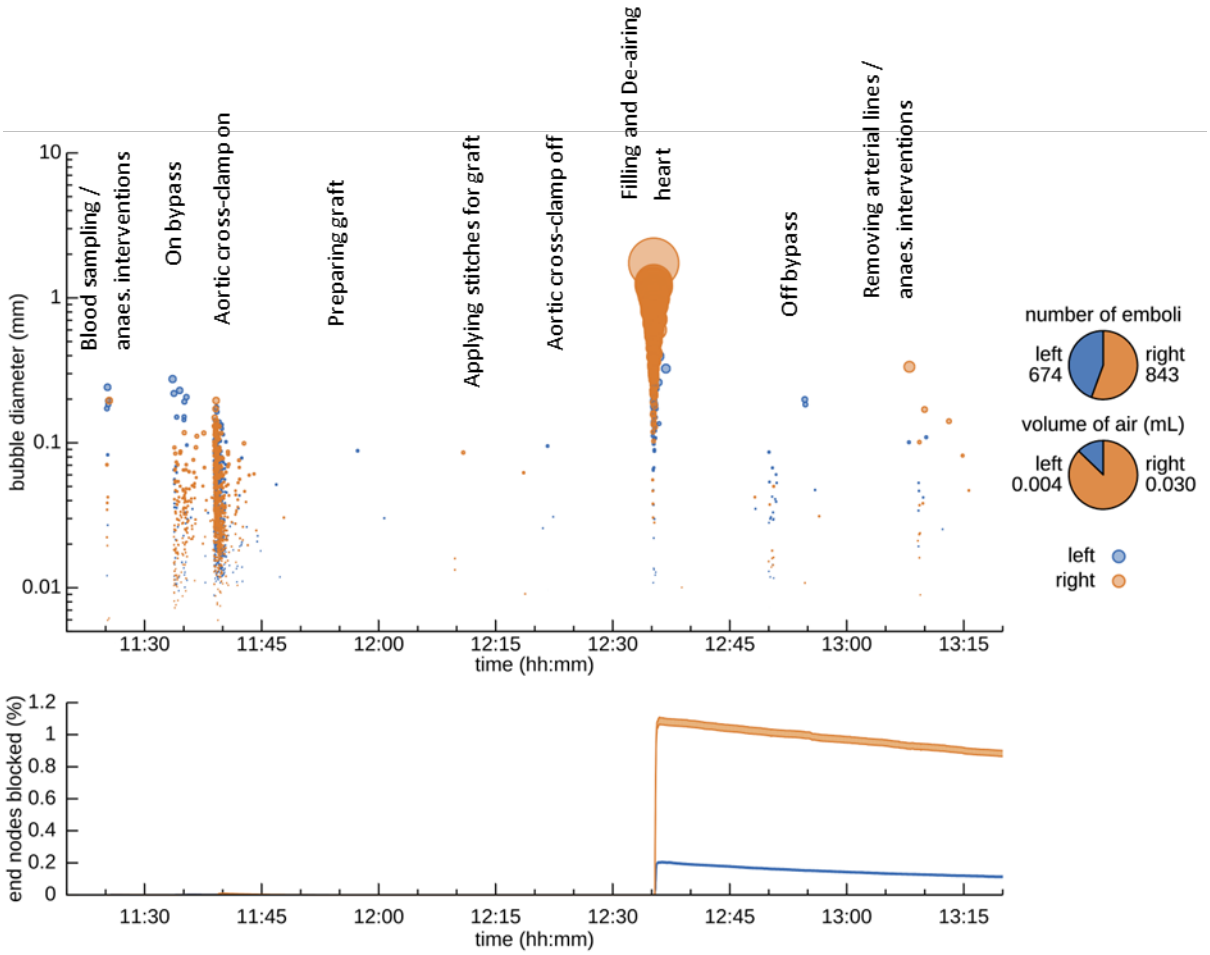


Figure 6.7 Bubble diameters estimated for patient 4 undergoing CABG. Markers denote individual embolic events (blue: left MCA events, orange: right MCA events) where the y-axis and marker size indicate estimated bubble diameter. The lower panel displays the predicted number of blocked arterioles obtained by Monte-Carlo simulation. The inset on the right summarises estimated total number of emboli and volume of air.

Figure 6.7 Presents data from a 71 year old female with no POCD and one new MRI lesion (1383 mm^3/right-MCA territory). This patient suffered from perioperative stroke confirmed radiologically to be a lacunar infarct in the right corona radiata. This patient

received a total of 1517 emboli with a total estimated volume of air of 0.03 ml. She had a CPB time of 108 mins (aortic cross-clamp time: 40 mins) with no major complications reported in the surgical transcript. Larger bubbles for this patient coincided with de-airing and filling the heart with blood with the largest bubble estimated to be ~1.92 mm. Monte-Carlo simulations predicted these bubbles to transiently obstruct just over 1% of the right MCA, and ~0.2% of the left MCA.

Patient 45: MVR/TVR, POCD, no new MRI lesions.

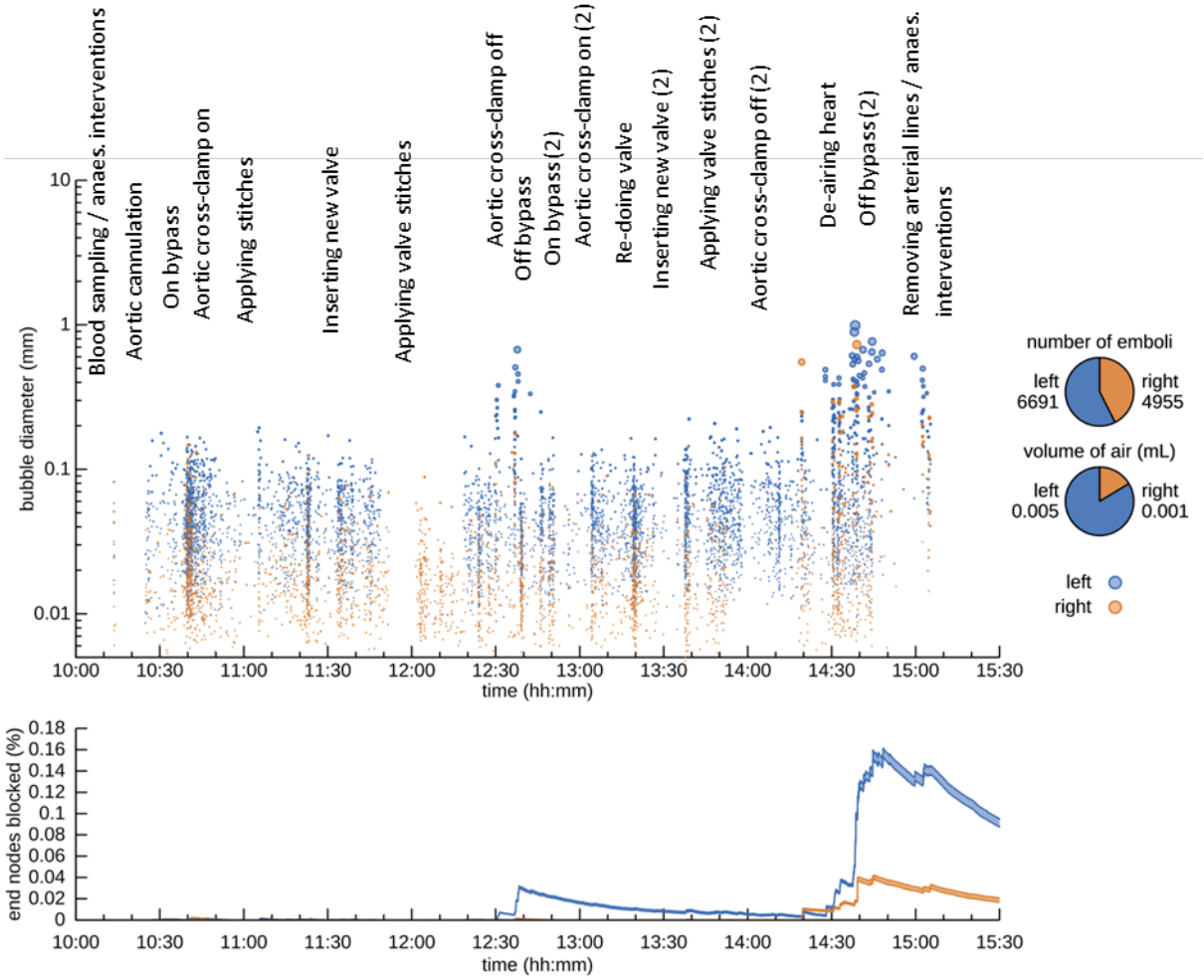


Figure 6.8 Bubble diameters estimated for patient 45 undergoing MVR/TVR. Markers denote individual embolic events (blue: left MCA events, orange: right MCA events). The y-axis and marker size indicate estimated bubble diameter. The lower panel displays the predicted number of blocked arterioles obtained by Monte-Carlo simulation. The inset on the right summarises the estimated total number of emboli and volume of air.

Figure 6.8 presents data from a 72 year old male with POCD (1/8 tests: grooved pegboard (non-dom) *z*-score change: -2.86) and no new MRI lesions who underwent MVR/TVR. This patient received a total of 11646 emboli with a total estimated volume of air of 0.006 ml. He had a CPB time of 271 mins (aortic cross-clamp time: 225 mins). The number of emboli received by this patient was over 3 times greater than the average number. This patient underwent successful tricuspid valve replacement but unfortunately the mitral valve surgery had to be repeated, which is the reason why CPB was reinitiated at 12:48 pm. This patient experienced high numbers of emboli throughout CPB but did not receive any large macrobubbles and 95% of the bubbles detected were estimated to be less than <0.1 mm. The largest bubble this patient received was estimated to be 0.99 mm in diameter during de-airing. Monte-Carlo simulations predicted ~0.16% obstruction of the model vasculature in the left MCA and ~0.04% in the right MCA during de-airing of the heart and weaning from bypass.

Our Monte-Carlo simulations confirm that small showers of filtered bubbles (<40 μm) occurring during bypass do not have any negative impact on cerebral blood flow. The greatest threat to perfusion due to bubbles was consistently predicted to occur due to unfiltered bubbles in the later stages of surgery (following the removal of aortic cross-clamp).

6.3.1 Application and release of the aortic cross-clamp

As seen from figures 6.5-6.8, showers typically coincided with the introduction and removal of cannulas, preparing and stitching the grafts, and injections. Dense showers containing largest bubbles were consistently seen after restarting the heart following the release of the aortic cross-clamp. Bubbles occurring during CPB were found to be numerous but were estimated to be considerably smaller than those entering during the later stages of the surgery.

The majority of emboli were generated at stage 1 of the procedure (from the start of the surgery to the release of the aortic cross-clamp) (61385) compared to stage 4 (30830) release of aortic cross-clamp to the end of surgery. Approximately two-thirds of bubbles (67%) occurred prior to release of the aortic cross-clamp, fig 6.9(a).

The estimated median bubble diameter of 30 µm (IQR: 20 to 40 µm) prior to the release of the aortic cross-clamp is consistent with the use of a 38 µm filter, which is positioned in the aortic line of the CPB circuit. The majority of large bubbles were observed as the heart begins to eject following removal of the aortic cross-clamp. Although signals observed following the removal of the aortic cross-clamp only contributed to 33% of embolic signals, their estimated median diameter, and the spread of bubble sizes, was considerably broader, 56 µm (IQR: 20 to 72 µm) than during CPB (median [IQR] diameter (µm); 30 [20-40]), (p=0.009, t-test). Figure 6.9(b) presents the size distribution of bubbles for all 46 patients in stages 1 and 4.

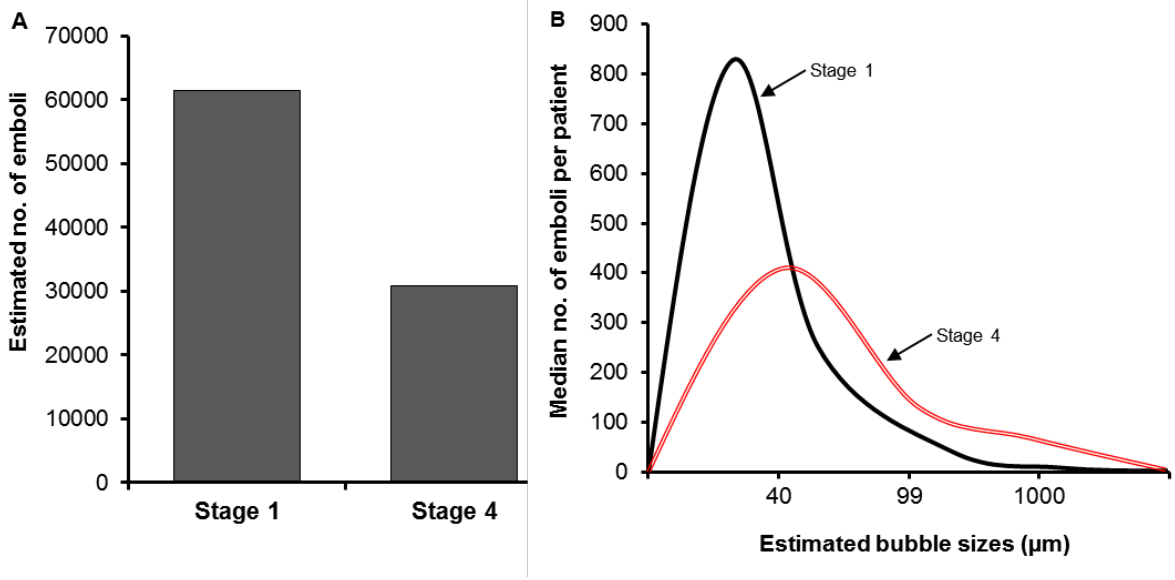


Figure 6.9 (A) Estimated number of emboli during Stage 1; start of surgery to removal of aortic-cross clamp, Stage 4; release of aortic cross-clamp to end of surgery. (B) Size distribution of emboli at stages 1 and 4 for all patients.

6.3.2 One minute following application and release of the aortic cross-clamp

Embolic signals associated with the application and removal of arterial clamps were noted in patients undergoing CABG during release of the cross-clamp in 48 patients with severe aortic atheroma burden of which 7 (15%) had new ischaemic lesions (Kumral *et al.*, 2001). Therefore embolic signals detected during the release of the aortic cross-clamp are of particular interest, since these are likely to contain solid emboli, which are potentially more hazardous than air.

We noted similar numbers of emboli in the minute following aortic cross-clamp application (median: 14.5) and release of the aortic cross-clamp (median: 17.5) (Mann Whitney U test, p=0.568). However, large macro-bubbles were more frequent following release of the aortic cross-clamp, with an average maximum diameter of 61 µm during CPB (IQR: 26 to 81) compared to 1160 µm (IQR: 510 to 1760 µm) (p=0.001, t-test). The largest bubble detected during our study was estimated to be ~3.48 mm, approximately the size of the MCA (patient 39).

6.4 Total number and distribution of emboli and volume of air

Bilateral MCA monitoring of 46 patients during their surgery revealed a total of 92215 individual embolic signals over 115 hours of recordings. Details of the patient's age and sex, type of surgery, duration of CPB, aortic-cross clamp time, numbers of emboli, curtain duration, estimated total volume of air and tests exhibiting cognitive decline are listed in table 6.5 (page 150). A total of 49485 (54%) emboli were detected in the left MCA and 42730 (46%) detected in the right MCA (fig. 6.10). Total numbers of emboli entering the MCAs during a single operation varied from 203 (patient 11) to 11646 (patient 45).

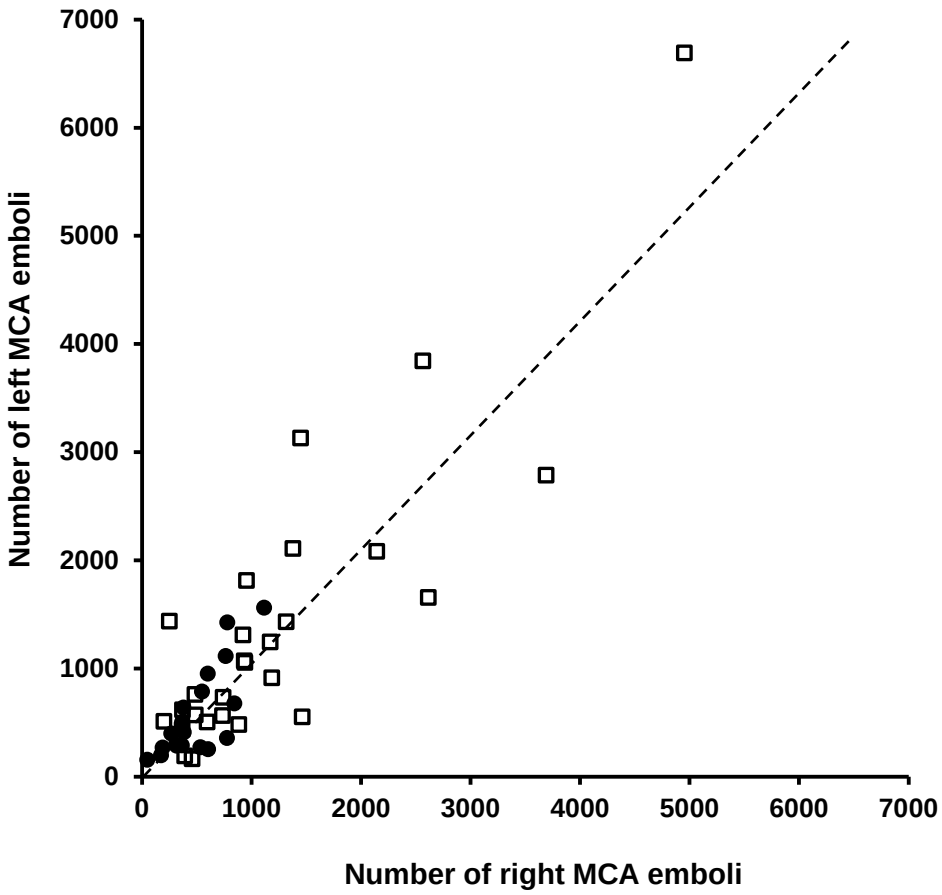


Figure 6.10 Total numbers of emboli entering the right/left MCA for all 46 patients**.** CABG patients are marked with ● and intra-cardiac patients with □.

Conversion of bubble diameters to volume of air (using $V = \frac{4}{3}\pi r^3$) was used to estimate the total volume of air entering the MCA territories for each patient. The estimated total volume of air entering the left MCA was 410 µl and 490 µl in the right MCA (fig. 6.11).

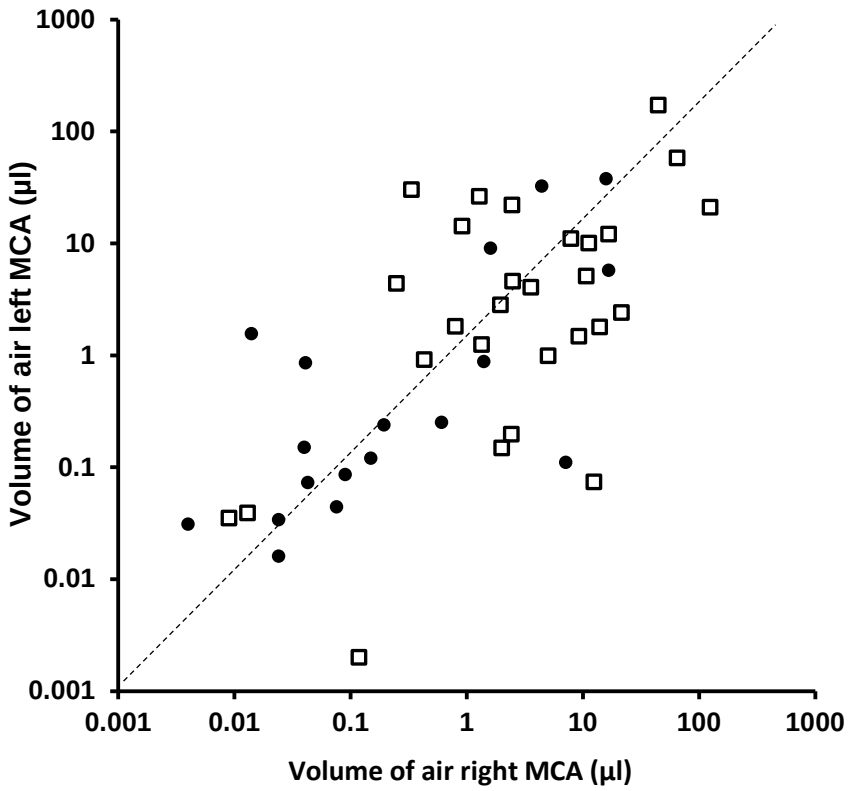


Figure 6.11 Estimated total volume of air (µl) entering the right/left MCA (*n*=46). CABG patients are marked with ● and intra-cardiac patients with □.

The estimated volumes of air entering the MCAs of individual patients ranged between 0.04 µl (patient 9, 16 and 28) and 216 µl (patient 30). Patients undergoing intra-cardiac procedures tended to receive a higher volume of air than CABG patients. Although bubble diameters ranged from 6.3 µm to 3.4 mm, the majority (87%) were less than 100 µm (fig 6.12). Patient-specific bubble sizing revealed that 87.1% of bubbles were less than 100 µm and only 0.3 % of bubbles were larger than 1 mm, fig 6.12.

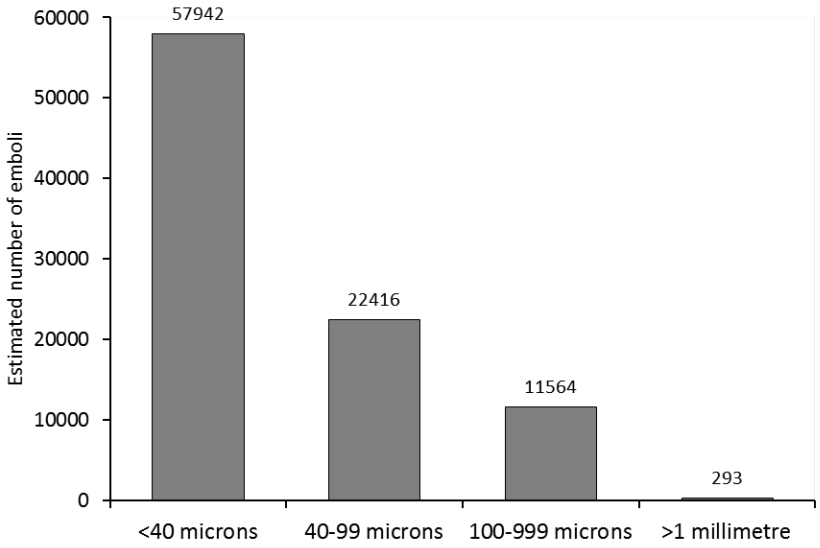


Figure 6.12 Estimated diameters of bubbles received during surgery

Larger bubbles were more frequent during intra-cardiac procedures compared to CABG. Median bubble diameters were 20 µm during CABG and 30 µm during intra-cardiac surgery, but the upper size limit was considerably extended (fig 6.13).

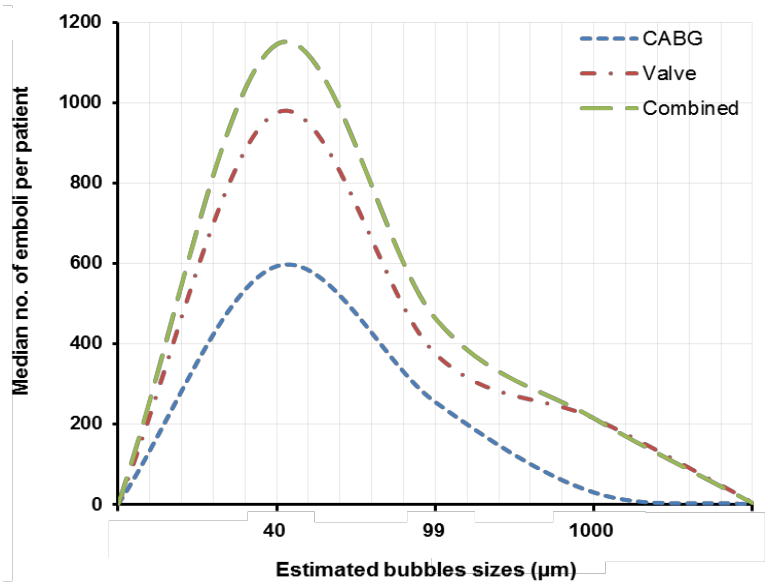


Figure 6.13 Distribution of estimated bubbles sizes for CABG (*n*=865 emboli), valve (*n*=1995 emboli), and combined (*n*=2769 emboli) procedures shows that more complex intra-cardiac procedures attract a significantly higher number of large bubbles (>100 µm).

Bar charts showing patients ranked in order of the number of embolic signals received suggests that the number and sizes of bubbles are unrelated to cognitive decline. The distribution of bubble diameters for patients undergoing CABG, valve surgery and combined procedures are shown in fig 6.14, 6.15 and 6.16 respectively.

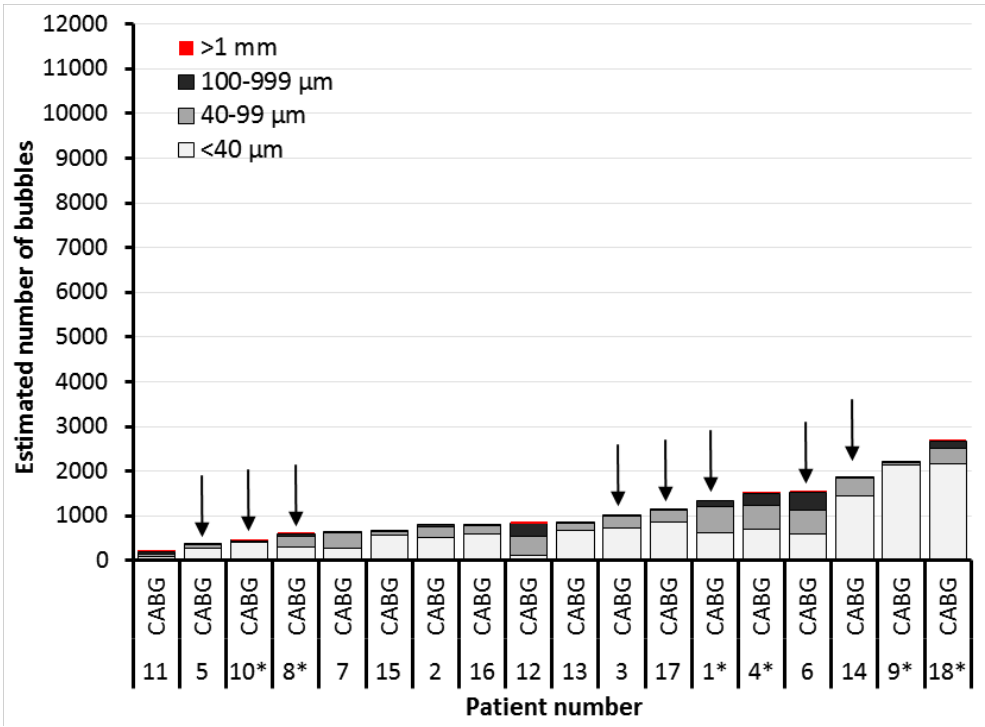


Figure 6.14 Total estimated numbers of bubbles detected for each patient undergoing CABG, ranked in order of the total number of emboli. Patients exhibiting POCD in at least one test are indicated by the arrows. * denotes patients with new MRI lesions.

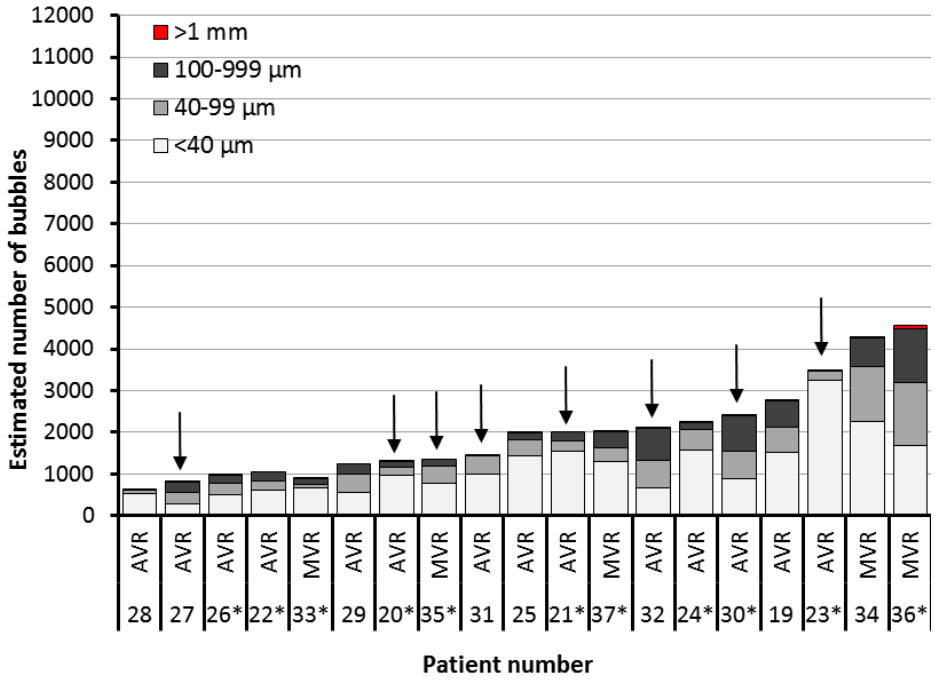


Figure 6.15 Total estimated numbers of bubbles detected for each patient undergoing valve procedures, ranked in order of the total number of emboli. Patients exhibiting POCD in at least one test are indicated by the arrows. * denotes patients with new MRI lesions.

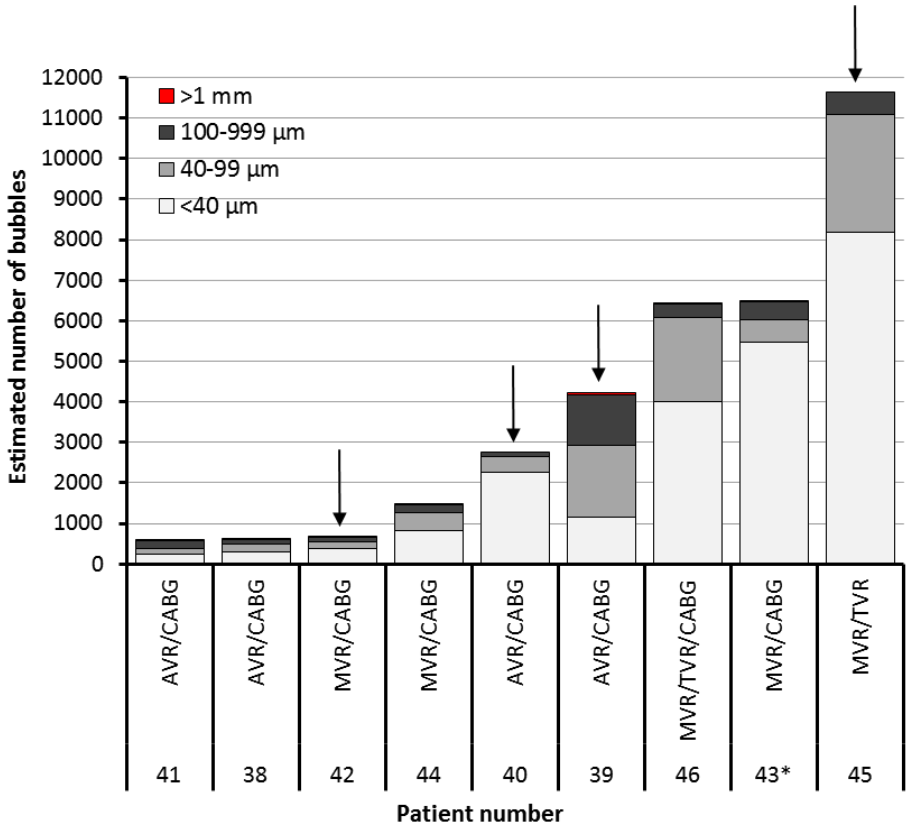


Figure 6.16 Total estimated numbers of bubbles detected for each patient undergoing combined procedures, ranked in order of the total number of emboli. Patients exhibiting POCD in at least one test are indicated by the arrows. * denotes patients with new MRI lesions.

Higher numbers of emboli were experienced in patients undergoing valve and combined procedures. Visual inspection suggested no correlation between receiving high numbers of macrobubbles, or a high total number of bubbles with cognitive decline or new MRI lesions.

A detailed summary of the patients' surgical characteristics and neurological outcome is provided in table 6.5. Patients are listed in order of procedure, showing their respective blood pressure (BP), haematocrit (HCT), carbon dioxide levels (CO_2) and body temperature (temp.), all measured during CPB. CPB and aortic cross-clamp times are also shown together with the total number emboli and number of emboli detected in the left and right MCA. Where emboli were too numerous to be individually analysed, curtain duration for each patient was noted in seconds. The estimated volume of air is given in µl. The table also presents the number of tests exhibiting cognitive decline for each patient and the number and volume (mm^3) of new MRI lesions.

Table 6.5 Detailed summary of age, sex, type of procedure, blood pressure (BP), haematocrit (HCT), carbon dioxide levels (CO_2), body temperature during CPB (temp.), cardiopulmonary bypass (CPB) duration, aortic cross-clamp (AxC) duration, total number of emboli, length of dense embolic showers (curtain) total volume of air, and outcome of MRI and neurocognitive testing for all 46 patients whose TCD recordings were analysed in detail.

Patient no.	Sex/Age	Surgical procedure	Mean values				CPB (AxC) (mins)	Total number of emboli			Length of curtain (secs)	Estimated total volume of air (µl)	No. of tests exhibiting cognitive decline	New MRI lesions No./volume (mm^3)
			BP (mm Hg)	HCT (%)	CO_2 (l/min)	Temp. (°C)		Left	Right	Total				
1	M/61	CABG	62.8	31.0	5.3	31.9	77 (55)	784	549	1333	0	0.86	5	1/17
2	M/60	CABG	54.8	31.0	4.8	31.0	73 (39)	409	383	792	0	0.27	0	0
3	M/65	CABG	83.4	28.4	5.0	35.7	48 (34)	636	380	1016	0	0.06	6	0
4*	F/71	CABG	80.5	22.2	5.6	32.2	108 (40)	674	843	1517	0	36.83	0	1/1383
5	M/71	CABG	74.6	27.9	4.7	31.4	76 (48)	196	175	371	0	0.19	4	0
6	M/76	CABG	55.2	35.9	5.0	32.3	86 (45)	950	601	1551	37	22.46	1	0
7	M/68	CABG	55.7	22.2	4.5	33.9	54 (24)	286	364	650	0	0.12	0	0
8	M/69	CABG	53.1	26.1	5.8	30.3	58 (43)	284	317	601	0	2.29	4	1/51
9	M/63	CABG	80.7	33.1	4.6	36.3	66 (47)	1423	779	2202	0	0.04	0	1/63
10*	M/66	CABG	59.6	27.9	5.2	33.1	95 (44)	267	191	458	0	1.57	1	1/175
11	M/77	CABG	61.8	25.2	5.5	33.5	75 (47)	154	49	203	4	7.24	0	0
12	M/57	CABG	62.6	27.9	4.5	31.5	62 (50)	253	606	859	10	53.61	0	0
13	M/77	CABG	57.4	31.8	5.2	32.4	54 (25)	503	367	870	0	0.43	8	0
14	M/72	CABG	62.0	32.6	4.7	32.1	53 (33)	1114	766	1880	0	0.12	7	0
15	M/56	CABG	63.2	29.6	5.3	31.1	74 (56)	398	268	666	0	0.90	0	0
16	M/53	CABG	69.1	29.3	5.4	30.9	62 (44)	270	534	804	0	0.04	0	0
17	F/62	CABG	62.7	26.4	4.4	36.1	35 (13)	354	777	1131	0	0.18	7	0
18	M/76	CABG	60.3	31.8	5.6	31.0	122 (58)	1559	1116	2675	110	10.63	0	2/49
19	M/62	AVR	56.0	27.8	5.5	31.8	80 (42)	1429	1319	2748	18	15.77	0	0
20	F/71	AVR	60.7	25.1	5.6	30.7	66 (45)	564	736	1300	102	15.18	7	1/309
21	M/59	AVR	62.6	37.6	5.3	32.6	89 (58)	1069	936	2005	10	1.35	6	1/28

22	M/46	AVR	68.5	27.6	5.6	31.6	80 (44)	568	489	1057	0	2.61	0	1/26
23	M/80	AVR	51.6	21.4	5.3	35.8	65 (42)	2107	1378	3485	664	0.05	7	2/167
24*	M/50	AVR	55.0	28.3	4.4	31.0	63 (35)	1308	922	2230	12	7.62	0	2/389
25	M/59	AVR	80.9	35.9	5.1	32.6	71 (46)	1055	940	1995	96	4.62	0	0
26	M/65	AVR	62.6	26.5	5.8	30.9	120 (80)	617	371	988	86	27.56	0	1/15
27	M/78	AVR	59.5	25.7	5.0	31.1	62 (36)	434	367	801	110	23.88	5	0
28	M/54	AVR	58.3	34.3	5.7	32.0	87 (63)	164	458	622	20	0.04	0	0
29	M/72	AVR	69.8	29.6	5.7	32.8	92 (64)	757	485	1242	18	2.16	0	0
30	M/68	AVR	64.9	30.5	5.3	32.4	87 (65)	1244	1172	2416	0	216.00	6	1/67
31	M/54	AVR	56.5	26.8	4.6	32.8	112 (85)	1435	41	1476	40	0.12	7,8	0
32	M/63	AVR	86.4	28.2	5.0	31.4	72 (45)	911	1185	2096	28	18.86	6	0
33	M/71	MVR	61.1	30.2	6.0	31.4	75 (50)	502	596	1098	14	21.30	0	2/224
34	M/41	MVR	52.8	31.0	4.8	31.4	153 (105)	1656	2616	4272	74	30.45	0	0
35	M/64	MVR	65.3	28.3	5.2	32.4	100 (77)	480	886	1366	62	2.59	2,8	1/5
36*	M/64	MVR	59.7	27.4	4.6	35.9	64 (46)	3130	1449	4579	140	145.51	0	1/81
37*	M/57	MVR	55.7	26.1	4.3	37.1	44 (34)	550	1465	2015	2178	28.73	0	5/979
38	M/64	AVR/CABG	59.6	31.5	5.4	30.8	80 (50)	509	88	597	0	12.56	0	0
39	M/55	AVR/CABG	51.8	28.7	5.4	31.0	102 (71)	2080	2144	4224	130	122.89	2,8	0
40	M/69	AVR/CABG	60.9	36.4	5.3	31.7	111 (95)	1813	956	2769	180	2.62	8	0
41	M/65	AVR/CABG	60.9	25.3	5.6	33.4	219 (72)	191	391	582	0	7.07	0	0
42	M/66	MVR/CABG	45.7	27.8	4.7	30.5	110 (80)	349	322	671	0	15.80	2	0
43	M/74	MVR/CABG	64.6	33.1	4.6	36.3	53 (55)	2785	3691	6476	0	4.77	0	1/37
44	M/56	MVR/CABG	63.1	22.5	5.8	31.0	119 (80)	730	742	1472	0	24.40	0	0
45	M/72	MVR/TVR	61.4	29.7	5.2	32.4	271 (225)	6691	4955	11646	0	6.03	8	0
46	M/61	MVR/TVR/CABG	54.1	28.7	5.5	31.8	254 (234)	3843	2565	6408	30	10.70	0	0

Patients marked with * had perioperative stroke diagnosed clinically. CABG indicates coronary artery bypass graft; AVR, aortic valve replacement; MVR, mitral valve replacement; TVR, tricuspid valve replacement. Cognitive test 1 indicates immediate memory; 2, Delayed memory; 3, Verbal; 4, Performance; 5, Trail Making A; 6, Trail Making B; 7, Grooved Pegboard (dominant); 8, Grooved Pegboard (non-dominant).

6.5 Comparison of the number, timing and size distribution of emboli to type of procedure, MRI and neuropsychological outcome

6.5.1 Type of procedure

The number and timing of embolic events, and size distribution of emboli, were compared between patients undergoing CABG (*n* =18) and intra-cardiac (*n* =28) procedures. Cardiopulmonary bypass and aortic cross-clamp times were significantly higher in the intra-cardiac group fig 6.1. (Mann Whitney U test, *p*=0.009 and *p*=0.001 respectively), table 6.6.

Patients undergoing intra-cardiac procedures received over twice as many bubbles per procedure [median: 2000 vs. 865] (Mann Whitney U test, *p*=0.004) (fig 6.17(a), & table 6.6), and 7 times as many macro-bubbles [median: 218 vs. 30] (Mann Whitney U test, *p*=0.001) (fig 6.17(b)). However, some intra-cardiac procedures also tended to be associated with longer CPB times (median: intra-cardiac: 87 mins, vs CABG: 69 mins) (fig 6.17(c)) so higher numbers of emboli may also be consistent with a positive correlation between CPB time and number of emboli. The estimated volume of air entering the MCAs ranged from 0.04 µl (patients 9, 16 and 28) to 216 µl (patient 30). A significantly higher volume of air was received during intra-cardiac surgery than CABG [median: 11.6 vs. 0.7 µL] (Mann Whitney U test, *p*=0.005), fig 6.17(d). Of the 92215 bubbles analysed, only 13% were classified as macro-bubbles > 0.1 mm. There was no significant difference in the incidence of new MRI lesions or cognitive decline between procedure types.

Table 6.6 Comparison of CPB duration, total number of emboli, emboli immediately following removal of the aortic cross-clamp, curtain duration, volume of air, bubble diameter, and number of micro (<0.1 mm) and macro (>0.1 mm) bubbles by type of procedure. All values describe median and IQR unless stated otherwise.

	CABG *n* =18		**Intra-cardiac** *n* =28		***p*-value**
CPB duration (mins)	69	54-79	87	67-112	0.009†
Total emboli	865	637-1526	2000	1067-3306	0.004†
Emboli: <0.1 mm	815	545-1200	1498	781-2845	0.013†
Emboli: ≥0.1 mm	30	18-150	218	135-534	0.001†
Emboli: 1 min after removal of AxC	7	2-29	37	7-79	0.103†
Curtain duration (seconds)	0	0-1	24	0-101	0.001†
Bubble diameter (μm)	20	10-30	30	20-40	0.824†
Total volume of air (μL)	0.7	0.1-8.1	11.6	2.6-24.3	0.005†
New FLAIR MRI lesions, *n* (%)	6 (33)	-	12 (43)	-	0.554‡
Neuropsychological decline, *n* (%)	9 (50)	-	12 (43)	-	0.764‡

IQR; Interquartile Range (25^{th} – 75^{th} percentile) AxC; Aortic cross-clamp, CPB; cardiopulmonary bypass, †Mann-Whitney U test, ‡Chi-squared test, significant factors are highlighted

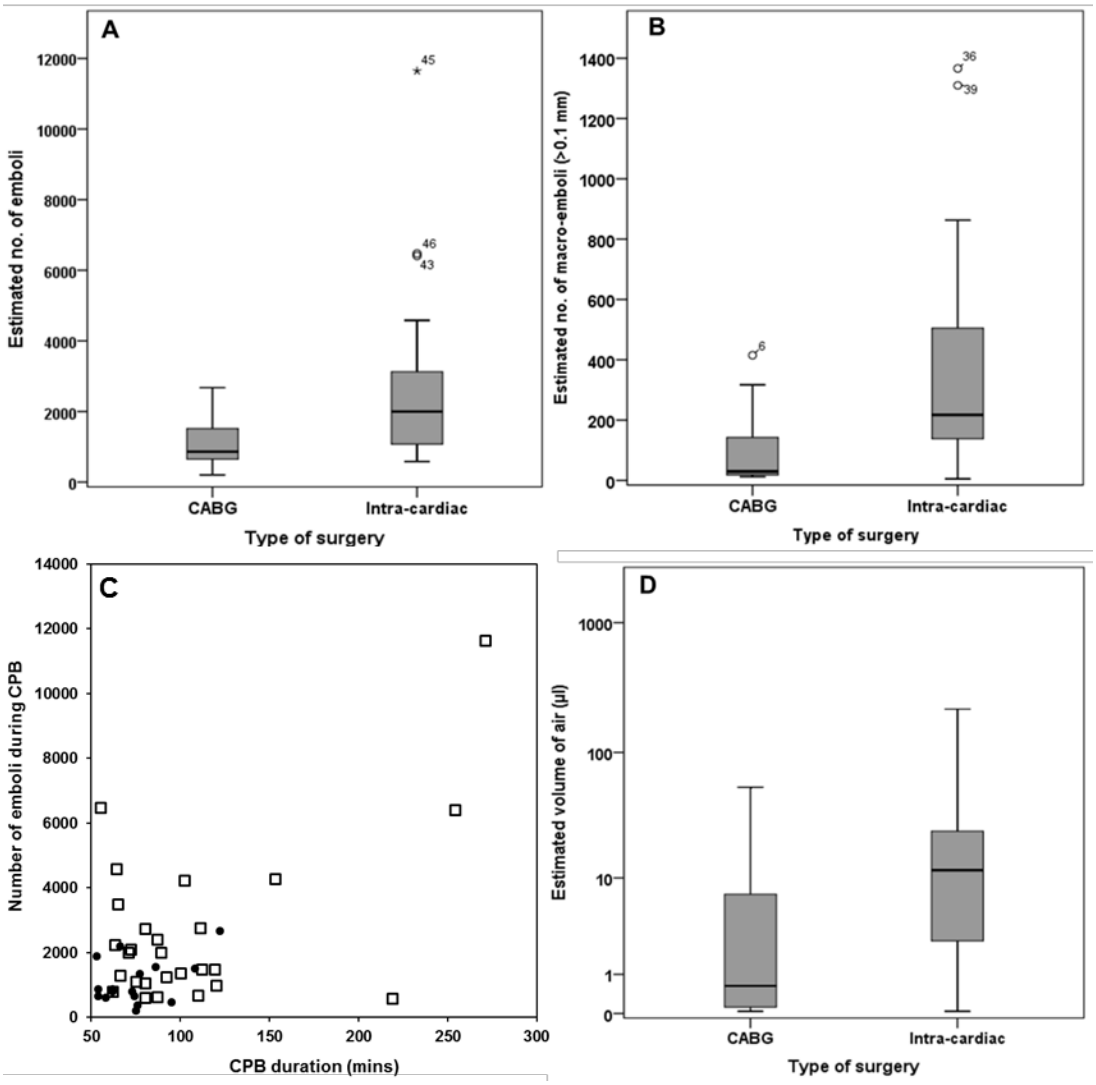


Figure 6.17 (A) Estimated number of emboli (median [IQR]) in CABG (865 [637-1526]) and intra-cardiac procedures (2000 [1067-3306]) (B) Estimated number of macro-emboli in CABG (30 [18-150]) and intra-cardiac procedures (218 [135-534]). (C) The total number of emboli increased slightly with CPB duration. CABG patients are marked with ● and intra-cardiac patients with □. (D) Estimated total volume of air in CABG (0.7 [0.1-8.1])) and intra-cardiac procedures (11.6 [2.6-24.3]). Mild outliers are marked with the patient number and o, extreme outliers are marked with the patient number and * in panels A and B.

6.5.2 Curtain of emboli

Curtains of emboli (seconds) were rarely observed during CABG (median [IQR]: 0 [0-1]) compared to a median curtain duration of 24 [0-101] seconds for intra-cardiac procedures (p=0.001). This is unsurprising given the more invasive nature of open chamber surgery. Figure 6.18 summarises curtain duration with respect to type of procedure and neurocognitive and MRI outcome for individual patients. Visual

inspection suggested no correlation between curtain duration >1 minute and either new MRI lesions or cognitive decline.

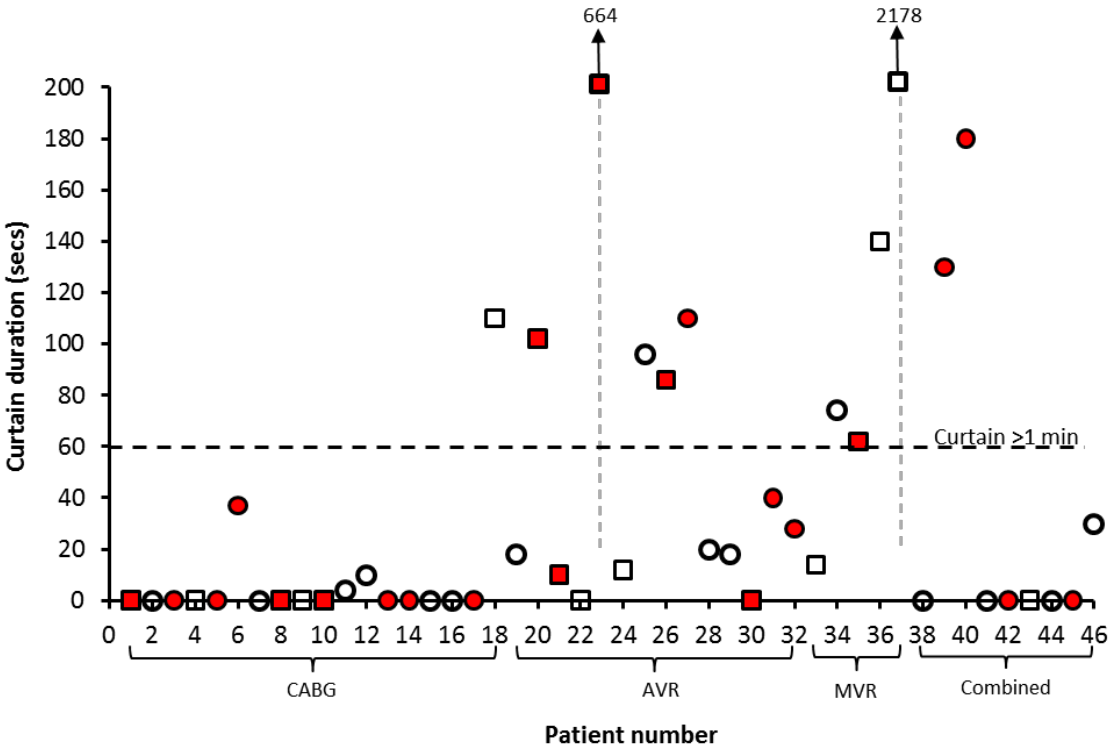


Figure 6.18 Total curtain duration for all 46 operations. o denotes patients with no new MRI lesions, and □ denotes patients with new MRI lesions. Markers filled in red represents patients who experienced cognitive decline in one or more tests (indicated by a *z*-score change ≥1 SD).

6.5.3 Release of the aortic cross-clamp

The number of emboli detected within 1 minute following release of the aortic cross-clamp was over 5 times higher in the intra-cardiac group (37 [7-79]) compared to the CABG group (7 [2-29]), however, due to large variations between patients this did not reach significance (p=0.103) (table 6.6). Additionally, the incidence of large bubbles after the removal of the aortic cross-clamp was also higher in the intra-cardiac group (median [IQR]; 1.53 [0.70-2.14]) compared to the CABG group (median [IQR]; 0.55 [0.15-1.29]) (Mann Whitney U test, p=0.018).

Having explored the data to quantify differences in the number and size of emboli we went on to test the following hypotheses: (i) the total number of emboli, (ii) emboli > 0.1 mm, (iii) volume of air, (iv) curtain duration >60s, or (v) number of emboli detected

1 min following removal of the aortic cross-clamp were linked to the presence of new MRI lesions or cognitive decline.

6.5.4 MRI outcome

The impact of surgical factors, number and timing of embolic events, and size distribution of emboli were tested for patients with (n =18) and without (n =28) new MRI lesions. The median number of emboli was higher in the MRI lesion group (median, [IQR]; 1761 [1087-2480]) compared to patients without new MRI lesions (median, [IQR]; 1073 [667-2070]) but this difference was not significant (Mann Whitney U test, p=0.130). With the current sample size, we found no evidence that bubble size had any significant impact on MRI outcome (table 6.7 and fig 6.19)

Table 6.7 Comparison of CPB duration, total number of emboli, emboli immediately following removal of the aortic cross-clamp, curtain duration, volume of air, bubble diameter, and number of micro (<0.1 mm) and macro (>0.1 mm) bubbles with and without new MRI lesions. All values give median and IQR value unless stated otherwise.

	No new MRI lesions n =28		**New MRI lesions** n =18		***p*-value**
CPB duration (mins)	78	62-110	76	63-96	0.692†
Total emboli	1073	667-2070	1761	1087-2480	0.130†
Emboli: <0.1 mm	1003	561-1846	1390	809-2264	0.159†
Emboli: ≥0.1 mm	131	26-327	171	112-316	0.493†
Emboli: 1 min after removal of AxC	8	0-39	46	11-102	0.037†
Curtain duration (seconds)	2	0-35	11	0-104	0.452†
Bubble diameter (μm)	30	20-40	30	20-40	0.221†
Total volume of air (μL)	5.3	0.2-18.1	6.2	1.5-27.9	0.378†
CABG: intra-cardiac procedures	12:16	-	6:12	-	0.518‡
Neuropsychological decline, *n* (%)	13 (46)	-	8 (39)	-	0.895‡

IQR; Interquartile Range (25^{th} – 75^{th} percentile), AxC; Aortic cross-clamp, CPB; cardiopulmonary bypass, †Mann-Whitney U test, ‡Chi-squared test, significant factors are highlighted

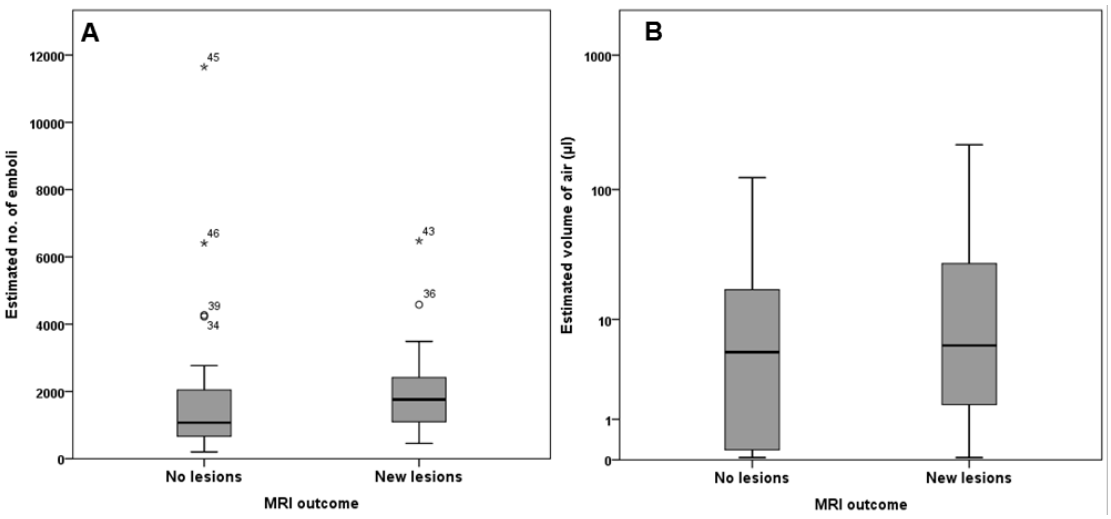


Figure 6.19 (A) Numbers of emboli (median [IQR]) were higher in the new lesions group (1761 [1087-2480]) compared to the no new lesions group (1073 [667-2070]) but this difference was not significant (Mann-Whitney U test: *p*=0.130). (B) There was no significant difference in the estimated volume of air (µl) (median [IQR]) received by the patients with (6.2 [1.5-27.9]) and without (5.3 [0.2-18.1]) new lesions (Mann-Whitney U test: *p*=0.378).

The median value for the total duration of curtains (in seconds) was higher in patients with new lesions (median [IQR]; 11 [0-104]) compared to no new lesions (median [IQR]; 2 [0-35]) but, this difference was not significant (Mann Whitney U test: *p*=0.452). More than half of the patients who experienced 'curtains' lasting longer than 1 minute had new MRI lesions compared to one third of patients where curtains were absent or less than 1 minute. However, this difference was also not significant (Fisher's exact test: *p*=0.170).

The median number of emboli detected within 1 minute of release of the aortic cross-clamp was higher in patients with new lesions (median, [IQR]; 46 [11-102]) compared to patients with no new lesions (median, [IQR]; 8 [0-39]), (Mann Whitney U test, *p*=0.037), fig 6.20. However, this finding was of borderline significance and due to the lack of a correction for multiple testing, this result should be interpreted with caution.

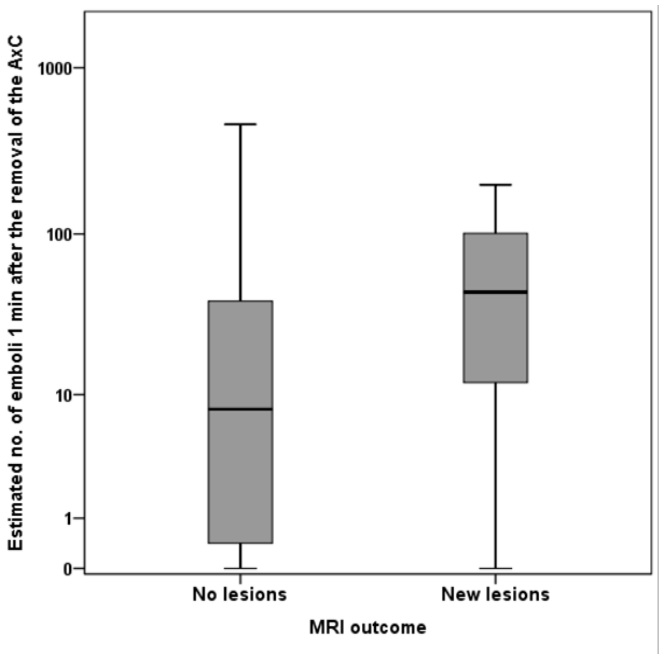


Figure 6.20 Estimated numbers of emboli following release of the aortic cross-clamp (AxC) against MRI outcome for all 46 patients (Mann Whitney U test, p=0.037).

6.5.5 Neuropsychological outcome

Similar embolic burden was observed between patients with cognitive decline vs. no decline (see table 6.8). We found no evidence to support an association between total number of emboli, macro-emboli (≥ 0.1 mm), emboli following aortic cross-clamp removal, total volume of air, or curtain duration, and subsequent cognitive decline (table 6.8). The only significant factor predicting post-operative cognitive decline was age (*t*-test: p=0.022, table 6.4), which is consistent with the findings of previous research (Moller *et al.*, 1998; Carrascal *et al.*, 2005).

Table 6.8 Comparison of CPB duration, total number of emboli, emboli immediately following removal of the aortic cross-clamp, curtain duration, volume of air, bubble diameter, and number of micro (<0.1 mm) and macro (>0.1 mm) bubbles by cognitive outcome. All values give the median.

	No cognitive decline *n* =25		**Cognitive decline** *n* =21		***p*-value**
CPB duration (mins)	75	62-92	71	53-87	0.427†
Total emboli	1357	729-2453	1349	870-2096	0.844†
Emboli: <0.1 mm	1008	632-2153	1191	692-1823	0.874†
Emboli: ≥0.1 mm	194	55-324	132	22-335	0.332†
Emboli: 1 min after removal of AxC	12	4-68	23	2-75	0.839†
Curtain duration (seconds)	10	0-52	0	0-82	0.986†
Bubble diameter (μm)	30	20-40	30	20-40	0.956†
Total volume of air (μL)	7.4	1.5-25.9	2.4	0.2-18.9	0.261†
CABG: intra-cardiac procedures	9:16	-	9:12	-	0.764‡
New FLAIR MRI lesions, *n* (%)	10 (40)	-	8 (38)	-	0.895‡

IQR; Interquartile Range (25^{th} – 75^{th} percentile), AxC; Aortic cross-clamp, CPB; cardiopulmonary bypass, †Mann-Whitney U test, ‡Chi-squared test.

We found no evidence that the number of emboli observed within 1 minute of release of the aortic cross-clamp was linked to adverse cognitive outcome (Mann Whitney U test, p=0.839), fig 6.21.

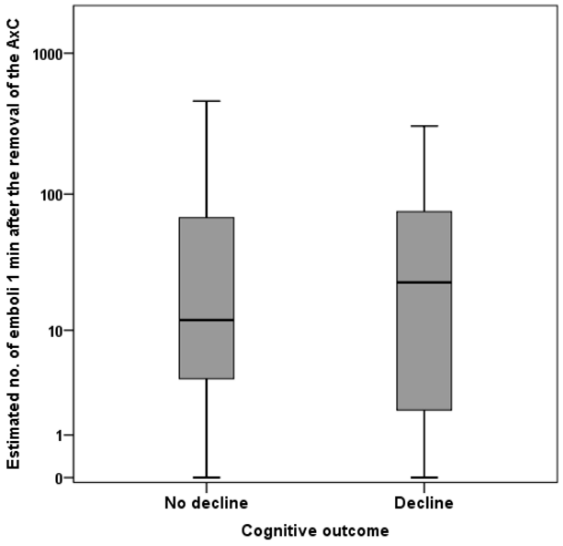


Figure 6.21 Estimated numbers of emboli following release of the aortic cross-clamp (AxC) against cognitive outcome (in one or more tests by a *z*-score change of ≥1 SD) for all 46 patients.

The total estimated number of emboli within the cognitive decline group (1349 [870-22096]) and the no cognitive decline group (median [IQR]); 1357 [729-2453]) were similar, fig 6.22(a) (Mann-Whitney U test: p=0.844). The estimated volume of air (µl) received per patient was lower in the cognitive decline group (median [IQR]); 2.4 [0.2-18.9]) compared to the no cognitive decline group (median [IQR]); 7.4 [1.5-25.9]), fig 6.22(b), but this difference was not significant (Mann-Whitney U test: p=0.261).

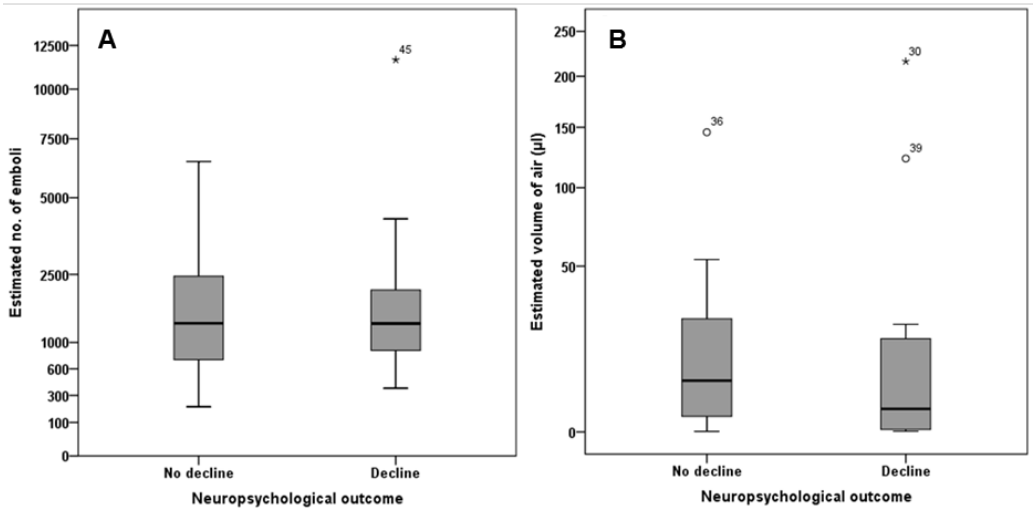


Figure 6.22 (A) Number of emboli (median [IQR]) were similar in the decline (1349 [870-2096]) and no decline groups (1357 [729-2453]) (Mann-Whitney U test: p=0.844). (B) There was no significant difference in the estimated volume of air (µl) (median [IQR]) received by the patients with (2.4 [0.2-18.9]) and without (7.4 [1.5-25.9]) cognitive decline (Mann-Whitney U test: p=0.261).

6.6 Summary

The main findings of this chapter are:

1. Patients undergoing intra-cardiac procedures experience greater embolic burden, including higher total numbers of emboli, higher numbers of macrobubbles, higher numbers of emboli following removal of the aortic cross-clamp, greater total volume of air, longer curtain durations, and longer CPB times.
2. We found no evidence that the total estimated number of emboli, volume of air or embolus size distribution influences cognition or MRI outcome.
3. Patients with higher numbers of emboli detected in the first minute following the release of the aortic cross-clamp were more likely to receive new MRI lesions (p=0.037). This is consistent with the release of some solid debris following clamp removal. However, our finding should be interpreted with caution as it is of borderline significance and would not be robust to adjustment, for multiple testing.

In summary, we found no evidence that the total number of emboli and volume of air received by patients during cardiac surgery is linked to cognitive decline or the presence of new MRI lesions. Assuming all emboli are gaseous, 87% have estimated diameters of less than 100 microns, with an average total estimated volume of air entering the MCA territory of approximately 5.4 µl.

Although cerebral microemboli during cardiac surgery have been implicated in the pathogenesis of cognitive decline, this study concludes that the overall impact of the majority of air bubbles is negligible and does not account for the 46% incidence of cognitive decline that was observed in our patients. Emboli released after the removal of the aortic cross-clamp were sufficiently large in size to cause temporary occlusion of arterioles, and patients with new MRI lesions tended to receive larger bubbles than patients with no lesions. However, the overall number of emboli appeared to have no bearing on MRI or cognitive outcome.

Chapter 7

7 Discussion

7.1 Introduction

In this clinical observational study of patients undergoing cardiac surgery, we sought to investigate proposed links between intraoperative cerebral emboli, declining cognitive test scores, and new post-operative lesions detected using MRI. With the aid of a novel MR image subtraction algorithm (Horsfield, Patel, *et al*., under revision in AJNR) we evaluated the volume and distribution of new lesions compared to pre-existing ischaemic lesions associated with chronic cerebrovascular disease (Patel *et al.*, 2015). We compared CABG and intra-cardiac procedures and assessed whether new lesions were associated with a decline in cognition (Patel *et al.*, 2015). Finally, we used transcranial Doppler ultrasound in conjunction with a specially developed bubble sizing algorithm (Banahan *et al.*, 2012) and Monte-Carlo simulations (Hague *et al.*, 2013) to estimate the size range and impact of bubbles entering the brain during surgery, and to assess whether high volumes of macro-bubbles were linked to an increased risk of cognitive decline or the development of new MRI lesions post-operatively (Chung *et al.*, 2015).

The incidence of cognitive decline in our cohort was 46% and the prevalence of new cerebral ischaemic lesions was 31%. Outcomes were similar for both CABG and intra-cardiac procedures. The biggest factor predicting cognitive decline was confirmed to be advanced age. Whereas, the most influential factor predicting risk of acquiring new lesions during cardiac surgery was the presence of pre-existing lesions. Bilateral TCD monitoring of our patients during their surgery revealed a total of 92,215 individual embolic signals, with estimated volume of air entering the MCAs ranging between 0.04 µl and 216 µl (table 6.5). Our findings suggest that, 5.4 µl (median) of air typically enters the MCA territories during cardiac surgery, and that this is insufficient to result in impaired cognitive outcome. We found no strong evidence to support a link between large or numerous bubbles and cognitive decline or new MRI lesions.

7.2 Cerebral ischaemic lesions and post-operative neuropsychological outcome

FLuid Attenuated Inversion Recovery (FLAIR) is an inversion recovery pulse sequence which uses a combination of T_1 and T_2 weighting to null the signal from fluid so that it appears dark, while tissue damaged by ischaemia remains bright. Although some studies have used 1.5-T FLAIR MRI to identify new chronic ischaemic lesions following surgery (Agarwal *et al.*, 2010; Lund *et al.*, 2005; Floyd *et al.*, 2006; Merino *et al.*, 2013) few studies report the characteristics of pre-existing lesions, and only 2 studies have used FLAIR in conjunction with neuropsychological testing (Agarwal *et al.*, 2010; Lund *et al.*, 2005). Agarwal (2010) studied 10 CABG patients using 1.5-T FLAIR, but as none of their patients developed new MR lesions or cognitive decline, their results were inconclusive (Agarwal *et al.*, 2010). Lund *et al.* (2005) previously detected new lesions (>2 mm) in 9 of 52 (17%) patients at 3 months post-operatively using 1.5-T FLAIR and found a correlation between new and pre-existing lesions. However, as cognitive decline had resolved at 3 months, no association was observed between post-operative lesions and cognitive decline (Lund *et al.*, 2005). In this study, the higher resolution afforded by MRI at 3-T, coupled with subtraction of 'before' and 'after' FLAIR images, provided a highly sensitive means of detecting small ischaemic lesions and distinguishing new lesions from old. Overall, 31% of patients were found to possess at least one new FLAIR-MRI lesion 6-8 weeks post-operatively, compared to 17% in the 1.5-T FLAIR-MRI study conducted at 3 months by Lund *et al.* (2005). Our higher detection rate is most likely due to the use of digital subtraction to help confidently identify ischaemic changes, and the higher resolution afforded by 3-T MRI. Previous DW-MRI studies revealed perioperative cerebral ischaemia immediately following surgery in 29% to 61% of patients (Stolz *et al.*, 2004; Messe *et al.*, 2014) suggesting that many acute changes seen on DW-MRI translate to small persistent lesions on FLAIR, rather than completely resolving.

The distribution of new FLAIR lesions observed in our study was consistent with a cardio-embolic pathogenesis. Digital registration and subtraction of MR images, combined with the expertise of a qualified neuroradiologist, enabled us to confidently estimate the size and location of new lesions. The distribution of new lesions suggests that larger emboli favour the right side of the brain, predominantly coming to rest in territories supplied by the MCA. This is consistent with a cardio-embolic source, in

which larger pieces of embolic debris travel along the brachiocephalic artery (which emerges first from the ascending aorta), and is consistent with a tendency for larger emboli to disproportionately favour major vessels (Chung *et al.*, 2010).

The total volume of new lesions estimated for each patient was generally small when compared to the volume of pre-existing cerebrovascular disease. Our analysis of pre-existing cerebrovascular ischaemic lesions suggested that ~0.16 % of total brain volume was typically affected by pre-existing ischaemic white matter disease prior to surgery. New lesions acquired peri-operatively comprised only ~4% of the total burden of ischaemic white matter disease, occupying approximately 0.004% of total brain volume.

Our findings concur with those of Lund *et al.,* who also found that patients with pre-existing lesions identified using MR-FLAIR were at exceptionally high risk of developing new lesions post-operatively (Lund *et al.*, 2005). In our study, patients with pre-existing lesions were ten times more likely to experience new lesions post-surgery than patients without pre-existing disease. Pre-operative MRI assessment may be useful for identifying high-risk patients for targeted intervention to reduce embolisation of atheromatous debris and reduce the risk of stroke.

Our study found no evidence that small subclinical lesions on MRI affect either baseline or post-operative cognitive test results. In comparing the incidence of new lesions with cognitive outcome, the incidence of cognitive decline was 46%, regardless of whether new lesions were present (results Chapter 5). This is similar to the incidence reported by other studies using similar criteria (paired *z*-score analysis with 1 SD as significant) (Puskas *et al.*, 2007; Toeg *et al.*, 2013). Conversely, the proportion of patients with new MRI lesions was 31% regardless of cognitive status. In previous research, the incidence of neurocognitive impairment ranged from 0 to 50% when measured between 1 and 3 months following surgery and was found to be related to multiple risk factors, including age, pre-existing white matter disease, decline in pre-existing cognition, and complexity of surgery (Ahonen & Salmenpera, 2004). Our study failed to identify any link between new MRI lesions and cognitive decline, but confirmed that older patients with aortic stenosis are most likely to suffer post-operative neuropsychological impairment (Chapter 5, table 5.2). Since lesions tended to be small and highly localised, this may explain why new lesions identified by our study following surgery did not significantly impair cognition.

Strengths of our study included higher resolution afforded by 3-T MRI and a larger sample size than the majority of previous MRI reports. By performing scans at 6-8 weeks postoperatively, we were able to perform neuropsychological tests at the same time-points as the MRI scans. DW-MRI lesions observed in the acute phase are known to resolve with time (Hauth *et al.*, 2005), so lesions and cognitive changes observed at 6-8 weeks will underestimate acute ischaemic burden, but are more likely to be representative of persistent changes than tests performed immediately following surgery, which can be affected by anaesthetics and other peri-operative factors.

Unfortunately, some of the patients recruited to our study were unable to undergo MRI scans, leading to full datasets for only 77 of 103 patients. As these data were missing prospectively at random, they are unlikely to have affected our conclusions. However, it is possible that with greater statistical power a small contribution of new lesions to neurocognitive decline could have been differentiated from other more dominant contributions such as age and pre-existing cardiovascular disease.

Our MRI study confirmed that:

1. New FLAIR lesions in the left hemisphere were significantly smaller and more numerous than those in the right hemisphere. The distribution of new lesions was consistent with a cardio-embolic pathogenesis.
2. The total volume of new lesions was small in comparison to the embolic burden from pre-existing cerebrovascular disease.
3. Patients with pre-existing lesions were at increased risk of receiving new lesions.
4. Increased age and mild/moderate atheroma burden were the only significant pre-operative risk factors found to be associated with postoperative cognitive decline.
5. We found no evidence that either pre-existing or new lesions had an adverse impact on baseline or post-operative cognitive test results.

This part of the thesis, which was published in *Stroke* (Patel *et al.*, 2015), confirmed that neurological injury is common in patients undergoing cardiac surgery; 7% of patients suffered a perioperative stroke, 31% received new MRI lesions, and 46% exhibited signs of neuropsychological impairment 6-8 weeks postoperatively. Older patients with aortic disease were confirmed to be most likely to experience cognitive decline, but

there was no significant association between a decline in cognitive function and the presence, size, or number of new MRI lesions. Pre-existing lesions affected up to 0.16% of total brain volume, and were observed in 64% of patients prior to surgery. Patients with pre-existing lesions faced an exceptionally high risk of receiving new lesions peri-operatively. New lesions did not appear to contribute significantly to the 46% incidence of cognitive decline observed in our cohort, however, with increased power it is possible that a small contribution of new lesions to cognitive decline could have been observed. The striking relationship between new and pre-existing lesions suggests that a deeper understanding of complex interactions between perioperative stressors and chronic cerebrovascular disease will be useful for gaining further insights into the causes of brain injury during cardiac surgery to inform personalised strategies for risk stratification and intervention.

7.3 Intraoperative management and cognitive decline

Comparison of intraoperative transcripts, physiological measurements and TCD embolus detection with neuropsychological and cognitive outcome were published in PLOS ONE (Chung *et al.*, 2015) and highlighted a number of interesting observations.

Although patients undergoing intra-cardiac procedures received almost twice as many emboli during cardiopulmonary bypass than CABG patients these corresponded to small bubbles and were not predicted by our simulations to generate significant vascular obstruction. This confirms the results of previous RCTs comparing on and off pump surgery (see Chapter 2 for a literature review), demonstrating that the use of CPB does not contribute to perioperative cerebral injury. Several RCTs that randomised patients to on-pump or off-pump surgery have consistently shown no difference in neurocognitive outcomes, stroke rates, or mortality (Lamy *et al.*, 2012; Lamy *et al.*, 2013). In previous research, high numbers of cerebral emboli detected during CPB were not found to be associated with neurocognitive deficits (Liu *et al.*, 2009; Hillis, 2011), which is consistent with our findings.

Our study found that blood pressures were similar between CABG and intra-cardiac procedures. Mean arterial pressure for the majority of our patients ranged between 50-70 mmHg. Low blood pressure (<60 mmHg) during surgery did not appear to increase

the risk of experiencing cognitive decline or acquiring new MRI lesions (see results Chapter 6). Several previous studies have attempted to define the optimum blood pressure that would result in fewer patients experiencing neurological complications (for a review see Chapter 1). Four out of the five studies reported in our review found a decline in postoperative outcome with lower blood pressure (50-60 mmHg) during CPB. Our results failed to confirm a link between low blood pressure (<60 mmHg) and poor cognitive outcome. However, our results concur with the largest RCT investigating blood pressure and cognitive outcome by Charlson *et al* who also failed to show any association (Charlson *et al.*, 2007).

The majority of our patients underwent 'mild hypothermia' (31-34°C) during CPB. Analysis of the temperature and rate of rewarming of patients during surgery revealed no evidence that 'mild hypothermia', or an increased rate of re-warming, had any impact on the risk of cognitive decline or of acquiring new MRI lesions (see results Chapter 6). This agrees with previous research (see Chapter 1, page 25).

A higher number of patients with mild/severe aortic stenosis received new MRI lesions (67%) than patients without aortic disease (49%), but this difference did not reach statistical significance. However, a borderline significant (p=0.042) association between mild/severe aortic stenosis and cognitive decline was observed. Degree of aortic stenosis has previously been found to be associated with perioperative stroke (Hillis, 2011) and the presence of significant cardiac atheroma and has also been found by some researchers to be associated with an increased risk of cognitive decline (Hammon *et al.*, 2006) and new lesions on MRI (Cook *et al.*, 2007). A limitation of our study was that cardiovascular disease within the ascending aorta tends not to be visible using TOE and was therefore not routinely assessed as part of our study. Although surgeons did perform manual palpation of the aorta prior to cross-clamp application, ultrasound assessment of the aorta (epiaortic scanning) is recommended by the American Heart Association and would have provided a better technique for grading aortic plaque (Glas *et al.*, 2008; Hillis, 2011). Whether epiaortic ultrasound-guided application of the aortic cross-clamp and site of cannulation would improve neuropsychological or MRI outcome is currently unclear as no trials have been conducted. The presence of particulate emboli associated with chronic cardiovascular disease provides the most likely explanation of why a high proportion of cardiac surgery patients exhibit new ischaemic lesions both pre- and post-operatively.

Our cohort of patients experienced lowered mean haematocrit between 25-33% during cardiopulmonary bypass. Haematocrit values were similar in both types of procedure and did not appear to be associated with an increased risk of cognitive decline or new lesions on MRI (see results Chapter 5). In some previous research a low haematocrit was found to be linked to a higher risk of stroke (Karkouti *et al.*, 2005) and postoperative neuropsychological decline (Mathew *et al.*, 2007), for a review see Chapter 1. However, the TRACS trial (Transfusion requirements After Cardiac Surgery) in 2010 compared cognition of patients with haematocrit targets of 24% and >30% and observed a 6% incidence of neuropsychological decline in both groups (Hajjar *et al.*, 2010) suggesting that haemodilution has no major influence on cognition. Our findings also suggest that haematocrit values maintained between 25-33% had no adverse impact on cognition.

Analysis of intra-operative management provided no evidence that:

6. Bubbles during CPB contribute to cognitive decline.
7. Low intra-operative blood pressure, haematocrit, and temperature change are linked to cognitive decline.

7.4 Characteristics of intraoperative emboli detected during cardiac surgery

Embolic signals detected by Transcranial Doppler (TCD) are common during cardiac surgery, even in low-risk patients. However, the results of previous TCD embolus detection studies can be difficult to interpret due to differences in study methodology, such as intensity thresholds used to detect embolic signals (Rodriguez *et al.*, 2006), inconsistencies in signal reviewing procedures (manual versus automated) (Ringelstein *et al.*, 1998; Rodriguez *et al.*, 2006), quality of TCD recordings (Ringelstein *et al.*, 1998), and intermittent embolus detection (limited to selected times in the procedure). We sought to overcome these limitations by obtaining good quality bilateral TCD recordings throughout the entire procedure and insisting on adopting a consistent semi-automated offline procedure for reviewing embolic signals. To the best of our knowledge, this study represents one of the most detailed investigations to date of the timing and a characteristic of Doppler embolic signals detected during cardiac surgery,

and provides researchers with an initial estimate of the likely size distributions of bubbles and volume of air entering the cerebral circulation (Chung *et al.*, 2015). It also provides a first insight into the likely impact of air entering the brain during cardiac surgery and the potential for air bubbles to influence neuropsychological outcome.

Our study confirms that showers of bubbles are generated during cardiopulmonary bypass (CPB), and are associated with specific operative procedures (e.g. aortic manipulation, grafting and cross-clamp applications). We found that the majority of embolic signals detected during heart surgery were generated by small microemboli (<100 μm) and are therefore likely to be benign. The majority (87%) of bubbles entering the cerebral circulation were found to correspond to microbubbles less than 100 μms in diameter. Only 0.3% of bubbles were estimated to be greater than or equal to 1 mm in diameter. The number and dimensions of air emboli revealed by our analysis was broadly consistent with previous autopsy studies by Moody *et al.*, which revealed numerous small capillary arteriolar dilatations post-operatively (Moody *et al.*, 1995). Moody and colleagues studied 100 μm thick slices of the basal ganglia of patients who died within one week of surgery and observed numerous empty ~40 μm dilatations, with a density of approximately 40 dilatations per cm^2 of tissue. The median diameter of air emboli of 33 μm (IQR: 18-71) estimated by our analysis is similar to Moody's findings.

Patients undergoing intra-cardiac procedures received over twice as many bubbles per procedure, and 7 times as many macro-bubbles. Significantly higher volumes of air were received during intra-cardiac surgery than CABG. CPB times tended to be longer for intra-cardiac procedures than CABG. Curtains of emboli were rarely observed during CABG compared to intra-cardiac procedures. Although the number of emboli observed during the minute following the release of the aortic cross-clamp was over 5 times higher in the intra-cardiac group than the CABG group, there were large variations between patients and this did not reach significance. Our findings are in agreement with the majority of previous research suggesting that more complex procedures with a higher number of surgical interventions are associated with lengthier operations, and consequently, a greater chance of receiving a higher embolic load. Macrobubbles were most likely to be generated during the latter stages of the surgery

(after the release of the aortic cross-clamp), and were more common during intra-cardiac procedures.

A detailed analysis of our TCD recordings suggests that the small volume of air received over the course of the surgery is unlikely to generate significant cerebral injury. The average (median) estimated total volume of air entering the MCA territory was 5.4 µl, which is exceedingly small in comparison with the area of the vasculature. Our findings demonstrate that up to 0.22 mL of air typically enters the MCA territories during cardiac surgery. This is lower than levels expected to cause acute cerebral injury. Previous animal studies by Haines et al., investigated the impact of air bubbles injected to the cerebral vasculature of dogs in the form of a microbubble mix over a period of ~20 mins (Haines *et al.*, 2013). The authors found that the dogs presented multiple DWI lesions when a volume of air between 1-2 mL was introduced. Our findings in humans suggest that the volume of air entering the human brain during surgery is much less than this (0.22 mL), table 8.1. Given time taken for an air embolus to completely dissolve, and proportion of the vascular tree that becomes obstructed, are both sensitively dependent on bubble size (Barak & Katz, 2005); small bubbles are not expected to be harmful.

To better understand the relationship between vascular obstruction and bubble size relative to the dimensions of the arterial tree we used a Monte-Carlo simulation of gas bubbles moving through a model MCA vasculature (Chung *et al.*, 2007; Hague & Chung, 2009; Hague *et al.*, 2013). Based on the results of these simulations, showers containing bubbles less than ~38 µm in diameter did not generate any significant obstruction. Showers of larger (>100 µm) macrobubbles detected following removal of the aortic-cross clamp and during weaning from bypass were predicted to affect up to 2.2% of the model vasculature for several hours. However, as the dissolve time for an individual bubble depends crucially on surface area, and multiple bubbles have potential to coalesce, the potential for more subtle localised injuries cannot be completely discounted.

Strengths of our embolus detection study include estimation of bubble size and use of Monte-Carlo simulations to provide a deeper understanding of the likely impact of air emboli on cerebral blood flow. The presence of dense showers and curtains of emboli made it difficult to distinguish individual emboli during some sections of our recordings

(see table 6.5 for curtain durations). This impacted mainly valve and combined procedure patients, where showers were particularly heavy. Based on these limitations, the numbers of emboli reported in our study for patients 18, 20, 23, 27, 37, 39 and 40 should be considered conservative estimates. The total number of emboli and estimated volume of air entering the circulation is therefore expected to be underestimated. Unfortunately, we were unable to distinguish solid from gaseous emboli. Therefore, our estimates of bubble size are based on an assumption that the majority of emboli were bubbles. Our estimates of bubble size are associated with additional inaccuracies, particularly when the MCA diameters were difficult to measure, or in the event of poor vessel-beam alignment. To reduce errors in bubble sizing, every effort was taken to accurately measure MCA diameter and to optimise beam-vessel alignment. However, the true errors associated with our bubble size estimates are difficult to confirm. Since bubbles are likely to be harmless, our findings also underline the importance of developing and validating methods to confidently distinguish solid and gaseous emboli, along with technologies aimed at preventing particulate embolic debris from reaching the brain.

A limitation of our Monte-Carlo model was the absence of a mechanism for allowing multiple small bubbles to coalesce. Large bubbles pose a much greater threat to blood flow because they take longer to dissolve and become lodged higher up in the arterial tree. If our existing model can be considered to reflect true levels of microvascular obstruction and rates of embolus clearance, the greatest threat to cerebrovascular perfusion is predicted to occur following removal of the aortic cross-clamp during weaning from bypass.

Overall, our TCD embolus detection study confirms that:

8. Assuming all emboli are gaseous, 87% have estimated diameters of less than 100 µm with the average total estimated volume of air entering the MCA territory of approximately 5.4 µl.
9. Patients undergoing intra-cardiac procedures tend to experience significantly greater overall embolic burden than patients undergoing CABG-only procedures. This includes higher total numbers of emboli, more macro-bubbles and greater volume of air, longer curtain durations, and high numbers of emboli following release of the aortic cross-clamp.

10. Our Monte-Carlo simulations predict that small bubbles (<38 μm) do not impair cerebral perfusion. However, macro-bubbles were predicted to obstruct a small percentage of the model vasculature for several hours.

7.5 Cerebral emboli and neuropsychological and MRI outcome

Previous research has suggested that embolisation of gaseous and solid material into the cerebral vasculature has potential to result in cerebral damage (Pugsley *et al.*, 1994). However, evidence for a direct association between embolic load and postoperative cognitive dysfunction (POCD) in a cardiac surgery setting has proved elusive (Stump *et al.*, 1996; Bar-Yosef *et al.*, 2004; Hogue *et al.*, 2006). Although several studies reported a significant correlation between high numbers of embolic signals and cognitive decline (see literature review, Chapter 2), as the majority of studies are observational, associations could also be explained by confounding factors such as the length and complexity of surgery, which are also likely to be associated with higher emboli counts. As embolic signal analysis is time consuming, sample sizes tend to be small (<100 patients), and there are also differences in methodologies used for the collection and analysis of TCD recordings between studies.

Overall, we found no evidence to support a link between the volume of air received by the patient during cardiac surgery and cognitive decline (results Chapter 6). This is consistent with previous research (Gaunt *et al.*, 1994; Dittrich & Ringelstein, 2008) confirming that gaseous emboli are less damaging to the brain than solid emboli. The biggest risk factors predicting cognitive decline in previous research were the patient's age, cognitive status at baseline, and presence of pre-existing chronic cardio and cerebro-vascular disease. As the number of older patients undergoing cardiac surgery is increasing there are likely to be higher rates of cognitive decline in the future (Andrell *et al.*, 2005). Other intra-operative risk factors and mechanisms leading to brain injury such as cerebral oedema, inflammation, response to surgical insult, cerebral hypoperfusion and ischaemia (Boodhwani *et al.*, 2007; Bayram *et al.*, 2013) may also require further investigation.

Regarding the proportion of patients with new MRI lesions following surgery, patients with new lesions tended to have received a greater embolic burden during surgery, but differences were not statistically significant. The only association observed in our data was between new MRI lesions and the total number of emboli observed in the first minute following release of the aortic cross-clamp. However, this result was of borderline significance and was not robust to adjustment for multiple testing. This stage of the surgery is of particular interest, since removal of the cross-clamp has potential to release a mixture of bubbles and solid pieces of atheromatous debris into the bloodstream. Although, our finding of a potential association should be interpreted with caution, it seems consistent with previous research suggesting a link between cardiac and aortic atheroma and new lesions following surgery (Katz *et al.*, 1992; Stern *et al.*, 1999; Djaiani *et al.*, 2004; Cook *et al.*, 2007). In a recent randomised trial by Bolotin et al., which investigated 66 patients undergoing valve or combined surgery, a special arterial cannula (Cardio Cannula) was used to capture solid emboli during cross-clamp manipulation. A lower proportion of patients exhibited new DW MRI lesions in the group receiving the novel cannula (44%) than the control group (66%) (Bolotin *et al.*, 2014). In a previous RCT featuring 1,289 patients randomised to receive the Embol-X filter, particulate emboli were identified in 598 (97%) of 618 filters, demonstrating that significant numbers of solid emboli are released (Banbury *et al.*, 2003), particularly following release of the aortic cross clamp (Christenson *et al.*, 2005).

Although bubbles have long been hypothesised to be a cause of cognitive decline, our findings and simulations concur with mounting evidence suggesting that bubbles during surgery are largely benign. Our analysis suggests that the volume of air received by patients during cardiac surgery does not strongly influence cognition or generate focal ischaemic lesions seen on MRI. However, due to difficulties in obtaining high quality recordings, and the time consuming nature of Doppler embolus detection, our sample size of 46 patients was too small to confidently reach reliable conclusions regarding bubble properties and clinical outcome measures. Although a small contribution of bubbles to cognitive decline cannot be ruled out, we can confidently conclude that bubbles alone do not provide an explanation for the 46% incidence of cognitive decline observed in our cohort, the majority of which will need to be explained by other mechanisms.

Overall, we conclude that:

1. Patients with higher numbers of emboli detected in the first minute following release of the aortic cross-clamp may be more likely to receive new MRI lesions due to solid emboli.
2. We found no evidence of a link between the number of bubbles, volume of air, or bubble size distribution and cognitive or MRI outcome.
3. The 46% incidence of cognitive decline observed in our patients is not explained by the impact of bubbles on cerebrovascular perfusion.

Chapter 8

8 Conclusions

8.1 Main findings and conclusions

As numbers of elderly patients undergoing cardiac surgery increase, neurological complications remain a common source of morbidity. It is clear from the results of this study, together with previously published data, that cerebral injury following cardiac surgery is likely to involve complex multifactorial mechanisms.

From this study, we conclude that patients with pre-existing lesions are at an increased risk of receiving new lesions during cardiac surgery; however, there was no evidence to suggest that either pre-existing or new lesions had an adverse impact on baseline or post-operative cognitive test results. We estimate that the majority of air emboli received during cardiac surgery are small and likely to be benign, and found no link between bubble properties or volume of air and adverse cognitive or MRI outcome. The 46% incidence of cognitive decline observed in our patients is not explained by the impact of bubbles on cerebrovascular perfusion and is not directly associated with new postoperative MRI lesions.

Solid emboli resulting from manipulation of the aorta during the application and removal of the aortic cross-clamp, hypoperfusion, perioperative arrhythmias, blood loss, inflammation (both cerebral and systemic), rapid re-warming, and genetic vulnerability to injury all provide alternative mechanisms for brain injury (Newman *et al.*, 2006; McKhann *et al.*, 2006; Grocott, 2007). Improved cognitive safety during cardiac surgery might be accomplished by hindering one or more of these factors and countering cascading events, but so far no single pathway for the successful prevention of cognitive decline has been identified. The current study is important for confirming that bubbles associated with surgery are not a major cause of cognitive decline, enabling future researchers to focus on other potential targets. New approaches may include novel neuroprotective agents, development of biochemical and genetic markers to facilitate risk stratification, and novel surgical and perfusionist strategies to minimise

physiological stress on the brain during surgery. Although most efforts currently focus on preventing decline, strategies could also be developed to strengthen and restore neurocognitive function.

Our study suggests that the number and timing of intraoperative emboli, haemodilution, temperature and blood pressure management during cardiac surgery do not individually increase the risk of acquiring new MRI lesions or cognitive decline. It seems likely that predisposing cerebrovascular disease, together with the stress of undergoing surgery may trigger a multifactorial cascade of events that leads to cerebral injury. New advances in personalised medicine potentially provide a better means of understanding complex diseases than cohort studies, and more stringent efforts may be needed to focus on preventing adverse outcomes on an individual basis. Ischaemic damage to the brain, regardless of whether it is correlated to cognitive decline after cardiac surgery is still worrying and should be minimised. Whether brain injury following cardiac surgery also has potential to contribute to the acceleration of serious chronic diseases such as dementia has yet to be discovered.

8.2 Future work

Cognitive protection in the future may include careful assessment to identify high-risk patients, coupled with improvements in perfusion guided by perioperative monitoring. Screening patients before they undergo surgery could also help with directing appropriate adjustment for co-existing morbidities and allow surgeons to modify their techniques (Selim, 2007). Other interventions may include preventing and treating secondary cerebral damage through the use of filters, or administration of anti-inflammatory drugs (Grocott, 2007). It would also be useful in future studies to be able to identify patients with pre-existing cerebrovascular disease, and to see how other pre-existing risk factors such as impaired cerebral autoregulation could have an impact on postoperative cognition. It would also be worthwhile using an appropriate control population to accurately validate the neuropsychological assessments, and assess whether surgery has any long-term impact on cognition or risk of dementia when separated for changes to the brain associated with progression of cardiovascular disease.

8.3 Closing remarks

Cardiac surgery is one of the great triumphs of 20th century medicine, and has become so safe that it is now regarded as a routine procedure. However, subtle cognitive decline remains a common complaint. As cardiac surgery procedures are now being challenged by less invasive methods, perhaps neuropsychological tests and neuroimaging will play an increasingly important role in optimising treatment. Although it is important to try to reduce the burden of cerebral ischaemia in patients undergoing cardiac surgery, our research suggests that we must try to better understand the relationship between surgery and progressive pre-existing cerebrovascular disease. By selecting patients with pre-existing cognitive and cerebrovascular diseases, and treating this subgroup of patients more carefully, patient specific treatment in the future might better assist in reducing cognitive deficits and eliminating the risk of stroke in patients undergoing heart surgery.

Appendices

9 Appendices

9.1 Appendix 4.A R&D approval

University Hospitals of Leicester NHS
NHS Trust

DIRECTORATE OF RESEARCH & DEVELOPMENT

Director: **Professor D Rowbotham**
Assistant Director: **Dr David Hetmanski**
R&D Manager: **Carolyn Maloney**

Research & Development Office
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

Direct Dial: (0116) 258 8351
Fax No: (0116) 258 4226

18th May 2011

Dr Emma ML Chung
British Heart Foundation Research Fellow
University of Leicester
Medical Physics
Level 1, Sandringham Building
Leicester Royal Infirmary
LE1 5WW

Dear Dr Chung

Ref: **CLRN 51454**
Title: **Causes of brain injury associated with cardiac interventions; A comparison of Doppler embolus detection and virtual patient predictions with postsurgical neurological outcome quantified by MRI and neuropsychological testing**
Project Status: **Approved**
End Date: **31-12-2013**

I am pleased to confirm that with effect from the date of this letter, the above study now has Trust Research & Development permission to commence at University Hospitals of Leicester NHS Trust.

All documents received by this office have been reviewed and form part of the approval. The documents received and approved are as follows:

Document Name	Version Number	Date
Protocol	2.0	23-09-2010
Invitation letter	2.0	23-09-2010
Participant information leaflet	2.0	23-09-2010
Participant consent form	2.0	23-09-2010
GP Letter	2.0	23-09-2010
Brain Injury MRI (specific protocol)	1.0	31-12-2010
Substantial amendment form	1.0	16-01-2011
REC Favourable opinion letter	NA	06-10-2010
REC amendment favourable opinion letter	1.0	15-02-2011

Version 5, 20.04.10

Please be aware that any changes to these documents after approval may constitute an amendment. The process of approval for amendments should be followed. Failure to do so may invalidate the approval of the study at this trust.

We are aware that undertaking research in the NHS comes with a range of regulatory responsibilities. Attached to this letter is a reminder of your responsibilities during the course of the research. Please ensure that you and the research team are familiar with and understand the roles and responsibilities both collectively and individually.

You are required to submit an annual progress report to the R&D Office and to the Research Ethics Committee. We will remind you when this is due.

The R&D Office is keen to support research, researchers and to facilitate approval. If you have any questions regarding this or other research you wish to undertake in the Trust, please contact this office.

We wish you every success with your research.

Yours sincerely

Carolyn Maloney
R&D Manager

Encs: .Researcher Information Sheet.

Please note that some of the documents may not apply to your study.

9.2 Appendix 4.B Ethical approval

NHS
National Research Ethics Service

Derbyshire Research Ethics Committee
1 Standard Court
Park Row
Nottingham
NG1 6GN

Telephone: 0115 8839435
Facsimile: 0115 9123300

06 October 2010

Dr Emma ML Chung
British Heart Foundation Research Fellow
University of Leicester
Medical Physics Group
Level 1, Sandringham Building
Leicester Royal Infirmary
LE1 5WW

Dear Dr Chung

Study Title: **Causes of brain injury associated with cardiac interventions; A comparison of Doppler embolus detection and virtual patient predictions with postsurgical neurological outcome quantified by MRI and neuropsychological testing.**

REC reference number: **10/H0401/78**

Thank you for your letter of 23 September 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Investigator CV		
Protocol	2	23 September 2010
Supplemental Lay Summary		
REC application	51454/138611/1/833	27 July 2010
Letter of invitation to participant	2	23 September 2010
Participant Information Sheet	2	23 September 2010
Response to Request for Further Information		23 September 2010
Participant Consent Form	2	23 September 2010
GP Letter	1	01 June 2010
Letter from Funder		08 July 2010
Evidence of insurance or indemnity		13 August 2010
Referees or other scientific critique report		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed

guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H0401/78	**Please quote this number on all correspondence**

Yours sincerely

Mr Apostolos Fakis
Vice-Chair

Email: lisa.gregory@nottspct.nhs.uk

Enclosures: "After ethical review – guidance for researchers" *SL- AR2 for other studies*

Copy to: *Graham Hewitt, University of Leicester*
R&D office for NHS care organisation at lead site - UHL

9.3 Appendix 4.C Study information sheet

University Hospitals of Leicester NHS
NHS Trust

Caring at its best

Leicester Royal Infirmary
Leicester
LE1 5WW

Tel: 0300 303 1573
Switchboard Fax: 0116 258 7565
Minicom: 0116 287 9852

RESEARCH PARTICIPANT INFORMATION SHEET (23/08/11, version 3a)

Causes of brain injury associated with cardiac surgery

Investigators: Dr E. Chung[1], Dr C. Banahan[2], Dr M Horsfield[1], Prof. T. Spyt[1,3], Mr N. Masala[3], Mr H. Abunsara[3], Mr J. Szostek[3], Mr M. Hickey[3], Prof V Egan[4], Prof. G. Cherryman[5], Prof. D.H. Evans[1,2], Mrs J. Janus[1] , Mr D. Spiers[1], Mr N. Patel[1]

1 Department of Cardiovascular Sciences, University of Leicester

2 Medical Physics Department, University Hospitals of Leicester NHS Trust

3 Department of Cardiothoracic Surgery, University Hospitals of Leicester NHS Trust

4 Department of Psychology, University of Leicester

5 Department of Neuroradiology, University Hospitals of Leicester NHS Trust

Invitation
You have been invited to take part in a research study. Before deciding if you wish to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if anything is not clear to you, or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?
The aim of this study is to improve our understanding of the adverse effects of particles and gas bubbles (emboli) that enter arteries supplying the brain during cardiac surgery. During your operation we would like to use ultrasound to detect emboli moving through the arteries. Ultrasound signals recorded during this study will be use to predict the risk of brain injury for comparison with the results of neurological tests and Magnetic Resonance Imaging (MRI) scans performed before and after surgery.

How long will it take?
The study involves a number of additional investigations which will be completed alongside your routine care so that no extra hospital visits other than those associated with your normal care will be required.

Before surgery:
As a preliminary examination we will use ultrasound to measure blood-flow through the arteries in the head and neck. These checks will take approximately 30 mins. We will then

Trust Headquarters, Level 3, Balmoral Building, Leicester Royal Infirmary, Leicester, LE1 5WW
Website: www.leicestershospitals.nhs.uk
Chairman Mr Karamjit Singh CBE **Chief Executive** Mr John Adler

ask you to complete a series of neuropsychological tests (questionnaires and puzzles) to assess brain function, reaction times, memory and IQ. These tests will take approximately 1 hour. We will then ask you to undergo an MRI scan of the brain. This will take approximately 30 mins.

During surgery:
Ultrasound monitoring for emboli will be performed for the duration of your surgery. Ultrasound signals will be recorded to computer for later analysis.

After surgery:
During your routine outpatients' appointment (approximately 6 weeks following surgery) we will ask you to repeat the neuropsychological tests (1 hour) and MRI scan (30 mins).

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign a consent form. Even if you have given your consent, you are still free to withdraw at any time without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will be involved if I take part in the study?
Ultrasound equipment emitting inaudible sound waves will be placed gently on the head or neck and adjusted to monitor the flow of blood and particles through the arteries. The probe is covered in a small amount of gel and held by hand or fixed in place using an adjustable headset. Ultrasound monitoring is completely painless, and over 20 years of diagnostic measurements has not been shown to be harmful.

As with all patients who have an MRI scan, you will be asked to complete a questionnaire beforehand to make sure that it is safe for you to have a scan. You will be asked to remove any metal objects, including jewellery. The scanners are quite noisy, making a hammering noise during the scan. You will be provided with ear plugs to protect your ears. You will be asked to lie very still during the scans, which can be uncomfortable. However, you will be able to get comfortable again during the rest periods between scans. The MRI scanner is quite narrow, and some people feel claustrophobic within the scanner, but there is a 'panic button' which will enable staff to get you out of the scanner straight away if necessary. Many thousands of MRI scans are performed every day, and it is not thought that there are any long-term risks.

The neuropsychological tests involve you doing about an hour's worth of puzzles and tasks of the kind you might see on game shows on television. However, the tasks measure different aspects of your memory, attention and problem-solving. All have been used in studies like this one many times before and help us to understand what kinds of practical problems any brain injury might cause.

What are the possible disadvantages and risks of taking part?
As you are aware, there is a small risk of stroke associated with your surgery. Involvement in this study has no effect on this risk.

MRI does not use X-rays and is safe for the majority of people. However, the strong magnet at the centre of the procedure can affect medical devices, such as heart pacemakers and inner ear implants. If you have metal close to an important organ then you will be advised not to have an MRI.

As with all additional medical tests, there is a risk that the brain MRI will reveal abnormalities that you may have been unaware of. MRI images will be examined by a Radiologist and any abnormalities will be reported to your GP.

What are the benefits of taking part?
There are no direct clinical benefits for participants but the information we get from the study may improve the safety of cardiac surgery in the future.

Will the information obtained in the study be confidential?
If you wish to take part in this study your participation will be noted in your medical records. All information that is collected about you during the course of the research will be kept strictly confidential. Researchers may have future access to the study data, but all information that leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What if I am harmed by the study?
It is highly unlikely that you will be harmed during this study and there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action against University Hospitals of Leicester NHS trust but you could have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated, the normal National Health Service complaints mechanisms would still be available to you

What if I have a complaint?
If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. (Please contact Dr Emma Chung, **Tel:** 0116 2585610). If you remain unhappy and wish to complain formally, please contact the University Hospitals of Leicester NHS Trust Patient Information and Liaison Service (PILS): Freephone: 0808 178 8337.

What will happen to the results of the research study?
The results of the study will be presented at medical conferences and will be published in specialised medical journals. The data will be completely anonymous and your identity will not be revealed in any publication or presentation of these results.

There will be an open lecture on research generated by the study to which all participants will be invited.

Who has reviewed the study?
All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision.

Contact for further information
If you have any questions or queries about this research project please do not hesitate to contact Dr Emma Chung. (**Tel:** 0116 2585610 **Email:** emlc1@le.ac.uk)

Thank you for reading this. This information leaflet is for you to keep.

9.4 Appendix 4.D Patient consent form

University Hospitals of Leicester NHS
NHS Trust

Caring at its best

Leicester Royal Infirmary
Leicester
LE1 5WW

Study number: CLRN 5145
Patient identification code for this trial:

Tel: 0300 303 1573
Switchboard Fax: 0116 258 7565
Minicom: 0116 287 9852

CONSENT FORM (23/08/11, version 3a)

Causes of brain injury associated with cardiac interventions

Principal investigator: Dr Emma Chung

		Please Initial
1.	I confirm that I have read and understood the patient information sheet dated 23/08/11, version 3a. I have had the opportunity to consider the information and ask questions and have had these answered satisfactorily.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected.	☐
3.	I consent for researchers involved in this study and regulatory authorities from the NHS Trust to have access to my medical records and imaging data where this is relevant to the research.	☐
4.	I agree to take part in the above study.	☐
5.	I would like my GP to be informed of my participation in the study. *Name and address of GP:*	☐

Name of Patient _____ Signature _____ Date _____

I confirm that I have explained the nature of the study, as detailed in the patient information sheet, in terms that in my judgement are suited to the understanding of the patient.

Name of Researcher _____ Signature _____ Date _____

Causes of brain injury associated with cardiac interventions, 23/08/11, version 3a. [1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.]

Trust Headquarters, Level 3, Balmoral Building, Leicester Royal Infirmary, Leicester, LE1 5WW
Website: www.leicestershospitals.nhs.uk
Chairman Mr Karamjit Singh CBE **Chief Executive** Mr John Adler

9.5 Appendix 4.E GP letter and patient appointment letter

University Hospitals of Leicester NHS
NHS Trust

Caring at its best

Leicester Royal Infirmary
Leicester
LE1 5WW

Tel: 0300 303 1573
Switchboard Fax: 0116 258 7565
Minicom: 0116 287 9852

Ref: 23/09/10_version2

Date:

Dear Dr

Your patient, Mr, has kindly agreed to participate in a research project.

Study title: Causes of brain injury associated with cardiac interventions
REC Reference number: 10/H0401/78

During this study we will be performing transcranial Doppler ultrasound detection of microemboli moving through the cerebral circulation for comparison with the results of neuropsychological tests and brain MRI conducted before and after cardiac surgery.

None of the diagnostic tests associated with this study have any known adverse clinical consequences. Participation in the study requires no changes to the normal treatment or medical management of your patient. If incidental findings are identified as a result of our imaging investigations you will be notified.

If you have any questions regarding this research, please do not hesitate to contact me.

Yours faithfully,

Dr Emma Chung
British Heart Foundation Research Fellow
University of Leicester, Department of Cardiovascular Sciences

Tel: +44 (0)116 2541414 ext 6065
Email: emlc1@le.ac.uk

Trust Headquarters, Gwendolen House, Gwendolen Road, Leicester, LE5 4QF
Tel: 0116 258 8665 Fax: 0116 258 4666 Website: www.uhl-tr.nhs.uk
Trust Headquarters, Level 3, Balmoral Building, Leicester Royal Infirmary, Leicester, LE1 5WW
Website: www.leicestershospitals.nhs.uk
Chairman Mr Martin Hindle **Chief Executive** Malcolm Love Laun
Chairman Mr Karamjit Singh CBE **Chief Executive** Mr John Adler

University Hospitals of Leicester NHS
NHS Trust

Caring at its best

Leicester Royal Infirmary
Leicester
LE1 5WW

Tel: 0300 303 1573
Switchboard Fax: 0116 258 7565
Minicom: 0116 287 9852

Date:

Dear

Re: "*Causes of brain injury associated with cardiac interventions*".

Thank you for your participation in our research study. I am writing to confirm that an appointment has been made for you to attend:

For: Neuropsychological tests

On: at:

For: MRI scan of the head for research

On: at:

At: Glenfield Hospital, Radiology Department

Please report to the Radiology Department, which is situated just inside the MAIN ENTRANCE of the hospital, and proceed to Waiting Area C.

If you are unable to attend this appointment, please telephone Miss Bharti Patel on **0116 258 5626** or **0116258 5486**

You will receive a green car parking pass from us at the day of your arrival. This will allow you to have a **free parking** for the whole day of your appointment at the clinic. You will need to add the registration no. of your car to the permit and then place it behind the windscreen.

If you have any questions or queries about this research project please do not hesitate to contact Dr Emma Chung (Tel: 07757611833, email: emlc1@le.ac.uk)

If you have any questions regarding the MRI scan procedure, please call 0116 2502353 to speak to one of the radiographers.

Dr Emma Chung
British Heart Foundation Research Fellow
University of Leicester, Department of Cardiovascular Sciences

Tel: +44 (0)116 2541414 ext 6065
Email: emlc1@le.ac.uk

9.6 Appendix 4.F TCD screening sheet

Appendix 4

University Hospitals of Leicester NHS
NHS Trust

Date:.....

"BICI" study

Patient name:.....
UHL Number:.....
Address::.....
.....
.....

Patient`s tel: .....
.....

GP Address:.....
.....
.....
.....

Car reg.:.....

1.Window checked ?	
2.Any medical devices?	
3. MRI scan ? (Before surgery)	
4. Neurological tests? (Before surgery)	
5. TCD monitoring	
3. MRI scan ? (After surgery)	
4. Neurological tests? (After surgery)	

Notes:.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....

Page 1

University Hospitals of Leicester NHS
NHS Trust

TCD Settings for Cardiac Surgery Monitoring

Patient name:.....
UHL Number:.....

Date..... **TCD Operator**.....
Date of surgery.....

Right side
Artery Monitored:.....
Depth (mm):.....
SVL (mm):.....
Mean velocity (cm s-1):.....

Left side
Artery Monitored:.....
Depth (mm):.....
SVL (mm):.....
Mean velocity (cm s-1):.....

Headset settings
Front or back lock.....
Clip position at the back.....
.....

Notes:.....
.....
.....
.....
.....
.....
.....
.....

Page 2

9.7 Appendix 4.G Medical records data collection

Medical records data collection sheet

Personal data

Patient name:..... DOB:..... AGE:..... File name: _____	SEX: F/M Date of surgery: ..... Employed : Y/N Education: .....

Part A: Medical Characteristics

Height.....(m) Weight (kg).....BMI(kg/m2).....

Smoking history		Never [ ] Ex-smoker [ ] Current [ ] Pack years [ ]
Alcohol intake	Y / N	Weekly units [ ] Monthly units [ ]
Diabetes mellitus	Y / N	Type: Duration: Treatment:
Hypercholesterolaemia	Y / N	Duration: Treatment:
Hypertension	Y / N	Notes:
Infection	Y/N	Notes:
Thyroid disease	Y/N	Notes:

Renal disease	Y/N	Renal function good fair poor
Respiratory disease	Y/N	Notes:
Histry of pulmonary disease	Y/N	Notes:
Chest pain/angina	Y/N	Notes:
Congenital abnormality	Y/N	Notes:
Ischaemic heart disease	Y/N	Notes:
Cardiovascular disease	Y/N	Notes:
Non-ischemic Cardiovascular disease	Y/N	Notes:
Previous TIA / stroke	Y/N	Notes:
Migraine	Y/N	Notes:
Epilepsy	Y/N	Notes:
Histry of neurological diseas		Notes
Other:		

Part B: Psychological and emotional Well Being

Sleeping difficulties	Y / N	Notes:
Preoperative depression	Y / N	Notes:
Preoperative anxiety	Y / N	Notes:
Preoperative stress	Y / N	Notes:

Is the patient at	Y / N	Notes:

risk of wandering?		
Therapy /treatement	Y / N	Notes:
Any medication?	Y / N	Notes:
Psychological/ psychiatric history	Y / N	Notes:
History of dementia	Y / N	Notes:
Drug Use	Y / N	Notes:
Family history	Y / N	Notes:
Other:		Notes:

Part C. Physiological data

1. Any ApoE-e4 genotype Y/N
2. Systolic blood pressure……
3. Diastolic blood pressure……
4. Pulse pressure……
5. LV dysfunction; Good.49% Fair 30-49% Poor<30%
6. Recent myocardial infraction <6h, 6-24h 1-30days 31-90days
7. Emergency procedure Y/N
8. Post infarct septal rupture Y/N
9. Pre-op heart rhytm
   *SR; *Atrial fibrillation/flutter; *VT/VF
   *complete heart blocked/paced * other abnormal rhytm
10. Previous non-surgical interventions (previous PCI)
11. Pre-op urea and electrolytes (U&Es)
12. Critical pre-operative state Y/N
13. MRI / CT scan result:
14. LVEF (Echocardiographic)
    >50% 30-49% <30%
15. Preoperative laboratory variables :

Pre-op FBS (full blood count)……
Partial Thromboplastin Time (PTT) [s] ……
International Normalized Ratio (INR) [U] ……
Hemoglobin [g/dL] ……
Creatinine [mg/dL] ……

16. Medicines:

ß-blockers……
ACE inhibitors ……
Calcium channel blockers……
Nitrates……
Others……

Part D- Surgical and hospital parameters

Type of surgery		
Length of surgery		
Type of anaesthesia & duration		
Cardiopulmonary Bypass used	Y / N	On bypass on…… Off bypass off…… Total bypass time :
Minimum temp on bypass		
Total complete cross-clamping time (min)		
Myocardial ischemic time (min)		
Time of hypoperfusion (min)		
Time of intubation		
Time of superior vena cava obstruction		
Total Heparin dose (U)		
Protamine dose (U)		
Intra-aortic balloon pump (IABP) use,		

Intraoperative vasopressor use	
Intrope infusion use	
Cold circulatory arrest Y/N	
Diathermy type	
Diathermy plate position	
Dehydration	
Co2 insufflations	
Blood Transfusion Auto transfusion..... Packed red blood cells [U] ..... Fresh Frozen plasma [U] ..... Platelets [U]	
Total blood loss	
Drains Y/N	

Part E-Examination Intra-op

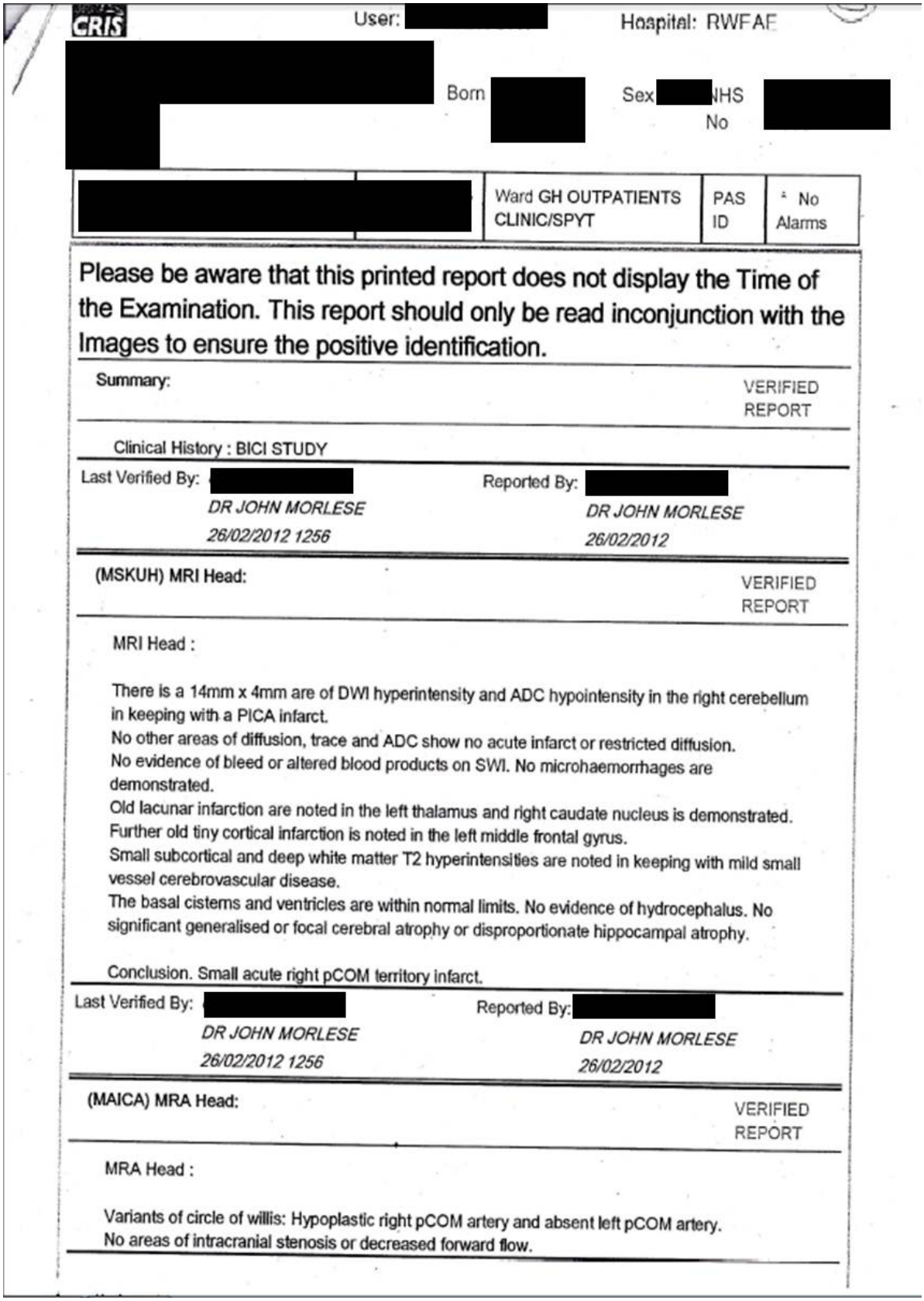
Glucose, fasting (mmol/l)..... Systolic BP (mmHg) ..... Diastolic BP (mmHg) ..... Pulse pressure (mmHg).....	Total cholesterol (mmol/l)..... LDL cholesterol (mmol/l) ..... HDL cholesterol (mmol/l) .....
Intra-op Laryngoscopy grade	
Intra-op TOE summary	
Intrao-op complications	

Drains used	
Number of coronary grafts placed	
Left anterior descending graft placed	
Right anterior descending graft placed	
Circumflex graft placed	
Coronary artery graft conduit used	
Other:	
Intra-op Infusions CNS..... CVS..... RS..... Abdomen/Renal..... Gases..... FBC..... U&Es.....	Lines inserted on day of surgery: CVP ..... Y/N Swan Sheath..... Y/N Arterial Line..... Y/N IABP..... Y/N Peripheral lines..... Y/N Peripheral lines..... Y/N Other:.....

Part F- Postoperative progress and complications

Arrhytmia	Y/N	Psychological distress	Y/N
Low cardiac output	Y/N	Postoperative stress	Y/N
Pulmonary complications	Y/N	Chest tube output (ml)	Y/N
Gastrointestinal problems	Y/N	Intensive care unit (ICU) length of stay	
Infective complications	Y/N	Post-operative morphine consumption	
Postoperative depression	Y/N	Post-operative extubation	
Postoperative anxiety	Y/N	Other:	

9.8 Appendix 4.H MRI report



CRIS User: [redacted] Hospital: RWFAE

[redacted] Born [redacted] Sex [redacted] NHS No [redacted]

[redacted] Ward GH OUTPATIENTS CLINIC/SPYT | PAS ID | No Alarms

Please be aware that this printed report does not display the Time of the Examination. This report should only be read inconjunction with the Images to ensure the positive identification.

Summary: VERIFIED REPORT

Clinical History : BICI STUDY

Last Verified By: [redacted]
DR JOHN MORLESE
26/02/2012 1256

Reported By: [redacted]
DR JOHN MORLESE
26/02/2012

(MSKUH) MRI Head: VERIFIED REPORT

MRI Head :

There is a 14mm x 4mm are of DWI hyperintensity and ADC hypointensity in the right cerebellum in keeping with a PICA infarct.
No other areas of diffusion, trace and ADC show no acute infarct or restricted diffusion.
No evidence of bleed or altered blood products on SWI. No microhaemorrhages are demonstrated.
Old lacunar infarction are noted in the left thalamus and right caudate nucleus is demonstrated.
Further old tiny cortical infarction is noted in the left middle frontal gyrus.
Small subcortical and deep white matter T2 hyperintensities are noted in keeping with mild small vessel cerebrovascular disease.
The basal cisterns and ventricles are within normal limits. No evidence of hydrocephalus. No significant generalised or focal cerebral atrophy or disproportionate hippocampal atrophy.

Conclusion. Small acute right pCOM territory infarct.

Last Verified By: [redacted]
DR JOHN MORLESE
26/02/2012 1256

Reported By: [redacted]
DR JOHN MORLESE
26/02/2012

(MAICA) MRA Head: VERIFIED REPORT

MRA Head :

Variants of circle of willis: Hypoplastic right pCOM artery and absent left pCOM artery.
No areas of intracranial stenosis or decreased forward flow.

(9)

CRIS

User: [redacted] Hospital: RWEAE

[redacted] Born [redacted] Sex [redacted] NHS No [redacted]

[redacted]	[redacted]	Ward GH OUTPATIENTS CLINIC/SPYT	PAS ID	No Alarms

Please be aware that this printed report does not display the Time of the Examination. This report should only be read inconjunction with the Images to ensure the positive identification.

Summary: VERIFIED REPORT

Clinical History : BICI STUDY

Last Verified By: [redacted] *PROF G CHERRYMAN* *16/12/2011 1041*

Reported By: [redacted] *PROF G CHERRYMAN* *16/12/2011*

(MSKUH) MRI Head: VERIFIED REPORT

MRI Head : FIRST SCAN 29.11.11.
No previous brain imaging.

Diffusion trace and ADC show no restricted diffusion or acute infarction.
No bleed or altered blood products.
T2 and FLAIR show minimal burden small vessel CVD in the periventricular white matter and in the anterior limb right internal capsule . No previous infarcts.
No global, lobar, focal or hippocampal atrophy.

No abnormality on the MRA. Both carotids show normal forward flow. Normal terminal vertebral arteries and basilar artery.
Incomplete circle of Willis - no posterior communicating arteries on either side.

Last Verified By: [redacted] *PROF G CHERRYMAN* *16/12/2011 1041*

Reported By: [redacted] *PROF G CHERRYMAN* *16/12/2011*

Event Number: [redacted]
Examination Date: *29/11/2011*

Ref Source: *SPYT TJ, GLENFIELD HOSPITAL, GROBY ROAD, LEICESTER, LEICESTERSHIRE. LE3 9QP*

University Hospitals of Leicester NHS Trust: Clinical Report Page 1 of 1

[redacted]
DoB : [redacted]
Hosp. No. :
CRIS No. :
NHS No.

Ref. Locn. : **GH OUTPATIENTS CLINIC**
Referrer : SPYT TJ, Glenfield Hospital, Groby Road, Leicester, Leicestershire, LE3 9QP

VERIFIED Verified By: DR JOHN MORLESE 26/02/12 Typed By: [redacted]
1257
Clinical History : BICI STUDY

MRI Head :

There is a 14mm x 4mm are of DWI hyperintensity and ADC hypointensity in the right cerebellum in keeping with a PICA infarct.
No other areas of diffusion, trace and ADC show no acute infarct or restricted diffusion.
No evidence of bleed or altered blood products on SWI. No microhaemorrhages are demonstrated.
Old lacunar infarction are noted in the left thalamus and right caudate nucleus is demonstrated. Further old tiny cortical infarction is noted in the left middle frontal gyrus.
Small subcortical and deep white matter T2 hyperintensities are noted in keeping with mild small vessel cerebrovascular disease.
The basal cisterns and ventricles are within normal limits. No evidence of hydrocephalus.
No significant generalised or focal cerebral atrophy or disproportionate hippocampal atrophy.

Conclusion. Small acute right pCOM territory infarct.

MRA Head :

Variants of circle of willis: Hypoplastic right pCOM artery and absent left pCOM artery.
No areas of intracranial stenosis or decreased forward flow.

Event Number : [redacted]
Copy To : ,
Examinations : **MRI Head,MRA Head**

Examination Date : **07/02/12**

9.9 Appendix 4.I Surgical transcript

University Hospitals of Leicester NHS
NHS Trust

Medical Physics, University Hospitals of Leicester NHS Trust

Intra-Operative Transcranial Doppler Monitoring

BICI no.:.....

Date of Op.....

Notes:.....

TCD Information

	Right	Left
Depth (mm):	_____	_____
Sample Volume (mm):	_____	_____

Type of Op.:.....

Time	Surgery stages/ Interventions/Drugs	Time	Surgery stages/ Interventions/Drugs

Appendix 5.A MRI results table

Detailed summary of age, sex, type of procedure, risk factors, cardiopulmonary bypass duration, number and size of MR FLAIR lesions, and outcome of neurocognitive testing for all 77 patients

Patient no.	Sex/Age	Procedure	Risk factors	CPB Time (mins)	Pre-existing lesions No./Volume (mm^3)	New FLAIR lesions No./Volume (mm^3)
1	M/57	CABG	HCL, HTN	84	0	0
2	M/72	CABG	SMK (ex), HTN, HCL	82	70/2656	0
3	M/76	CABG	SMK (ex), HTN, HCL	55	100/17568	0
4	M/64	CABG	SMK (ex), HCL, AS (mild)	93	16/387	0
5	M/71	CABG	HCL, HTN	35	0	0
6	M/57	CABG	HTN	32	29/1037	0
7	M/32	CABG	HTN	63	19/586	0
8	M/67	CABG	SMK (ex), HCL	46	0	0
9	M/61	CABG	SMK (ex), HTN, HCL, AS (mild)	51	0	0
10	M/61	CABG	SMK (ex), HCL, HTN, AS (mild)	77	15/958	1/17
11	M/60	CABG	HCL, HTN	73	0	0
12	M/65	CABG	HCL, HTN, AS (mild)	48	0	0
13*	F/71	CABG	SMK (ex), HCL, HTN	108	7/620	1/1383
14	M/71	CABG	HCL, HTN	76	13/772	0
15	M/76	CABG	SMK (ex), HCL, HTN	86	33/2649	0
16	M/68	CABG	SMK (ex), HCL, HTN	54	9/427	0
17	M/69	CABG	HCL, HTN, AS (mild),	58	0	1/51
18	M/63	CABG	HCL, HTN	66	5/186	1/63
19*	M/66	CABG	HCL, HTN	95	25/743	1/175
20	M/77	CABG	SMK (ex), HCL, HTN, AS (mild)	75	31/4078	0
21	M/57	CABG	SMK (ex), HCL, HTN, AS (mild)	62	33/1076	0

22	M/77	CABG	HCL	54	0	0
23	M/72	CABG	HCL	53	0	0
24	M/56	CABG	HCL, HTN	74	0	0
25	M/53	CABG	SMK (ex), HCL, HTN	62	0	0
26	F/62	CABG	HCL, HTN	35	23/750	0
27	M/76	CABG	SMK (ex), HCL, HTN	122	25/1060	2/49
28	F/45	AVR	SMK (ex), AS (mild)	76	15/322	0
29	M/65	AVR	HCL, HTN, AS (severe)	163	9/742	4/621
30	M/59	AVR	SMK (ex), HCL, HTN, AS (severe)	76	0	0
31	M/57	AVR	HTN, AS (severe)	122	60/5490	0
32	M/50	AVR	SMK (ex), AS (severe)	94	0	0
33	M/65	AVR	AS (severe)	123	23/650	0
34	F/40	AVR	HCL, HTN, AS (severe)	92	1/21	2/47
35	M/59	AVR	SMK (ex), HCL, HTN, AS (severe)	109	10/338	0
36	M/65	AVR	SMK (ex), HCL, AS (severe)	95	24/672	0
37	M/69	AVR	SMK (ex), HCL, HTN, AS (severe)	111	0	0
38	M/72	AVR	SMK (ex), HTN, HCL, AS (severe)	88	0	0
39	M/49	AVR	SMK (ex), HTN, AS (mild)	84	22/1736	1/13
40	M/60	AVR	HTN, HCL, AS (mild)	273	11/190	3/132
41	M/62	AVR	None	80	25/575	0
42	F/71	AVR	SMK (ex), HCL, AS (severe)	66	67/7055	1/309
43	M/59	AVR	AS (severe)	89	0	1/28
44	M/46	AVR	SMK, HCL, HTN, AS (severe)	80	49/3416	1/26
45	M/32	AVR	None	40	0	0
46	M/80	AVR	HTN, AS (severe)	65	8/260	2/167
47*	M/50	AVR	SMK (ex), HCL, AS (severe)	63	70/3516	2/389
48	M/59	AVR	HCL, HTN, AS (severe)	71	0	0
49	M/65	AVR	SMK (ex), AS (severe)	120	11/602	1/15
50	M/78	AVR	SMK (ex), HCL, HTN, AS (severe)	62	8/1073	0

51	M/54	AVR	HCL, HTN, AS (severe)	87	0	0
52	M/71	AVR	SMK (ex), HCL, HTN, AS (severe)	90	17/1146	0
53	M/72	AVR	HTN, AS (mild)	92	0	0
54	M/68	AVR	HCL, HTN, AS (severe)	87	78/27950	1/67
55	M/54	AVR	SMK (ex), HCL, HTN, AS (severe)	112	0	0
56	M/63	AVR	HCL, HTN, AS (severe)	72	0	0
57	M/59	MVR	HTN, HCL	87	28/1098	0
58	M/71	MVR	SMK (ex), HCL, HTN, AS (mild)	75	42/1308	2/224
59	M/65	MVR	None	185	19/550	0
60	M/41	MVR	HCL, HTN	153	0	0
61	M/64	MVR	None	100	30/914	1/5
62*	M/64	MVR	None	64	42/1110	1/81
63*	M/57	MVR	None	44	36/911	5/979
64	M/75	AVR/CABG	HCL, HTN, AS (severe)	139	19/1974	2/241
65	M/79	AVR/CABG	HTN, AS (severe)	100	58/6446	0
66	M/68	AVR/CABG	SMK (ex), HCL, AS (severe)	103	13/711	1/44
67	M/75	AVR/CABG	SMK (ex), HTN, HCL	78	88/3655	0
68	M/61	AVR/CABG	SMK (ex), HCL, HTN	107	0	0
69	M/64	AVR/CABG	HTN	80	20/768	0
70	M/55	AVR/CABG	SMK, HCL, AS(severe)	102	16/1876	0
71	M/69	AVR/CABG	SMK (ex), HCL, HTN, AS (severe)	111	61/3790	0
72	M/65	AVR/CABG	HCL, SMK (ex), HTN	219	38/1146	0
73	M/66	MVR/CABG	SMK (ex), HCL, HTN, AS (mild)	110	0	0
74	M/74	MVR/CABG	HCL, HTN	55	25/1231	1/37
75	M/56	MVR/CABG	SMK (ex), HCL	119	0	0
76	M/72	MVR/TVR	SMK (ex), HCL, HTN, AS (mild)	271	0	0
77	M/61	MVR/TVR/CABG	HCL, HTN	254	0	0

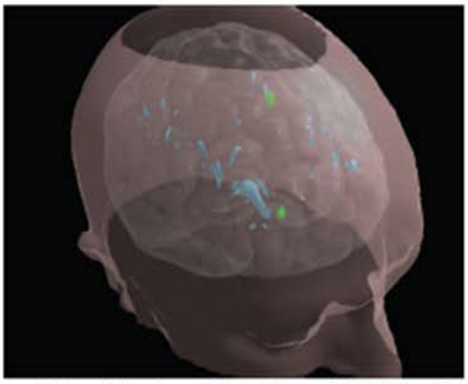
Patients marked with * had perioperative stroke diagnosed clinically. CABG=Coronary Artery Bypass Graft; AVR=Aortic Valve Replacement; MVR=Mitral Valve Replacement; TVR=Tricuspid Valve Replacement. In the list of risk factors SMK=Smoker; HCL=hypercholesterolemia; HTN=hypertension; AS=aortic stenosis.

9.10 Appendix 5.B March 2015 Issue Stroke Cover

Volume 46, Number 3, March 2015
ISSN 0039-2499
http://stroke.ahajournals.org

American Heart Association | American Stroke Association.

Stroke



Preexisting (Blue) and New (Green) MRI Lesions After Cardiac Surgery

10 Bibliography

1. Aaslid, R., Markwalder, T.M., Nornes, H., 1982. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *Journal of Neurosurgery.* **57,** 769-774.

2. Aaslid, R., Newell, D.W., Stooss, R., Sorteberg, W., Lindegaard, K.F., 1991. Assessment of cerebral autoregulation dynamics from simultaneous arterial and venous transcranial Doppler recordings in humans. *Stroke; a Journal of Cerebral Circulation.* **22,** 1148-1154.

3. Abbott, N.J., 2000. Inflammatory mediators and modulation of blood-brain barrier permeability. *Cellular and Molecular Neurobiology.* **20,** 131-147.

4. Abu-Omar, Y., Balacumaraswami, L., Pigott, D.W., Matthews, P.M., Taggart, D.P., 2004. Solid and gaseous cerebral microembolization during off-pump, on-pump, and open cardiac surgery procedures. *The Journal of Thoracic and Cardiovascular Surgery.* **127,** 1759-1765.

5. Abu-Omar, Y., Cader, S., Guerrieri Wolf, L., Pigott, D., Matthews, P.M., Taggart, D.P., 2006. Short-term changes in cerebral activity in on-pump and off-pump cardiac surgery defined by functional magnetic resonance imaging and their relationship to microembolization. *The Journal of Thoracic and Cardiovascular Surgery.* **132,** 1119-1125.

6. Ackerstaff, R.G., Vos, J.A., Antonius Carotid Endarterectomy, Angioplasty, and Stenting Study Group, 2004. TCD-detected cerebral embolism in carotid endarterectomy versus angioplasty and stenting of the carotid bifurcation. *Acta Chirurgica Belgica.* **104,** 55-59.

7. Agarwal, R., Kalita, J., Pandey, S., Agarwal, S.K., Misra, U.K., 2010. Evaluation of cognitive function and P300 in patients undergoing cardiac surgery. *Electromyography and Clinical Neurophysiology.* **50,** 259-264.

8. Ahonen, J. & Salmenpera, M., 2004. Brain injury after adult cardiac surgery. *Acta Anaesthesiologica Scandinavica.* **48,** 4-19.

9. Andrell, P., Jensen, C., Norrsell, H., Ekre, O., Ekholm, S., Norrsell, U., Eliasson, T., Mannheimer, C., Blomstrand, C., 2005. White matter disease in magnetic resonance imaging predicts cerebral complications after coronary artery bypass grafting. *The Annals of Thoracic Surgery.* **79,** 74-9; discussion 79-80.

10. Antiga, L., Piccinelli, M., Botti, L., Ene-Iordache, B., Remuzzi, A., Steinman, D.A., 2008. An image-based modeling framework for patient-specific computational hemodynamics. *Medical & Biological Engineering & Computing.* **46,** 1097-1112.

11. Arrowsmith, J.E., Harrison, M.J., Newman, S.P., Stygall, J., Timberlake, N., Pugsley, W.B., 1998. Neuroprotection of the brain during cardiopulmonary bypass: a

randomized trial of remacemide during coronary artery bypass in 171 patients. *Stroke; a Journal of Cerebral Circulation.* **29,** 2357-2362.

12. Aylard, P.R., Gooding, J.H., McKenna, P.J., Snaith, R.P., 1987. A validation study of three anxiety and depression self-assessment scales. *Journal of Psychosomatic Research.* **31,** 261-268.

13. Baird, A.E., Lovblad, K.O., Dashe, J.F., Connor, A., Burzynski, C., Schlaug, G., Straroselskaya, I., Edelman, R.R., Warach, S., 2000. Clinical correlations of diffusion and perfusion lesion volumes in acute ischemic stroke. *Cerebrovascular Diseases (Basel, Switzerland).* **10,** 441-448.

14. Baker, R.A. & Willcox, T.W., 2006. Australian and New Zealand perfusion survey: equipment and monitoring. *The Journal of Extra-Corporeal Technology.* **38,** 220-229.

15. Banahan, C., Hague, J.P., Evans, D.H., Patel, R., Ramnarine, K.V., Chung, E.M., 2012. Sizing gaseous emboli using Doppler embolic signal intensity. *Ultrasound in Medicine & Biology.* **38,** 824-833.

16. Banbury, M.K., Kouchoukos, N.T., Allen, K.B., Slaughter, M.S., Weissman, N.J., Berry, G.J., Horvath, K.A., ICEM 2000 Investigators, 2003. Emboli capture using the Embol-X intraaortic filter in cardiac surgery: a multicentered randomized trial of 1,289 patients. *The Annals of Thoracic Surgery.* **76,** 508-15; discussion 515.

17. Barak, M. & Katz, Y., 2005. Microbubbles: pathophysiology and clinical implications. *Chest.* **128,** 2918-2932.

18. Barber, P.A., Hach, S., Tippett, L.J., Ross, L., Merry, A.F., Milsom, P., 2008. Cerebral ischemic lesions on diffusion-weighted imaging are associated with neurocognitive decline after cardiac surgery. *Stroke; a Journal of Cerebral Circulation.* **39,** 1427-1433.

19. Barbut, D., Hinton, R.B., Szatrowski, T.P., Hartman, G.S., Bruefach, M., Williams-Russo, P., Charlson, M.E., Gold, J.P., 1994. Cerebral emboli detected during bypass surgery are associated with clamp removal. *Stroke; a Journal of Cerebral Circulation.* **25,** 2398-2402.

20. Barbut, D., Yao, F.S., Hager, D.N., Kavanaugh, P., Trifiletti, R.R., Gold, J.P., 1996. Comparison of transcranial Doppler ultrasonography and transesophageal echocardiography to monitor emboli during coronary artery bypass surgery. *Stroke; a Journal of Cerebral Circulation.* **27,** 87-90.

21. Bar-Yosef, S., Anders, M., Mackensen, G.B., Ti, L.K., Mathew, J.P., Phillips-Bute, B., Messier, R.H., Grocott, H.P., Neurological Outcome Research Group and CARE Investigators of the Duke Heart Center, 2004. Aortic atheroma burden and cognitive dysfunction after coronary artery bypass graft surgery. *The Annals of Thoracic Surgery.* **78,** 1556-1562.

22. Basile, A.M., Fusi, C., Conti, A.A., Paniccia, R., Trefoloni, G., Pracucci, G., Di Carlo, A., Noferi, D., Carbonetto, F., Pretelli, P., Calamai, G., Vaccari, M., Abbate, R.,

Inzitari, D., 2001. S-100 protein and neuron-specific enolase as markers of subclinical cerebral damage after cardiac surgery: preliminary observation of a 6-month follow-up study. *European Neurology.* **45,** 151-159.

23. Baufreton, C., Allain, P., Chevailler, A., Etcharry-Bouyx, F., Corbeau, J.J., Legall, D., de Brux, J.L., 2005. Brain injury and neuropsychological outcome after coronary artery surgery are affected by complement activation. *The Annals of Thoracic Surgery.* **79,** 1597-1605.

24. Bayram, H., Hidiroglu, M., Cetin, L., Kucuker, A., Iriz, E., Uguz, E., Saglam, F., Sener, E., 2013. Comparing S-100 beta protein levels and neurocognitive functions between patients undergoing on-pump and off-pump coronary artery bypass grafting. *The Journal of Surgical Research.* **182,** 198-202.

25. Bendszus, M., Reents, W., Franke, D., Mullges, W., Babin-Ebell, J., Koltzenburg, M., Warmuth-Metz, M., Solymosi, L., 2002. Brain damage after coronary artery bypass grafting. *Archives of Neurology.* **59,** 1090-1095.

26. Blauth, C.I., Smith, P.L., Arnold, J.V., Jagoe, J.R., Wootton, R., Taylor, K.M., 1990. Influence of oxygenator type on the prevalence and extent of microembolic retinal ischemia during cardiopulmonary bypass. Assessment by digital image analysis. *The Journal of Thoracic and Cardiovascular Surgery.* **99,** 61-69.

27. Blumenthal, J.A., Mahanna, E.P., Madden, D.J., White, W.D., Croughwell, N.D., Newman, M.F., 1995. Methodological issues in the assessment of neuropsychologic function after cardiac surgery. *The Annals of Thoracic Surgery.* **59,** 1345-1350.

28. Boivie, P., Hansson, M., Engstrom, K.G., 2003. Embolic material generated by multiple aortic crossclamping: a perfusion model with human cadaveric aorta. *The Journal of Thoracic and Cardiovascular Surgery.* **125,** 1451-1460.

29. Bokeriia, L.A., Golukhova, E.Z., Breskina, N.Y., Polunina, A.G., Davydov, D.M., Begachev, A.V., Kazanovskaya, S.N., 2007. Asymmetric cerebral embolic load and postoperative cognitive dysfunction in cardiac surgery. *Cerebrovascular Diseases (Basel, Switzerland).* **23,** 50-56.

30. Bolotin, G., Huber, C.H., Shani, L., Mohr, F.W., Carrel, T.P., Borger, M.A., Falk, V., Taggart, D., Nir, R.R., Englberger, L., Seeburger, J., Caliskan, E., Starck, C.T., 2014. Novel emboli protection system during cardiac surgery: a multi-center, randomized, clinical trial. *The Annals of Thoracic Surgery.* **98,** 1627-33; discussion 1633-4.

31. Boodhwani, M., Rubens, F., Wozny, D., Rodriguez, R., Nathan, H.J., 2007. Effects of sustained mild hypothermia on neurocognitive function after coronary artery bypass surgery: a randomized, double-blind study. *The Journal of Thoracic and Cardiovascular Surgery.* **134,** 1443-50; discussion 1451-2.

32. Boodhwani, M., Rubens, F.D., Wozny, D., Rodriguez, R., Alsefaou, A., Hendry, P.J., Nathan, H.J., 2006. Predictors of early neurocognitive deficits in low-risk patients undergoing on-pump coronary artery bypass surgery. *Circulation.* **114,** I461-6.

33. Borger, M.A., Peniston, C.M., Weisel, R.D., Vasiliou, M., Green, R.E., Feindel, C.M., 2001. Neuropsychologic impairment after coronary bypass surgery: effect of gaseous microemboli during perfusionist interventions. *The Journal of Thoracic and Cardiovascular Surgery.* **121,** 743-749.

34. Borger, M.A., Taylor, R.L., Weisel, R.D., Kulkarni, G., Benaroia, M., Rao, V., Cohen, G., Fedorko, L., Feindel, C.M., 1999. Decreased cerebral emboli during distal aortic arch cannulation: a randomized clinical trial. *The Journal of Thoracic and Cardiovascular Surgery.* **118,** 740-745.

35. Bottio, T., Bisleri, G., Piccoli, P., Negri, A., Manzato, A., Muneretto, C., 2007. Heart valve surgery in a very high-risk population: a preliminary experience in awake patients. *The Journal of Heart Valve Disease.* **16,** 187-194.

36. Braekken, S.K., Reinvang, I., Russell, D., Brucher, R., Svennevig, J.L., 1998. Association between intraoperative cerebral microembolic signals and postoperative neuropsychological deficit: comparison between patients with cardiac valve replacement and patients with coronary artery bypass grafting. *Journal of Neurology, Neurosurgery, and Psychiatry.* **65,** 573-576.

37. Bramley, P.N., Easton, A.M., Morley, S., Snaith, R.P., 1988. The differentiation of anxiety and depression by rating scales. *Acta Psychiatrica Scandinavica.* **77,** 133-138.

38. Brott, T., Adams, H.P.,Jr, Olinger, C.P., Marler, J.R., Barsan, W.G., Biller, J., Spilker, J., Holleran, R., Eberle, R., Hertzberg, V., 1989. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke; a Journal of Cerebral Circulation.* **20,** 864-870.

39. Browndyke, J.N., Moser, D.J., Cohen, R.A., O'Brien, D.J., Algina, J.J., Haynes, W.G., Staples, E.D., Alexander, J., Davies, L.K., Bauer, R.M., 2002. Acute neuropsychological functioning following cardiosurgical interventions associated with the production of intraoperative cerebral microemboli. *The Clinical Neuropsychologist.* **16,** 463-471.

40. Bucerius, J., Gummert, J.F., Borger, M.A., Walther, T., Doll, N., Onnasch, J.F., Metz, S., Falk, V., Mohr, F.W., 2003. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. *The Annals of Thoracic Surgery.* **75,** 472-478.

41. CAGUIN, F. & CARTER, M.G., 1963. Fat Embolization with Cardiotomy with the use of Cardiopulmonary Bypass. *The Journal of Thoracic and Cardiovascular Surgery.* **46,** 665-672.

42. Calafiore, A.M., Bar-El, Y., Vitolla, G., Di Giammarco, G., Teodori, G., Iaco, A.L., D'Alessandro, S., Di Mauro, M., 2001. Early clinical experience with a new sutureless anastomotic device for proximal anastomosis of the saphenous vein to the aorta. *The Journal of Thoracic and Cardiovascular Surgery.* **121,** 854-858.

43. Carnevale, D., Mascio, G., Ajmone-Cat, M.A., D'Andrea, I., Cifelli, G., Madonna, M., Cocozza, G., Frati, A., Carullo, P., Carnevale, L., Alleva, E., Branchi, I., Lembo,

G., Minghetti, L., 2012. Role of neuroinflammation in hypertension-induced brain amyloid pathology. *Neurobiology of Aging.* **33,** 205.e19-205.e29.

44. Carr, J.J., 2012. The revolution in risk assessment and disease detection made possible with non-invasive imaging: implications for population science. *Ethnicity & Disease.* **22,** S1-24-7.

45. Carrascal, Y., Casquero, E., Gualis, J., Di Stefano, S., Florez, S., Fulquet, E., Echevarria, J.R., Fiz, L., 2005. Cognitive decline after cardiac surgery: proposal for easy measurement with a new test. *Interactive Cardiovascular and Thoracic Surgery.* **4,** 216-221.

46. Cavarocchi, N.C., Pluth, J.R., Schaff, H.V., Orszulak, T.A., Homburger, H.A., Solis, E., Kaye, M.P., Clancy, M.S., Kolff, J., Deeb, G.M., 1986. Complement activation during cardiopulmonary bypass. Comparison of bubble and membrane oxygenators. *The Journal of Thoracic and Cardiovascular Surgery.* **91,** 252-258.

47. Chalela, J.A., Kidwell, C.S., Nentwich, L.M., Luby, M., Butman, J.A., Demchuk, A.M., Hill, M.D., Patronas, N., Latour, L., Warach, S., 2007. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. *Lancet.* **369,** 293-298.

48. Challa, V.R., Lovell, M.A., Moody, D.M., Brown, W.R., Reboussin, D.M., Markesbery, W.R., 1998. Laser microprobe mass spectrometric study of aluminum and silicon in brain emboli related to cardiac surgery. *Journal of Neuropathology and Experimental Neurology.* **57,** 140-147.

49. Charlson, M.E., Peterson, J.C., Krieger, K.H., Hartman, G.S., Hollenberg, J.P., Briggs, W.M., Segal, A.Z., Parikh, M., Thomas, S.J., Donahue, R.G., Purcell, M.H., Pirraglia, P.A., Isom, O.W., 2007. Improvement of outcomes after coronary artery bypass II: a randomized trial comparing intraoperative high versus customized mean arterial pressure. *Journal of Cardiac Surgery.* **22,** 465-472.

50. Chaudhuri, K. & Marasco, S.F., 2011. The effect of carbon dioxide insufflation on cognitive function during cardiac surgery. *Journal of Cardiac Surgery.* **26,** 189-196.

51. Chaves, C.J., Silver, B., Schlaug, G., Dashe, J., Caplan, L.R., Warach, S., 2000. Diffusion- and perfusion-weighted MRI patterns in borderzone infarcts. *Stroke; a Journal of Cerebral Circulation.* **31,** 1090-1096.

52. Christenson, J.T., Vala, D.L., Licker, M., Sierra, J., Kalangos, A., 2005. Intra-aortic filtration: capturing particulate emboli during aortic cross-clamping. *Texas Heart Institute Journal / from the Texas Heart Institute of St.Luke's Episcopal Hospital, Texas Children's Hospital.* **32,** 515-521.

53. Chung, E.M., Banahan, C., Patel, N., Janus, J., Marshall, D., Horsfield, M.A., Rousseau, C., Keelan, J., Evans, D.H., Hague, J.P., 2015. Size Distribution of Air Bubbles Entering the Brain during Cardiac Surgery. *PloS One.* **10,** e0122166.

54. Chung, E.M., Hague, J.P., Chanrion, M.A., Ramnarine, K.V., Katsogridakis, E., Evans, D.H., 2010. Embolus trajectory through a physical replica of the major cerebral arteries. *Stroke; a Journal of Cerebral Circulation.* **41,** 647-652.

55. Chung, E.M., Hague, J.P., Evans, D.H., 2007. Revealing the mechanisms underlying embolic stroke using computational modelling. *Physics in Medicine and Biology.* **52,** 7153-7166.

56. Cibelli, M., Fidalgo, A.R., Terrando, N., Ma, D., Monaco, C., Feldmann, M., Takata, M., Lever, I.J., Nanchahal, J., Fanselow, M.S., Maze, M., 2010. Role of interleukin-1beta in postoperative cognitive dysfunction. *Annals of Neurology.* **68,** 360-368.

57. Clark, R.E., Brillman, J., Davis, D.A., Lovell, M.R., Price, T.R., Magovern, G.J., 1995. Microemboli during coronary artery bypass grafting. Genesis and effect on outcome. *The Journal of Thoracic and Cardiovascular Surgery.* **109,** 249-57; discussion 257-8.

58. Cook, D.J., Huston, J.,3rd, Trenerry, M.R., Brown, R.D.,Jr, Zehr, K.J., Sundt, T.M.,3rd, 2007. Postcardiac surgical cognitive impairment in the aged using diffusion-weighted magnetic resonance imaging. *The Annals of Thoracic Surgery.* **83,** 1389-1395.

59. Crisostomo, R.A., Garcia, M.M., Tong, D.C., 2003. Detection of diffusion-weighted MRI abnormalities in patients with transient ischemic attack: correlation with clinical characteristics. *Stroke; a Journal of Cerebral Circulation.* **34,** 932-937.

60. Dagirmanjian, A., Davis, D.A., Rothfus, W.E., Goldberg, A.L., Deeb, Z.L., 2000. Detection of clinically silent intracranial emboli ipsilateral to internal carotid occlusions during cerebral angiography. *AJR.American Journal of Roentgenology.* **174,** 367-369.

61. David, T. & Moore, S., 2008. Modeling perfusion in the cerebral vasculature. *Medical Engineering & Physics.* **30,** 1227-1245.

62. Delphin, E., Jackson, D., Gubenko, Y., Botea, A., Esrig, B., Fritz, W., Mavridis, S., 2007. Sevoflurane provides earlier tracheal extubation and assessment of cognitive recovery than isoflurane in patients undergoing off-pump coronary artery bypass surgery. *Journal of Cardiothoracic and Vascular Anesthesia.* **21,** 690-695.

63. Derkach, D.N., Okamoto, H., Takahashi, S., 2000. Neuronal and astroglial injuries in patients undergoing coronary artery bypass grafting and aortic arch replacement during hypothermic cardiopulmonary bypass. *Anesthesia and Analgesia.* **91,** 1066-1072.

64. Deverall, P.B., Padayachee, T.S., Parsons, S., Theobold, R., Battistessa, S.A., 1988. Ultrasound detection of micro-emboli in the middle cerebral artery during cardiopulmonary bypass surgery. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **2,** 256-260.

65. Diegeler, A., Hirsch, R., Schneider, F., Schilling, L.O., Falk, V., Rauch, T., Mohr, F.W., 2000. Neuromonitoring and neurocognitive outcome in off-pump versus

conventional coronary bypass operation. *The Annals of Thoracic Surgery.* **69,** 1162-1166.

66. Dittrich, R. & Ringelstein, E.B., 2008. Occurrence and clinical impact of microembolic signals during or after cardiosurgical procedures. *Stroke; a Journal of Cerebral Circulation.* **39,** 503-511.

67. Djaiani, G., Fedorko, L., Borger, M., Mikulis, D., Carroll, J., Cheng, D., Karkouti, K., Beattie, S., Karski, J., 2004. Mild to moderate atheromatous disease of the thoracic aorta and new ischemic brain lesions after conventional coronary artery bypass graft surgery. *Stroke; a Journal of Cerebral Circulation.* **35,** e356-8.

68. Djaiani, G., Fedorko, L., Borger, M.A., Green, R., Carroll, J., Marcon, M., Karski, J., 2007. Continuous-flow cell saver reduces cognitive decline in elderly patients after coronary bypass surgery. *Circulation.* **116,** 1888-1895.

69. Dowd, N.P., Karski, J.M., Cheng, D.C., Gajula, S., Seneviratne, P., Munro, J.A., Fiducia, D., 2001. Fast-track cardiac anaesthesia in the elderly: effect of two different anaesthetic techniques on mental recovery. *British Journal of Anaesthesia.* **86,** 68-76.

70. Dumas, A., Dupuis, G.H., Searle, N., Cartier, R., 1999. Early versus late extubation after coronary artery bypass grafting: effects on cognitive function. *Journal of Cardiothoracic and Vascular Anesthesia.* **13,** 130-135.

71. Ebinger, M., Galinovic, I., Rozanski, M., Brunecker, P., Endres, M., Fiebach, J.B., 2010. Fluid-attenuated inversion recovery evolution within 12 hours from stroke onset: a reliable tissue clock? *Stroke; a Journal of Cerebral Circulation.* **41,** 250-255.

72. Eckenhoff, R.G., Johansson, J.S., Wei, H., Carnini, A., Kang, B., Wei, W., Pidikiti, R., Keller, J.M., Eckenhoff, M.F., 2004. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. *Anesthesiology.* **101,** 703-709.

73. Edmunds, L.H.,Jr, Clark, R.E., Cohn, L.H., Grunkemeier, G.L., Miller, D.C., Weisel, R.D., 1996. Guidelines for reporting morbidity and mortality after cardiac valvular operations. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **10,** 812-816.

74. Eifert, S., Reichenspurner, H., Pfefferkorn, T., Baur, B., von Schlippenbach, C., Mayer, T.E., Hamann, G., Reichart, B., 2003. Neurological and neuropsychological examination and outcome after use of an intra-aortic filter device during cardiac surgery. *Perfusion.* **18 Suppl 1,** 55-60.

75. Ernest, C.S., Worcester, M.U., Tatoulis, J., Elliott, P.C., Murphy, B.M., Higgins, R.O., Le Grande, M.R., Goble, A.J., 2006. Neurocognitive outcomes in off-pump versus on-pump bypass surgery: a randomized controlled trial. *The Annals of Thoracic Surgery.* **81,** 2105-2114.

76. Evered, L., Scott, D.A., Silbert, B., Maruff, P., 2011. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesthesia and Analgesia.* **112,** 1179-1185.

77. Farsak, B., Gunaydin, S., Yorgancioglu, C., Zorlutuna, Y., 2003. Elevated levels of s-100beta correlate with neurocognitive outcome after cardiac surgery. *The Journal of Cardiovascular Surgery.* **44,** 31-35.

78. Fearn, S.J., Pole, R., Wesnes, K., Faragher, E.B., Hooper, T.L., McCollum, C.N., 2001. Cerebral injury during cardiopulmonary bypass: emboli impair memory. *The Journal of Thoracic and Cardiovascular Surgery.* **121,** 1150-1160.

79. Fitch, J.C., Rollins, S., Matis, L., Alford, B., Aranki, S., Collard, C.D., Dewar, M., Elefteriades, J., Hines, R., Kopf, G., Kraker, P., Li, L., O'Hara, R., Rinder, C., Rinder, H., Shaw, R., Smith, B., Stahl, G., Shernan, S.K., 1999. Pharmacology and biological efficacy of a recombinant, humanized, single-chain antibody C5 complement inhibitor in patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass. *Circulation.* **100,** 2499-2506.

80. Floyd, T.F., Shah, P.N., Price, C.C., Harris, F., Ratcliffe, S.J., Acker, M.A., Bavaria, J.E., Rahmouni, H., Kuersten, B., Wiegers, S., McGarvey, M.L., Woo, J.Y., Pochettino, A.A., Melhem, E.R., 2006. Clinically silent cerebral ischemic events after cardiac surgery: their incidence, regional vascular occurrence, and procedural dependence. *The Annals of Thoracic Surgery.* **81,** 2160-2166.

81. Funder, K.S., Steinmetz, J., Rasmussen, L.S., 2010. Methodological issues of postoperative cognitive dysfunction research. *Seminars in Cardiothoracic and Vascular Anesthesia.* **14,** 119-122.

82. Gaunt, M.E., Martin, P.J., Smith, J.L., Rimmer, T., Cherryman, G., Ratliff, D.A., Bell, P.R., Naylor, A.R., 1994. Clinical relevance of intraoperative embolization detected by transcranial Doppler ultrasonography during carotid endarterectomy: a prospective study of 100 patients. *The British Journal of Surgery.* **81,** 1435-1439.

83. Georgiadis, D., Berger, A., Kowatschev, E., Lautenschlager, C., Borner, A., Lindner, A., Schulte-Mattler, W., Zerkowski, H.R., Zierz, S., Deufel, T., 2000. Predictive value of S-100beta and neuron-specific enolase serum levels for adverse neurologic outcome after cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery.* **119,** 138-147.

84. Gerriets, T., Schwarz, N., Bachmann, G., Kaps, M., Kloevekorn, W.P., Sammer, G., Tschernatsch, M., Nottbohm, R., Blaes, F., Schonburg, M., 2010. Evaluation of methods to predict early long-term neurobehavioral outcome after coronary artery bypass grafting. *The American Journal of Cardiology.* **105,** 1095-1101.

85. Gerriets, T., Schwarz, N., Sammer, G., Baehr, J., Stolz, E., Kaps, M., Kloevekorn, W.P., Bachmann, G., Schonburg, M., 2010. Protecting the brain from gaseous and solid micro-emboli during coronary artery bypass grafting: a randomized controlled trial. *European Heart Journal.* **31,** 360-368.

86. GIBBON, J.H.,Jr, 1954. Application of a mechanical heart and lung apparatus to cardiac surgery. *Minnesota Medicine.* **37,** 171-85; passim.

87. GILMAN, S., 1965. Cerebral Disorders After Open-Heart Operations. *The New England Journal of Medicine.* **272,** 489-498.

88. Glas, K.E., Swaminathan, M., Reeves, S.T., Shanewise, J.S., Rubenson, D., Smith, P.K., Mathew, J.P., Shernan, S.K., Council for Intraoperative Echocardiography of the American Society of Echocardiography, Society of Cardiovascular Anesthesiologists, Society of Thoracic Surgeons, 2008. Guidelines for the performance of a comprehensive intraoperative epiaortic ultrasonographic examination: recommendations of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists; endorsed by the Society of Thoracic Surgeons. *Anesthesia and Analgesia.* **106,** 1376-1384.

89. Gold, J.P., Charlson, M.E., Williams-Russo, P., Szatrowski, T.P., Peterson, J.C., Pirraglia, P.A., Hartman, G.S., Yao, F.S., Hollenberg, J.P., Barbut, D., 1995. Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. *The Journal of Thoracic and Cardiovascular Surgery.* **110,** 1302-11; discussion 1311-4.

90. Gorna, R., Kustrzycki, W., Kiejna, A., Rymaszewska, J., 2001. Assessment of short-term neuropsychologic changes after normothermic versus hypothermic coronary artery bypass grafting. *Psychiatria Polska.* **35,** 781-795.

91. Goto, T., Baba, T., Honma, K., Shibata, Y., Arai, Y., Uozumi, H., Okuda, T., 2001. Magnetic resonance imaging findings and postoperative neurologic dysfunction in elderly patients undergoing coronary artery bypass grafting. *The Annals of Thoracic Surgery.* **72,** 137-142.

92. Gottesman, R.F., Hillis, A.E., Grega, M.A., Borowicz, L.M.,Jr, Selnes, O.A., Baumgartner, W.A., McKhann, G.M., 2007. Early postoperative cognitive dysfunction and blood pressure during coronary artery bypass graft operation. *Archives of Neurology.* **64,** 1111-1114.

93. Govier, A.V., Reves, J.G., McKay, R.D., Karp, R.B., Zorn, G.L., Morawetz, R.B., Smith, L.R., Adams, M., Freeman, A.M., 1984. Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. *The Annals of Thoracic Surgery.* **38,** 592-600.

94. Grieco, G., d'Hollosy, M., Culliford, A.T., Jonas, S., 1996. Evaluating neuroprotective agents for clinical anti-ischemic benefit using neurological and neuropsychological changes after cardiac surgery under cardiopulmonary bypass. Methodological strategies and results of a double-blind, placebo-controlled trial of GM1 ganglioside. *Stroke; a Journal of Cerebral Circulation.* **27,** 858-874.

95. Grigore, A.M., Grocott, H.P., Mathew, J.P., Phillips-Bute, B., Stanley, T.O., Butler, A., Landolfo, K.P., Reves, J.G., Blumenthal, J.A., Newman, M.F., Neurologic Outcome Research Group of the Duke Heart Center, 2002. The rewarming rate and increased peak temperature alter neurocognitive outcome after cardiac surgery. *Anesthesia and Analgesia.* **94,** 4-10, table of contents.

96. Grigore, A.M., Mathew, J., Grocott, H.P., Reves, J.G., Blumenthal, J.A., White, W.D., Smith, P.K., Jones, R.H., Kirchner, J.L., Mark, D.B., Newman, M.F., Neurological Outcome Research Group, CARE Investigators of the Duke Heart Center. Cardiothoracic Anesthesia Research Endeavors, 2001. Prospective randomized trial of normothermic versus hypothermic cardiopulmonary bypass on cognitive function after coronary artery bypass graft surgery. *Anesthesiology.* **95,** 1110-1119.

97. Grimm, M., Czerny, M., Baumer, H., Kilo, J., Madl, C., Kramer, L., Rajek, A., Wolner, E., 2000. Normothermic cardiopulmonary bypass is beneficial for cognitive brain function after coronary artery bypass grafting--a prospective randomized trial. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **18,** 270-275.

98. Grocott, H.P., 2007. Pharmacologic neuroprotection: the search continues. *The Journal of Extra-Corporeal Technology.* **39,** 296-301.

99. Grocott, H.P., Mackensen, G.B., Grigore, A.M., Mathew, J., Reves, J.G., Phillips-Bute, B., Smith, P.K., Newman, M.F., Neurologic Outcome Research Group (NORG), Cardiothoracic Anesthesiology Research Endeavors (CARE) Investigators' of the Duke Heart Center, 2002. Postoperative hyperthermia is associated with cognitive dysfunction after coronary artery bypass graft surgery. *Stroke; a Journal of Cerebral Circulation.* **33,** 537-541.

100. Grosset, D.G., Cowburn, P., Georgiadis, D., Dargie, H.J., Faichney, A., Lee, K.R., 1994. Ultrasound detection of cerebral emboli in patients with prosthetic heart valves. *The Journal of Heart Valve Disease.* **3,** 128-132.

101. Hague, J.P., Banahan, C., Chung, E.M., 2013. Modelling of impaired cerebral blood flow due to gaseous emboli. *Physics in Medicine and Biology.* **58,** 4381-4394.

102. Hague, J.P. & Chung, E.M., 2009. Statistical physics of cerebral embolization leading to stroke. *Physical Review.E, Statistical, Nonlinear, and Soft Matter Physics.* **80,** 051912.

103. Haines, D.E., Stewart, M.T., Barka, N.D., Kirchhof, N., Lentz, L.R., Reinking, N.M., Urban, J.F., Halimi, F., Deneke, T., Kanal, E., 2013. Microembolism and catheter ablation II: effects of cerebral microemboli injection in a canine model. *Circulation.Arrhythmia and Electrophysiology.* **6,** 23-30.

104. Hajjar, L.A., Vincent, J.L., Galas, F.R., Nakamura, R.E., Silva, C.M., Santos, M.H., Fukushima, J., Kalil Filho, R., Sierra, D.B., Lopes, N.H., Mauad, T., Roquim, A.C., Sundin, M.R., Leao, W.C., Almeida, J.P., Pomerantzeff, P.M., Dallan, L.O., Jatene, F.B., Stolf, N.A., Auler, J.O.,Jr, 2010. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *Jama.* **304,** 1559-1567.

105. Haljan, G., Maitland, A., Buchan, A., Arora, R.C., King, M., Haigh, J., Culleton, B., Faris, P., Zygun, D., 2009. The erythropoietin neuroprotective effect: assessment in CABG surgery (TENPEAKS): a randomized, double-blind, placebo controlled, proof-of-concept clinical trial. *Stroke; a Journal of Cerebral Circulation.* **40,** 2769-2775.

106. Hammon, J.W., Stump, D.A., Butterworth, J.F., Moody, D.M., Rorie, K., Deal, D.D., Kincaid, E.H., Oaks, T.E., Kon, N.D., 2006. Single crossclamp improves 6-month cognitive outcome in high-risk coronary bypass patients: the effect of reduced aortic manipulation. *The Journal of Thoracic and Cardiovascular Surgery.* **131,** 114-121.

107. Harman-Smith, Y.E., Mathias, J.L., Bowden, S.C., Rosenfeld, J.V., Bigler, E.D., 2013. Wechsler Adult Intelligence Scale-Third Edition profiles and their relationship to self-reported outcome following traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology.* **35,** 785-798.

108. Hartman, G.S., Yao, F.S., Bruefach, M.,3rd, Barbut, D., Peterson, J.C., Purcell, M.H., Charlson, M.E., Gold, J.P., Thomas, S.J., Szatrowski, T.P., 1996. Severity of aortic atheromatous disease diagnosed by transesophageal echocardiography predicts stroke and other outcomes associated with coronary artery surgery: a prospective study. *Anesthesia and Analgesia.* **83,** 701-708.

109. Hauth, E.A., Jansen, C., Drescher, R., Schwartz, M., Forsting, M., Jaeger, H.J., Mathias, K.D., 2005. MR and clinical follow-up of diffusion-weighted cerebral lesions after carotid artery stenting. *AJNR.American Journal of Neuroradiology.* **26,** 2336-2341.

110. HELMSWORTH, J.A., GALL, E.A., PERRIN, E.V., BRALEY, S.A., FLEGE, J.B.,Jr, KAPLAN, S., KEIRLE, A.M., 1963. Occurrence of emboli during perfusion with an oxygenator pump. *Surgery.* **53,** 177-185.

111. Hernandez, F.,Jr, Brown, J.R., Likosky, D.S., Clough, R.A., Hess, A.L., Roth, R.M., Ross, C.S., Whited, C.M., O'Connor, G.T., Klemperer, J.D., 2007. Neurocognitive outcomes of off-pump versus on-pump coronary artery bypass: a prospective randomized controlled trial. *The Annals of Thoracic Surgery.* **84,** 1897-1903.

112. Heyer, E.J., Adams, D.C., Delphin, E., McMahon, D.J., Steneck, S.D., Oz, M.C., Michler, R.E., Rose, E.A., 1997. Cerebral dysfunction after coronary artery bypass grafting done with mild or moderate hypothermia. *The Journal of Thoracic and Cardiovascular Surgery.* **114,** 270-277.

113. Heyer, E.J., Lee, K.S., Manspeizer, H.E., Mongero, L., Spanier, T.B., Caliste, X., Esrig, B., Smith, C., 2002. Heparin-bonded cardiopulmonary bypass circuits reduce cognitive dysfunction. *Journal of Cardiothoracic and Vascular Anesthesia.* **16,** 37-42.

114. Heyer, E.J., Sharma, R., Winfree, C.J., Mocco, J., McMahon, D.J., McCormick, P.A., Quest, D.O., McMurtry, J.G.,3rd, Riedel, C.J., Lazar, R.M., Stern, Y., Connolly, E.S.,Jr, 2000. Severe pain confounds neuropsychological test performance. *Journal of Clinical and Experimental Neuropsychology.* **22,** 633-639.

115. Hillis, A.E., 2011. Setting new tracks: not just creating another pretty picture. *Brain : A Journal of Neurology.* **134,** 2798-2799.

116. Hiraoka, K., Kawatsu, S., Mori, E., Saiki, Y., 2012. Total aortic arch replacement using hypothermic circulatory arrest with antegrade selective cerebral perfusion: are

there cerebral deficits other than frank stroke? *General Thoracic and Cardiovascular Surgery.* **60,** 345-349.

117. Hogue, C.W.,Jr, Freedland, K., Hershey, T., Fucetola, R., Nassief, A., Barzilai, B., Thomas, B., Birge, S., Dixon, D., Schechtman, K.B., Davila-Roman, V.G., 2007. Neurocognitive outcomes are not improved by 17beta-estradiol in postmenopausal women undergoing cardiac surgery. *Stroke; a Journal of Cerebral Circulation.* **38,** 2048-2054.

118. Hogue, C.W.,Jr, Hershey, T., Dixon, D., Fucetola, R., Nassief, A., Freedland, K.E., Thomas, B., Schechtman, K., 2006. Preexisting cognitive impairment in women before cardiac surgery and its relationship with C-reactive protein concentrations. *Anesthesia and Analgesia.* **102,** 1602-8; table of contents.

119. Hogue, C.W.,Jr, Sundt, T.M.,3rd, Goldberg, M., Barner, H., Davila-Roman, V.G., 1999. Neurological complications of cardiac surgery: the need for new paradigms in prevention and treatment. *Seminars in Thoracic and Cardiovascular Surgery.* **11,** 105-115.

120. Holinski, S., Claus, B., Alaaraj, N., Dohmen, P.M., Neumann, K., Uebelhack, R., Konertz, W., 2011. Cerebroprotective effect of piracetam in patients undergoing open heart surgery. *Annals of Thoracic and Cardiovascular Surgery : Official Journal of the Association of Thoracic and Cardiovascular Surgeons of Asia.* **17,** 137-142.

121. Hudetz, J.A., Iqbal, Z., Gandhi, S.D., Patterson, K.M., Byrne, A.J., Hudetz, A.G., Pagel, P.S., Warltier, D.C., 2009. Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery. *Acta Anaesthesiologica Scandinavica.* **53,** 864-872.

122. Ito, A., Goto, T., Maekawa, K., Baba, T., Mishima, Y., Ushijima, K., 2012. Postoperative neurological complications and risk factors for pre-existing silent brain infarction in elderly patients undergoing coronary artery bypass grafting. *Journal of Anesthesia.* **26,** 405-411.

123. Jacobs, A., Neveling, M., Horst, M., Ghaemi, M., Kessler, J., Eichstaedt, H., Rudolf, J., Model, P., Bonner, H., de Vivie, E.R., Heiss, W.D., 1998. Alterations of neuropsychological function and cerebral glucose metabolism after cardiac surgery are not related only to intraoperative microembolic events. *Stroke; a Journal of Cerebral Circulation.* **29,** 660-667.

124. Jensen, B.O., Hughes, P., Rasmussen, L.S., Pedersen, P.U., Steinbruchel, D.A., 2006. Cognitive outcomes in elderly high-risk patients after off-pump versus conventional coronary artery bypass grafting: a randomized trial. *Circulation.* **113,** 2790-2795.

125. Jensen, B.O., Rasmussen, L.S., Steinbruchel, D.A., 2008. Cognitive outcomes in elderly high-risk patients 1 year after off-pump versus on-pump coronary artery bypass grafting. A randomized trial. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **34,** 1016-1021.

126. Jonsson, H., Johnsson, P., Alling, C., Backstrom, M., Bergh, C., Blomquist, S., 1999. S100beta after coronary artery surgery: release pattern, source of contamination, and relation to neuropsychological outcome. *The Annals of Thoracic Surgery.* **68,** 2202-2208.

127. Jonsson, H., Johnsson, P., Backstrom, M., Alling, C., Dautovic-Bergh, C., Blomquist, S., 2004. Controversial significance of early S100B levels after cardiac surgery. *BMC Neurology.* **4,** 24.

128. Kadoi, Y. & Goto, F., 2007. Sevoflurane anesthesia did not affect postoperative cognitive dysfunction in patients undergoing coronary artery bypass graft surgery. *Journal of Anesthesia.* **21,** 330-335.

129. Kadoi, Y., Saito, S., Kunimoto, F., Goto, F., Fujita, N., 2003. Comparative effects of propofol versus fentanyl on cerebral oxygenation state during normothermic cardiopulmonary bypass and postoperative cognitive dysfunction. *The Annals of Thoracic Surgery.* **75,** 840-846.

130. Kadoi, Y., Saito, S., Takahashi, K., Fujita, N., Goto, F., 2004. Jugular venous oxygen saturation during mild hypothermic versus normothermic cardiopulmonary bypass in elderly patients. *Surgery Today.* **34,** 399-404.

131. Kalman, J., Juhasz, A., Bogats, G., Babik, B., Rimanoczy, A., Janka, Z., Penke, B., Palotas, A., 2006. Elevated levels of inflammatory biomarkers in the cerebrospinal fluid after coronary artery bypass surgery are predictors of cognitive decline. *Neurochemistry International.* **48,** 177-180.

132. Kanbak, M., Saricaoglu, F., Akinci, S.B., Oc, B., Balci, H., Celebioglu, B., Aypar, U., 2007. The effects of isoflurane, sevoflurane, and desflurane anesthesia on neurocognitive outcome after cardiac surgery: a pilot study. *The Heart Surgery Forum.* **10,** E36-41.

133. Kang, D.W., Latour, L.L., Chalela, J.A., Dambrosia, J., Warach, S., 2003. Early ischemic lesion recurrence within a week after acute ischemic stroke. *Annals of Neurology.* **54,** 66-74.

134. Kang, D.W., Latour, L.L., Chalela, J.A., Dambrosia, J.A., Warach, S., 2004. Early and late recurrence of ischemic lesion on MRI: evidence for a prolonged stroke-prone state? *Neurology.* **63,** 2261-2265.

135. Karalis, D.G., Chandrasekaran, K., Victor, M.F., Ross, J.J.,Jr, Mintz, G.S., 1991. Recognition and embolic potential of intraaortic atherosclerotic debris. *Journal of the American College of Cardiology.* **17,** 73-78.

136. Karkouti, K., Djaiani, G., Borger, M.A., Beattie, W.S., Fedorko, L., Wijeysundera, D., Ivanov, J., Karski, J., 2005. Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. *The Annals of Thoracic Surgery.* **80,** 1381-1387.

137. Katz, E.S., Tunick, P.A., Rusinek, H., Ribakove, G., Spencer, F.C., Kronzon, I., 1992. Protruding aortic atheromas predict stroke in elderly patients undergoing cardiopulmonary bypass: experience with intraoperative transesophageal echocardiography. *Journal of the American College of Cardiology.* **20,** 70-77.

138. Kaukinen, L., Porkkala, H., Kaukinen, S., Pehkonen, E., Karkela, J., Aaran, R.K., Tarkka, M., 2000. Release of brain-specific creatine kinase and neuron-specific enolase into cerebrospinal fluid after hypothermic and normothermic cardiopulmonary bypass in coronary artery surgery. *Acta Anaesthesiologica Scandinavica.* **44,** 361-368.

139. Kaukuntla, H., Walker, A., Harrington, D., Jones, T., Bonser, R.S., Study Group, 2004. Differential brain and body temperature during cardiopulmonary bypass--a randomised clinical study. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **26,** 571-579.

140. Kawahara, F., Kadoi, Y., Saito, S., Goto, F., Fujita, N., 2003. Slow rewarming improves jugular venous oxygen saturation during rewarming. *Acta Anaesthesiologica Scandinavica.* **47,** 419-424.

141. Keizer, A.M., Hijman, R., van Dijk, D., Kalkman, C.J., Kahn, R.S., 2003. Cognitive self-assessment one year after on-pump and off-pump coronary artery bypass grafting. *The Annals of Thoracic Surgery.* **75,** 835-8; discussion 838-9.

142. Kilminster, S., Treasure, T., McMillan, T., Holt, D.W., 1999. Neuropsychological change and S-100 protein release in 130 unselected patients undergoing cardiac surgery. *Stroke; a Journal of Cerebral Circulation.* **30,** 1869-1874.

143. Kincaid, E.H., Jones, T.J., Stump, D.A., Brown, W.R., Moody, D.M., Deal, D.D., Hammon, J.W.,Jr, 2000. Processing scavenged blood with a cell saver reduces cerebral lipid microembolization. *The Annals of Thoracic Surgery.* **70,** 1296-1300.

144. KLOVE, H., 1963. Clinical Neuropsychology. *The Medical Clinics of North America.* **47,** 1647-1658.

145. Kneebone, A.C., Andrew, M.J., Baker, R.A., Knight, J.L., 1998. Neuropsychologic changes after coronary artery bypass grafting: use of reliable change indices. *The Annals of Thoracic Surgery.* **65,** 1320-1325.

146. Knipp, S.C., Matatko, N., Schlamann, M., Wilhelm, H., Thielmann, M., Forsting, M., Diener, H.C., Jakob, H., 2005. Small ischemic brain lesions after cardiac valve replacement detected by diffusion-weighted magnetic resonance imaging: relation to neurocognitive function. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **28,** 88-96.

147. Knipp, S.C., Matatko, N., Wilhelm, H., Schlamann, M., Massoudy, P., Forsting, M., Diener, H.C., Jakob, H., 2004. Evaluation of brain injury after coronary artery bypass grafting. A prospective study using neuropsychological assessment and diffusion-weighted magnetic resonance imaging. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **25,** 791-800.

148. Knipp, S.C., Matatko, N., Wilhelm, H., Schlamann, M., Thielmann, M., Losch, C., Diener, H.C., Jakob, H., 2008. Cognitive outcomes three years after coronary artery bypass surgery: relation to diffusion-weighted magnetic resonance imaging. *The Annals of Thoracic Surgery.* **85,** 872-879.

149. Kobayashi, J., Tashiro, T., Ochi, M., Yaku, H., Watanabe, G., Satoh, T., Tagusari, O., Nakajima, H., Kitamura, S., Japanese Off-Pump Coronary Revascularization Investigation (JOCRI) Study Group, 2005. Early outcome of a randomized comparison of off-pump and on-pump multiple arterial coronary revascularization. *Circulation.* **112,** I338-43.

150. Kofke, W.A., Konitzer, P., Meng, Q.C., Guo, J., Cheung, A., 2004. The effect of apolipoprotein E genotype on neuron specific enolase and S-100beta levels after cardiac surgery. *Anesthesia and Analgesia.* **99,** 1323-5; table of contents.

151. Kong, R.S., Butterworth, J., Aveling, W., Stump, D.A., Harrison, M.J., Hammon, J., Stygall, J., Rorie, K.D., Newman, S.P., 2002. Clinical trial of the neuroprotectant clomethiazole in coronary artery bypass graft surgery: a randomized controlled trial. *Anesthesiology.* **97,** 585-591.

152. Kozora, E., Kongs, S., Collins, J.F., Hattler, B., Baltz, J., Hampton, M., Grover, F.L., Novitzky, D., Shroyer, A.L., 2010. Cognitive outcomes after on- versus off-pump coronary artery bypass surgery. *The Annals of Thoracic Surgery.* **90,** 1134-1141.

153. Kumral, E., Balkir, K., Yagdi, T., Kara, E., Evyapan, D., Bilkay, O., 2001. Microembolic signals in patients undergoing coronary artery bypass grafting. Effect of aortic atherosclerosis. *Texas Heart Institute Journal / from the Texas Heart Institute of St.Luke's Episcopal Hospital, Texas Children's Hospital.* **28,** 16-20.

154. Kunihara, T., Tscholl, D., Langer, F., Heinz, G., Sata, F., Schafers, H.J., 2007. Cognitive brain function after hypothermic circulatory arrest assessed by cognitive P300 evoked potentials. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **32,** 507-513.

155. Lamy, A., Devereaux, P.J., Prabhakaran, D., Hu, S., Piegas, L.S., Straka, Z., Paolasso, E., Taggart, D., Lanas, F., Akar, A.R., Jain, A., Noiseux, N., Ou, Y., Chrolavicius, S., Ng, J., Yusuf, S., 2012. Rationale and design of the coronary artery bypass grafting surgery off or on pump revascularization study: a large international randomized trial in cardiac surgery. *American Heart Journal.* **163,** 1-6.

156. Lamy, A., Devereaux, P.J., Yusuf, S., 2013. Off-pump or on-pump coronary-artery bypass grafting. *The New England Journal of Medicine.* **369,** 196.

157. Lansberg, M.G., Albers, G.W., Beaulieu, C., Marks, M.P., 2000. Comparison of diffusion-weighted MRI and CT in acute stroke. *Neurology.* **54,** 1557-1561.

158. Lasjaunias, P, Brugge, K.G, 2006. *Surgical Neuroangiography.* 3rd ed. United States of America: SpringerLink.

159. Lazibat, I., Sutlic, Z., Brkic, K., Nevajda, B., Sikic, J., Mestrovic, A.H., 2012. Predictors of short-term neurocognitive outcome following coronary revascularisation (CABG) depending on the use of cardiopulmonary bypass. *Collegium Antropologicum.* **36,** 827-833.

160. Lehmann, A., Schmidt, M., Zeitler, C., Kiessling, A.H., Isgro, F., Boldt, J., 2007. Bispectral index and electroencephalographic entropy in patients undergoing aortocoronary bypass grafting. *European Journal of Anaesthesiology.* **24,** 751-760.

161. Lingegowda, D., Thomas, B., Vaghela, V., Hingwala, D.R., Kesavadas, C., Sylaja, P.N., 2012. 'Susceptibility sign' on susceptibility-weighted imaging in acute ischemic stroke. *Neurology India.* **60,** 160-164.

162. Liu, J.F., Su, Z.K., Ding, W.X., 1992. Quantitation of particulate microemboli during cardiopulmonary bypass: experimental and clinical studies. *The Annals of Thoracic Surgery.* **54,** 1196-1202.

163. Liu, Y.H., Wang, D.X., Li, L.H., Wu, X.M., Shan, G.J., Su, Y., Li, J., Yu, Q.J., Shi, C.X., Huang, Y.N., Sun, W., 2009. The effects of cardiopulmonary bypass on the number of cerebral microemboli and the incidence of cognitive dysfunction after coronary artery bypass graft surgery. *Anesthesia and Analgesia.* **109,** 1013-1022.

164. Lloyd, C.T., Ascione, R., Underwood, M.J., Gardner, F., Black, A., Angelini, G.D., 2000. Serum S-100 protein release and neuropsychologic outcome during coronary revascularization on the beating heart: a prospective randomized study. *The Journal of Thoracic and Cardiovascular Surgery.* **119,** 148-154.

165. Lo, A.H., Humphreys, M., Byrne, G.J., Pachana, N.A., 2012. Test-retest reliability and practice effects of the Wechsler Memory Scale-III. *Journal of Neuropsychology.* **6,** 212-231.

166. Loop, F.D., Szabo, J., Rowlinson, R.D., Urbanek, K., 1976. Events related to microembolism during extracorporeal perfusion in man: effectiveness of in-line filtration recorded by ultrasound. *The Annals of Thoracic Surgery.* **21,** 412-420.

167. Luders, E., Steinmetz, H., Jancke, L., 2002. Brain size and grey matter volume in the healthy human brain. *Neuroreport.* **13,** 2371-2374.

168. Lund, C., Hol, P.K., Lundblad, R., Fosse, E., Sundet, K., Tennoe, B., Brucher, R., Russell, D., 2003. Comparison of cerebral embolization during off-pump and on-pump coronary artery bypass surgery. *The Annals of Thoracic Surgery.* **76,** 765-70; discussion 770.

169. Lund, C., Sundet, K., Tennoe, B., Hol, P.K., Rein, K.A., Fosse, E., Russell, D., 2005. Cerebral ischemic injury and cognitive impairment after off-pump and on-pump coronary artery bypass grafting surgery. *The Annals of Thoracic Surgery.* **80,** 2126-2131.

170. Lynch, J.E. & Riley, J.B., 2008. Microemboli detection on extracorporeal bypass circuits. *Perfusion.* **23,** 23-32.

171. Mackensen, G.B. & Gelb, A.W., 2004. Postoperative cognitive deficits: more questions than answers. *European Journal of Anaesthesiology.* **21,** 85-88.

172. Mackinnon, A.D., Aaslid, R., Markus, H.S., 2004. Long-term ambulatory monitoring for cerebral emboli using transcranial Doppler ultrasound. *Stroke; a Journal of Cerebral Circulation.* **35,** 73-78.

173. Mahanna, E.P., Blumenthal, J.A., White, W.D., Croughwell, N.D., Clancy, C.P., Smith, L.R., Newman, M.F., 1996. Defining neuropsychological dysfunction after coronary artery bypass grafting. *The Annals of Thoracic Surgery.* **61,** 1342-1347.

174. Marasco, S.F., Sharwood, L.N., Abramson, M.J., 2008. No improvement in neurocognitive outcomes after off-pump versus on-pump coronary revascularisation: a meta-analysis. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **33,** 961-970.

175. Markus, H., 2000. Monitoring embolism in real time. *Circulation.* **102,** 826-828.

176. Mathew, J.P., Fontes, M.L., Tudor, I.C., Ramsay, J., Duke, P., Mazer, C.D., Barash, P.G., Hsu, P.H., Mangano, D.T., Investigators of the Ischemia Research and Education Foundation, Multicenter Study of Perioperative Ischemia Research Group, 2004. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA : The Journal of the American Medical Association.* **291,** 1720-1729.

177. Mathew, J.P., Grocott, H.P., McCurdy, J.R., Ti, L.K., Davis, R.D., Laskowitz, D.T., Podgoreanu, M.V., Swaminathan, M., Lynch, J., Stafford-Smith, M., White, W.D., Newman, M.F., 2005. Preoperative statin therapy does not reduce cognitive dysfunction after cardiopulmonary bypass. *Journal of Cardiothoracic and Vascular Anesthesia.* **19,** 294-299.

178. Mathew, J.P., Grocott, H.P., Phillips-Bute, B., Stafford-Smith, M., Laskowitz, D.T., Rossignol, D., Blumenthal, J.A., Newman, M.F., Neurologic Outcome Research Group of the Duke Heart Center, Cardiothoracic Anesthesiology Research Endeavors Investigators of the Duke Heart Center, 2003. Lower endotoxin immunity predicts increased cognitive dysfunction in elderly patients after cardiac surgery. *Stroke; a Journal of Cerebral Circulation.* **34,** 508-513.

179. Mathew, J.P., Mackensen, G.B., Phillips-Bute, B., Grocott, H.P., Glower, D.D., Laskowitz, D.T., Blumenthal, J.A., Newman, M.F., Neurologic Outcome Research Group (NORG) of the Duke Heart Center, 2009. Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. *Stroke; a Journal of Cerebral Circulation.* **40,** 880-887.

180. Mathew, J.P., Podgoreanu, M.V., Grocott, H.P., White, W.D., Morris, R.W., Stafford-Smith, M., Mackensen, G.B., Rinder, C.S., Blumenthal, J.A., Schwinn, D.A., Newman, M.F., PEGASUS Investigative Team, 2007. Genetic variants in P-selectin and C-reactive protein influence susceptibility to cognitive decline after cardiac surgery. *Journal of the American College of Cardiology.* **49,** 1934-1942.

181. Mazziotta, J., Toga, A., Evans, A., Fox, P., Lancaster, J., Zilles, K., Woods, R., Paus, T., Simpson, G., Pike, B., Holmes, C., Collins, L., Thompson, P., MacDonald, D., Iacoboni, M., Schormann, T., Amunts, K., Palomero-Gallagher, N., Geyer, S., Parsons, L., Narr, K., Kabani, N., Le Goualher, G., Boomsma, D., Cannon, T., Kawashima, R., Mazoyer, B., 2001. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philosophical Transactions of the Royal Society of London.Series B, Biological Sciences.* **356,** 1293-1322.

182. McKhann, G.M., Grega, M.A., Borowicz, L.M.,Jr, Baumgartner, W.A., Selnes, O.A., 2006. Stroke and encephalopathy after cardiac surgery: an update. *Stroke; a Journal of Cerebral Circulation.* **37,** 562-571.

183. McKhann, G.M., Grega, M.A., Borowicz, L.M.,Jr, Bechamps, M., Selnes, O.A., Baumgartner, W.A., Royall, R.M., 2002. Encephalopathy and stroke after coronary artery bypass grafting: incidence, consequences, and prediction. *Archives of Neurology.* **59,** 1422-1428.

184. McLean, R.F., Wong, B.I., Naylor, C.D., Snow, W.G., Harrington, E.M., Gawel, M., Fremes, S.E., 1994. Cardiopulmonary bypass, temperature, and central nervous system dysfunction. *Circulation.* **90,** II250-5.

185. McRobbie, D.W., 2007. . *MRI from Picture to Proton.* 2nd ed. United States of America: Cambridge University Press. 27.

186. Merino, J.G., Latour, L.L., Tso, A., Lee, K.Y., Kang, D.W., Davis, L.A., Lazar, R.M., Horvath, K.A., Corso, P.J., Warach, S., 2013. Blood-brain barrier disruption after cardiac surgery. *AJNR.American Journal of Neuroradiology.* **34,** 518-523.

187. Messe, S.R., Acker, M.A., Kasner, S.E., Fanning, M., Giovannetti, T., Ratcliffe, S.J., Bilello, M., Szeto, W.Y., Bavaria, J.E., Hargrove, W.C.,3rd, Mohler, E.R.,3rd, Floyd, T.F., Determining Neurologic Outcomes from Valve Operations (DeNOVO) Investigators, 2014. Stroke after aortic valve surgery: results from a prospective cohort. *Circulation.* **129,** 2253-2261.

188. Mirow, N., Zittermann, A., Korperich, H., Borgermann, J., Koertke, H., Knobl, H., Gieseke, J., Ostertun, B., Coskun, T., Kleesiek, K., Burchert, W., Gummert, J.F., 2011. Diffusion-weighted magnetic resonance imaging for the detection of ischemic brain lesions in coronary artery bypass graft surgery: relation to extracorporeal circulation and heparinization. *The Journal of Cardiovascular Surgery.* **52,** 117-126.

189. Mitchell, S. & Gorman, D., 2002. The pathophysiology of cerebral arterial gas embolism. *The Journal of Extra-Corporeal Technology.* **34,** 18-23.

190. Mitchell, S.J., Merry, A.F., Frampton, C., Davies, E., Grieve, D., Mills, B.P., Webster, C.S., Milsom, F.P., Willcox, T.W., Gorman, D.F., 2009. Cerebral protection by lidocaine during cardiac operations: a follow-up study. *The Annals of Thoracic Surgery.* **87,** 820-825.

191. Mitchell, S.J., Willcox, T., Gorman, D.F., 1997. Bubble generation and venous air filtration by hard-shell venous reservoirs: a comparative study. *Perfusion.* **12,** 325-333.

192. Moehring, M.A. & Klepper, J.R., 1994. Pulse Doppler ultrasound detection, characterization and size estimation of emboli in flowing blood. *IEEE Transactions on Bio-Medical Engineering.* **41,** 35-44.

193. Moller, J.T., Cluitmans, P., Rasmussen, L.S., Houx, P., Rasmussen, H., Canet, J., Rabbitt, P., Jolles, J., Larsen, K., Hanning, C.D., Langeron, O., Johnson, T., Lauven, P.M., Kristensen, P.A., Biedler, A., van Beem, H., Fraidakis, O., Silverstein, J.H., Beneken, J.E., Gravenstein, J.S., 1998. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet.* **351,** 857-861.

194. Monk, T.G., Weldon, B.C., Garvan, C.W., Dede, D.E., van der Aa, M.T., Heilman, K.M., Gravenstein, J.S., 2008. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology.* **108,** 18-30.

195. Moody, D.M., Brown, W.R., Challa, V.R., Stump, D.A., Reboussin, D.M., Legault, C., 1995. Brain microemboli associated with cardiopulmonary bypass: a histologic and magnetic resonance imaging study. *The Annals of Thoracic Surgery.* **59,** 1304-1307.

196. Mora, C.T., Henson, M.B., Weintraub, W.S., Murkin, J.M., Martin, T.D., Craver, J.M., Gott, J.P., Guyton, R.A., 1996. The effect of temperature management during cardiopulmonary bypass on neurologic and neuropsychologic outcomes in patients undergoing coronary revascularization. *The Journal of Thoracic and Cardiovascular Surgery.* **112,** 514-522.

197. Motallebzadeh, R., Bland, J.M., Markus, H.S., Kaski, J.C., Jahangiri, M., 2007. Neurocognitive function and cerebral emboli: randomized study of on-pump versus off-pump coronary artery bypass surgery. *The Annals of Thoracic Surgery.* **83,** 475-482.

198. Mullges, W., Franke, D., Reents, W., Babin-Ebell, J., 2001. Brain microembolic counts during extracorporeal circulation depend on aortic cannula position. *Ultrasound in Medicine & Biology.* **27,** 933-936.

199. Mullges, W., Franke, D., Reents, W., Babin-Ebell, J., Toyka, K.V., 2003. Reduced rate of microembolism by optimized aortic cannula position does not influence early postoperative cognitive performance in CABG patients. *Cerebrovascular Diseases (Basel, Switzerland).* **15,** 192-198.

200. Murkin, J.M., Boyd, W.D., Ganapathy, S., Adams, S.J., Peterson, R.C., 1999. Beating heart surgery: why expect less central nervous system morbidity? *The Annals of Thoracic Surgery.* **68,** 1498-1501.

201. Murkin, J.M., Newman, S.P., Stump, D.A., Blumenthal, J.A., 1995. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. *The Annals of Thoracic Surgery.* **59,** 1289-1295.

202. Murphy, G.S., Hessel, E.A.,2nd, Groom, R.C., 2009. Optimal perfusion during cardiopulmonary bypass: an evidence-based approach. *Anesthesia and Analgesia.* **108,** 1394-1417.

203. Nathan, H.J., Munson, J., Wells, G., Mundi, C., Balaa, F., Wynands, J.E., 1995. The management of temperature during cardiopulmonary bypass: effect on neuropsychological outcome. *Journal of Cardiac Surgery.* **10,** 481-487.

204. Nathan, H.J., Rodriguez, R., Wozny, D., Dupuis, J.Y., Rubens, F.D., Bryson, G.L., Wells, G., 2007. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: five-year follow-up of a randomized trial. *The Journal of Thoracic and Cardiovascular Surgery.* **133,** 1206-1211.

205. Nathan, H.J., Wells, G.A., Munson, J.L., Wozny, D., 2001. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: a randomized trial. *Circulation.* **104,** I85-91.

206. Newman, M.F., Croughwell, N.D., Blumenthal, J.A., White, W.D., Lewis, J.B., Smith, L.R., Frasco, P., Towner, E.A., Schell, R.M., Hurwitz, B.J., 1994. Effect of aging on cerebral autoregulation during cardiopulmonary bypass. Association with postoperative cognitive dysfunction. *Circulation.* **90,** II243-9.

207. Newman, M.F., Kirchner, J.L., Phillips-Bute, B., Gaver, V., Grocott, H., Jones, R.H., Mark, D.B., Reves, J.G., Blumenthal, J.A., Neurological Outcome Research Group and the Cardiothoracic Anesthesiology Research Endeavors Investigators, 2001. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *The New England Journal of Medicine.* **344,** 395-402.

208. Newman, M.F., Kramer, D., Croughwell, N.D., Sanderson, I., Blumenthal, J.A., White, W.D., Smith, L.R., Towner, E.A., Reves, J.G., 1995. Differential age effects of mean arterial pressure and rewarming on cognitive dysfunction after cardiac surgery. *Anesthesia and Analgesia.* **81,** 236-242.

209. Newman, M.F., Mathew, J.P., Grocott, H.P., Mackensen, G.B., Monk, T., Welsh-Bohmer, K.A., Blumenthal, J.A., Laskowitz, D.T., Mark, D.B., 2006. Central nervous system injury associated with cardiac surgery. *Lancet.* **368,** 694-703.

210. Novitzky, D. & Boswell, B.B., 2000. Total myocardial revascularization without cardiopulmonary bypass utilizing computer-processed monitoring to assess cerebral perfusion. *The Heart Surgery Forum.* **3,** 198-202.

211. Ono, M., Joshi, B., Brady, K., Easley, R.B., Zheng, Y., Brown, C., Baumgartner, W., Hogue, C.W., 2012. Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke. *British Journal of Anaesthesia.* **109,** 391-398.

212. Padayachee, T.S., Parsons, S., Theobold, R., Gosling, R.G., Deverall, P.B., 1988. The effect of arterial filtration on reduction of gaseous microemboli in the middle cerebral artery during cardiopulmonary bypass. *The Annals of Thoracic Surgery.* **45,** 647-649.

213. Parolari, A., Alamanni, F., Naliato, M., Spirito, R., Franze, V., Pompilio, G., Agrifoglio, M., Biglioli, P., 2000. Adult cardiac surgery outcomes: role of the pump

type. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **18,** 575-582.

214. Parra, V.M., Sadurni, M., Donate, M., Rovira, I., Roux, C., Rios, J., Boget, T., Fita, G., 2011. Neuropsychological dysfunction after cardiac surgery: Cerebral saturation and bispectral index: A longitudinal study. *Revista Medica De Chile.* **139,** 1553-1561.

215. Patel, N., Horsfield, M.A., Banahan, C., Janus, J., Masters, K., Morlese, J., Egan, V., Chung, E.M., 2015. Impact of perioperative infarcts after cardiac surgery. *Stroke; a Journal of Cerebral Circulation.* **46,** 680-686.

216. Patel, R.L., Turtle, M.R., Chambers, D.J., James, D.N., Newman, S., Venn, G.E., 1996. Alpha-stat acid-base regulation during cardiopulmonary bypass improves neuropsychologic outcome in patients undergoing coronary artery bypass grafting. *The Journal of Thoracic and Cardiovascular Surgery.* **111,** 1267-1279.

217. Patel, R.L., Turtle, M.R., Chambers, D.J., Newman, S., Venn, G.E., 1993. Hyperperfusion and cerebral dysfunction. Effect of differing acid-base management during cardiopulmonary bypass. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **7,** 457-63; discussion 464.

218. Plaschke, K., Hauth, S., Jansen, C., Bruckner, T., Schramm, C., Karck, M., Kopitz, J., 2013. The influence of preoperative serum anticholinergic activity and other risk factors for the development of postoperative cognitive dysfunction after cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery.* **145,** 805-811.

219. Pugsley, W., Klinger, L., Paschalis, C., Treasure, T., Harrison, M., Newman, S., 1994. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke; a Journal of Cerebral Circulation.* **25,** 1393-1399.

220. Puskas, F., Grocott, H.P., White, W.D., Mathew, J.P., Newman, M.F., Bar-Yosef, S., 2007. Intraoperative hyperglycemia and cognitive decline after CABG. *The Annals of Thoracic Surgery.* **84,** 1467-1473.

221. Puskas, J.D., Stringer, A., Hwang, S.N., Hatfield, B., Smith, A.S., Kilgo, P.D., Williams, W.H., 2011. Neurocognitive and neuroanatomic changes after off-pump versus on-pump coronary artery bypass grafting: long-term follow-up of a randomized trial. *The Journal of Thoracic and Cardiovascular Surgery.* **141,** 1116-1127.

222. Ramlawi, B., Rudolph, J.L., Mieno, S., Feng, J., Boodhwani, M., Khabbaz, K., Levkoff, S.E., Marcantonio, E.R., Bianchi, C., Sellke, F.W., 2006. C-Reactive protein and inflammatory response associated to neurocognitive decline following cardiac surgery. *Surgery.* **140,** 221-226.

223. Rasmussen, L.S., Christiansen, M., Eliasen, K., Sander-Jensen, K., Moller, J.T., 2002. Biochemical markers for brain damage after cardiac surgery -- time profile and correlation with cognitive dysfunction. *Acta Anaesthesiologica Scandinavica.* **46,** 547-551.

224. Rasmussen, L.S., Christiansen, M., Hansen, P.B., Moller, J.T., 1999. Do blood levels of neuron-specific enolase and S-100 protein reflect cognitive dysfunction after coronary artery bypass? *Acta Anaesthesiologica Scandinavica.* **43,** 495-500.

225. Rasmussen, L.S., Larsen, K., Houx, P., Skovgaard, L.T., Hanning, C.D., Moller, J.T., ISPOCD group. The International Study of Postoperative Cognitive Dysfunction, 2001. The assessment of postoperative cognitive function. *Acta Anaesthesiologica Scandinavica.* **45,** 275-289.

226. Regragui, I., Birdi, I., Izzat, M.B., Black, A.M., Lopatatzidis, A., Day, C.J., Gardner, F., Bryan, A.J., Angelini, G.D., 1996. The effects of cardiopulmonary bypass temperature on neuropsychologic outcome after coronary artery operations: a prospective randomized trial. *The Journal of Thoracic and Cardiovascular Surgery.* **112,** 1036-1045.

227. Reich, D.L., Horn, L.M., Hossain, S., Uysal, S., 2004. Using jugular bulb oxyhemoglobin saturation to guide onset of deep hypothermic circulatory arrest does not affect post-operative neuropsychological function. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **25,** 401-6; discussion 406-8.

228. Reich, D.L., Uysal, S., Sliwinski, M., Ergin, M.A., Kahn, R.A., Konstadt, S.N., McCullough, J., Hibbard, M.R., Gordon, W.A., Griepp, R.B., 1999. Neuropsychologic outcome after deep hypothermic circulatory arrest in adults. *The Journal of Thoracic and Cardiovascular Surgery.* **117,** 156-163.

229. Reinsfelt, B., Ricksten, S.E., Zetterberg, H., Blennow, K., Freden-Lindqvist, J., Westerlind, A., 2012. Cerebrospinal fluid markers of brain injury, inflammation, and blood-brain barrier dysfunction in cardiac surgery. *The Annals of Thoracic Surgery.* **94,** 549-555.

230. Reinsfelt, B., Westerlind, A., Blennow, K., Zetterberg, H., Ricksten, S.E., 2013. Open-heart surgery increases cerebrospinal fluid levels of Alzheimer-associated amyloid beta. *Acta Anaesthesiologica Scandinavica.* **57,** 82-88.

231. Restrepo, L., Wityk, R.J., Grega, M.A., Borowicz, L.,Jr, Barker, P.B., Jacobs, M.A., Beauchamp, N.J., Hillis, A.E., McKhann, G.M., 2002. Diffusion- and perfusion-weighted magnetic resonance imaging of the brain before and after coronary artery bypass grafting surgery. *Stroke; a Journal of Cerebral Circulation.* **33,** 2909-2915.

232. Ringelstein, E.B., Droste, D.W., Babikian, V.L., Evans, D.H., Grosset, D.G., Kaps, M., Markus, H.S., Russell, D., Siebler, M., 1998. Consensus on microembolus detection by TCD. International Consensus Group on Microembolus Detection. *Stroke; a Journal of Cerebral Circulation.* **29,** 725-729.

233. Ringelstein, E.B., Kahlscheuer, B., Niggemeyer, E., Otis, S.M., 1990. Transcranial Doppler sonography: anatomical landmarks and normal velocity values. *Ultrasound in Medicine & Biology.* **16,** 745-761.

234. Ritzl, A., Meisel, S., Wittsack, H.J., Fink, G.R., Siebler, M., Modder, U., Seitz, R.J., 2004. Development of brain infarct volume as assessed by magnetic resonance imaging (MRI): follow-up of diffusion-weighted MRI lesions. *Journal of Magnetic Resonance Imaging : JMRI.* **20,** 201-207.

235. Robinson, T.N., Wu, D.S., Pointer, L.F., Dunn, C.L., Moss, M., 2012. Preoperative cognitive dysfunction is related to adverse postoperative outcomes in the elderly. *Journal of the American College of Surgeons.* **215,** 12-7; discussion 17-8.

236. Rocchi, L., Niccolini, F., Politis, M., 2015. Recent imaging advances in neurology. *Journal of Neurology.*

237. Rodriguez, R.A., Rubens, F., Belway, D., Nathan, H.J., 2006. Residual air in the venous cannula increases cerebral embolization at the onset of cardiopulmonary bypass. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **29,** 175-180.

238. Rodriguez, R.A., Rubens, F., Rodriguez, C.D., Nathan, H.J., 2006. Sources of variability in the detection of cerebral emboli with transcranial Doppler during cardiac surgery. *Journal of Neuroimaging : Official Journal of the American Society of Neuroimaging.* **16,** 126-132.

239. Royse, C.F., Andrews, D.T., Newman, S.N., Stygall, J., Williams, Z., Pang, J., Royse, A.G., 2011. The influence of propofol or desflurane on postoperative cognitive dysfunction in patients undergoing coronary artery bypass surgery. *Anaesthesia.* **66,** 455-464.

240. Rubens, F.D., Boodhwani, M., Mesana, T., Wozny, D., Wells, G., Nathan, H.J., Cardiotomy Investigators, 2007. The cardiotomy trial: a randomized, double-blind study to assess the effect of processing of shed blood during cardiopulmonary bypass on transfusion and neurocognitive function. *Circulation.* **116,** I89-97.

241. Rudolph, J.L., Babikian, V.L., Treanor, P., Pochay, V.E., Wigginton, J.B., Crittenden, M.D., Marcantonio, E.R., 2009. Microemboli are not associated with delirium after coronary artery bypass graft surgery. *Perfusion.* **24,** 409-415.

242. Rudolph, J.L., Schreiber, K.A., Culley, D.J., McGlinchey, R.E., Crosby, G., Levitsky, S., Marcantonio, E.R., 2010. Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review. *Acta Anaesthesiologica Scandinavica.* **54,** 663-677.

243. Sahu, B., Chauhan, S., Kiran, U., Bisoi, A., Lakshmy, R., Selvaraj, T., Nehra, A., 2009. Neurocognitive function in patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass: the effect of two different rewarming strategies. *Journal of Cardiothoracic and Vascular Anesthesia.* **23,** 14-21.

244. Saladin, K., 2014. *Anatomy & Physiology: The Unity of Form and Function.* 7th ed. United States of America: McGraw-Hill Higher Education.

245. Salazar, J.D., Wityk, R.J., Grega, M.A., Borowicz, L.M., Doty, J.R., Petrofski, J.A., Baumgartner, W.A., 2001. Stroke after cardiac surgery: short- and long-term outcomes. *The Annals of Thoracic Surgery.* **72,** 1195-201; discussion 1201-2.

246. Sarkar, S., Ghosh, S., Ghosh, S.K., Collier, A., 2007. Role of transcranial Doppler ultrasonography in stroke. *Postgraduate Medical Journal.* **83,** 683-689.

247. Schoen, J., Husemann, L., Tiemeyer, C., Lueloh, A., Sedemund-Adib, B., Berger, K.U., Hueppe, M., Heringlake, M., 2011. Cognitive function after sevoflurane- vs propofol-based anaesthesia for on-pump cardiac surgery: a randomized controlled trial. *British Journal of Anaesthesia.* **106,** 840-850.

248. Schoenburg, M., Kraus, B., Muehling, A., Taborski, U., Hofmann, H., Erhardt, G., Hein, S., Roth, M., Vogt, P.R., Karliczek, G.F., Kloevekorn, W.P., 2003. The dynamic air bubble trap reduces cerebral microembolism during cardiopulmonary bypass. *The Journal of Thoracic and Cardiovascular Surgery.* **126,** 1455-1460.

249. Schwamm, L.H., Koroshetz, W.J., Sorensen, A.G., Wang, B., Copen, W.A., Budzik, R., Rordorf, G., Buonanno, F.S., Schaefer, P.W., Gonzalez, R.G., 1998. Time course of lesion development in patients with acute stroke: serial diffusion- and hemodynamic-weighted magnetic resonance imaging. *Stroke; a Journal of Cerebral Circulation.* **29,** 2268-2276.

250. Schwarz, N., Schoenburg, M., Mollmann, H., Kastaun, S., Kaps, M., Bachmann, G., Sammer, G., Hamm, C., Walther, T., Gerriets, T., 2011. Cognitive decline and ischemic microlesions after coronary catheterization. A comparison to coronary artery bypass grafting. *American Heart Journal.* **162,** 756-763.

251. Scott, D.A., Silbert, B.S., Doyle, T.J., Blyth, C., Borton, M.C., O'brien, J.L., de L Horne, D.J., 2002. Centrifugal versus roller head pumps for cardiopulmonary bypass: effect on early neuropsychologic outcomes after coronary artery surgery. *Journal of Cardiothoracic and Vascular Anesthesia.* **16,** 715-722.

252. Selim, M., 2007. Perioperative stroke. *The New England Journal of Medicine.* **356,** 706-713.

253. Selnes, O.A., Grega, M.A., Borowicz, L.M.,Jr, Royall, R.M., McKhann, G.M., Baumgartner, W.A., 2003. Cognitive changes with coronary artery disease: a prospective study of coronary artery bypass graft patients and nonsurgical controls. *The Annals of Thoracic Surgery.* **75,** 1377-84; discussion 1384-6.

254. Selnes, O.A., McKhann, G.M., Borowicz, L.M.,Jr, Grega, M.A., 2006. Cognitive and neurobehavioral dysfunction after cardiac bypass procedures. *Neurologic Clinics.* **24,** 133-145.

255. Shaaban-Ali, M., Harmer, M., Vaughan, R.S., Dunne, J.A., Latto, I.P., Haaverstad, R., Kulatilake, E.N., Butchart, E.G., 2002. Changes in serum S100beta protein and Mini-Mental State Examination after cold (28 degrees C) and warm (34 degrees C) cardiopulmonary bypass using different blood gas strategies (alpha-stat and pH-stat). *Acta Anaesthesiologica Scandinavica.* **46,** 10-16.

256. Shann, K.G., Likosky, D.S., Murkin, J.M., Baker, R.A., Baribeau, Y.R., DeFoe, G.R., Dickinson, T.A., Gardner, T.J., Grocott, H.P., O'Connor, G.T., Rosinski, D.J., Sellke, F.W., Willcox, T.W., 2006. An evidence-based review of the practice of cardiopulmonary bypass in adults: a focus on neurologic injury, glycemic control, hemodilution, and the inflammatory response. *The Journal of Thoracic and Cardiovascular Surgery.* **132,** 283-290.

257. Shroyer, A.L., Grover, F.L., Hattler, B., Collins, J.F., McDonald, G.O., Kozora, E., Lucke, J.C., Baltz, J.H., Novitzky, D., Veterans Affairs Randomized On/Off Bypass (ROOBY) Study Group, 2009. On-pump versus off-pump coronary-artery bypass surgery. *The New England Journal of Medicine.* **361,** 1827-1837.

258. Siepe, M., Pfeiffer, T., Gieringer, A., Zemann, S., Benk, C., Schlensak, C., Beyersdorf, F., 2011. Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **40,** 200-207.

259. Silbert, B.S., Maruff, P., Evered, L.A., Scott, D.A., Kalpokas, M., Martin, K.J., Lewis, M.S., Myles, P.S., 2004. Detection of cognitive decline after coronary surgery: a comparison of computerized and conventional tests. *British Journal of Anaesthesia.* **92,** 814-820.

260. Silbert, B.S., Scott, D.A., Evered, L.A., Lewis, M.S., Kalpokas, M., Maruff, P., Myles, P.S., Jamrozik, K., 2006. A comparison of the effect of high- and low-dose fentanyl on the incidence of postoperative cognitive dysfunction after coronary artery bypass surgery in the elderly. *Anesthesiology.* **104,** 1137-1145.

261. Skrabal, C.A., Khosravi, A., Westphal, B., Steinhoff, G., Liebold, A., 2006. Effects of poly-2-methoxyethylacrylate (PMEA)-coating on CPB circuits. *Scandinavian Cardiovascular Journal : SCJ.* **40,** 224-229.

262. Snyder-Ramos, S.A., Gruhlke, T., Bauer, H., Bauer, M., Luntz, A.P., Motsch, J., Martin, E., Vahl, C.F., Missler, U., Wiesmann, M., Bottiger, B.W., 2004. Cerebral and extracerebral release of protein S100B in cardiac surgical patients. *Anaesthesia.* **59,** 344-349.

263. Sousa Uva, M., Cavaco, S., Oliveira, A.G., Matias, F., Silva, C., Mesquita, A., Aguiar, P., Bau, J., Pedro, A., Magalhaes, M.P., 2010. Early graft patency after off-pump and on-pump coronary bypass surgery: a prospective randomized study. *European Heart Journal.* **31,** 2492-2499.

264. Stern, A., Tunick, P.A., Culliford, A.T., Lachmann, J., Baumann, F.G., Kanchuger, M.S., Marschall, K., Shah, A., Grossi, E., Kronzon, I., 1999. Protruding aortic arch atheromas: risk of stroke during heart surgery with and without aortic arch endarterectomy. *American Heart Journal.* **138,** 746-752.

265. Stolz, E., Gerriets, T., Kluge, A., Klovekorn, W.P., Kaps, M., Bachmann, G., 2004. Diffusion-weighted magnetic resonance imaging and neurobiochemical markers after

aortic valve replacement: implications for future neuroprotective trials? *Stroke; a Journal of Cerebral Circulation.* **35,** 888-892.

266. Stroobant, N., Van Nooten, G., Van Belleghem, Y., Vingerhoets, G., 2005. Relation between neurocognitive impairment, embolic load, and cerebrovascular reactivity following on- and off-pump coronary artery bypass grafting. *Chest.* **127,** 1967-1976.

267. Stump, D.A., Rogers, A.T., Hammon, J.W., Newman, S.P., 1996. Cerebral emboli and cognitive outcome after cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia.* **10,** 113-8; quiz 118-9.

268. Sudo, K., Kishimoto, R., Tajima, Y., Matsumoto, A., Tashiro, K., 2004. A paralysed thumb. *Lancet.* **363,** 1364.

269. Svenarud, P., Persson, M., van der Linden, J., 2004. Effect of CO2 insufflation on the number and behavior of air microemboli in open-heart surgery: a randomized clinical trial. *Circulation.* **109,** 1127-1132.

270. Svensson, L.G., Nadolny, E.M., Kimmel, W.A., 2002. Multimodal protocol influence on stroke and neurocognitive deficit prevention after ascending/arch aortic operations. *The Annals of Thoracic Surgery.* **74,** 2040-2046.

271. Svensson, L.G., Nadolny, E.M., Penney, D.L., Jacobson, J., Kimmel, W.A., Entrup, M.H., D'Agostino, R.S., 2001. Prospective randomized neurocognitive and S-100 study of hypothermic circulatory arrest, retrograde brain perfusion, and antegrade brain perfusion for aortic arch operations. *The Annals of Thoracic Surgery.* **71,** 1905-1912.

272. Sylivris, S., Levi, C., Matalanis, G., Rosalion, A., Buxton, B.F., Mitchell, A., Fitt, G., Harberts, D.B., Saling, M.M., Tonkin, A.M., 1998. Pattern and significance of cerebral microemboli during coronary artery bypass grafting. *The Annals of Thoracic Surgery.* **66,** 1674-1678.

273. Szalma, I., Kiss, A., Kardos, L., Horvath, G., Nyitrai, E., Tordai, Z., Csiba, L., 2006. Piracetam prevents cognitive decline in coronary artery bypass: a randomized trial versus placebo. *The Annals of Thoracic Surgery.* **82,** 1430-1435.

274. Taggart, D.P., Browne, S.M., Wade, D.T., Halligan, P.W., 2003. Neuroprotection during cardiac surgery: a randomised trial of a platelet activating factor antagonist. *Heart (British Cardiac Society).* **89,** 897-900.

275. Tanaka, T., Kai, S., Koyama, T., Daijo, H., Adachi, T., Fukuda, K., Hirota, K., 2011. General anesthetics inhibit erythropoietin induction under hypoxic conditions in the mouse brain. *PloS One.* **6,** e29378.

276. Taylor, R.L., Borger, M.A., Weisel, R.D., Fedorko, L., Feindel, C.M., 1999. Cerebral microemboli during cardiopulmonary bypass: increased emboli during perfusionist interventions. *The Annals of Thoracic Surgery.* **68,** 89-93.

277. Terrando, N., Eriksson, L.I., Ryu, J.K., Yang, T., Monaco, C., Feldmann, M., Jonsson Fagerlund, M., Charo, I.F., Akassoglou, K., Maze, M., 2011. Resolving postoperative neuroinflammation and cognitive decline. *Annals of Neurology.* **70,** 986-995.

278. Thiel, A., Zimmer, M., Stertmann, W.A., Kaps, M., Hempelmann, G., 1997. Microembolizatoins during heart surgery under extracorporeal circulation. *Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie : AINS.* **32,** 715-720.

279. Toeg, H.D., Nathan, H., Rubens, F., Wozny, D., Boodhwani, M., 2013. Clinical impact of neurocognitive deficits after cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery.* **145,** 1545-1549.

280. Tombaugh, T.N., 2004. Trail Making Test A and B: normative data stratified by age and education. *Archives of Clinical Neuropsychology : The Official Journal of the National Academy of Neuropsychologists.* **19,** 203-214.

281. Toner, I., Hamid, S.K., Peden, C.J., Taylor, K.M., Smith, P.L., 1993. Magnetic resonance imaging and P300 (event-related auditory evoked potentials) in the assessment of postoperative cerebral injury following coronary artery bypass graft surgery. *Perfusion.* **8,** 321-329.

282. Toner, I., Peden, C.J., Hamid, S.K., Newman, S., Taylor, K.M., Smith, P.L., 1994. Magnetic resonance imaging and neuropsychological changes after coronary artery bypass graft surgery: preliminary findings. *Journal of Neurosurgical Anesthesiology.* **6,** 163-169.

283. Toyoda, K., Yasaka, M., Nagata, S., Yamaguchi, T., 1992. Aortogenic embolic stroke: a transesophageal echocardiographic approach. *Stroke; a Journal of Cerebral Circulation.* **23,** 1056-1061.

284. Tully, P.J., Baker, R.A., Kneebone, A.C., Knight, J.L., 2008. Neuropsychologic and quality-of-life outcomes after coronary artery bypass surgery with and without cardiopulmonary bypass: a prospective randomized trial. *Journal of Cardiothoracic and Vascular Anesthesia.* **22,** 515-521.

285. Uebelhack, R., Vohs, K., Zytowski, M., Schewe, H.J., Koch, C., Konertz, W., 2003. Effect of piracetam on cognitive performance in patients undergoing bypass surgery. *Pharmacopsychiatry.* **36,** 89-93.

286. van der Linden, J. & Casimir-Ahn, H., 1991. When do cerebral emboli appear during open heart operations? A transcranial Doppler study. *The Annals of Thoracic Surgery.* **51,** 237-241.

287. Van Dijk, D., Jansen, E.W., Hijman, R., Nierich, A.P., Diephuis, J.C., Moons, K.G., Lahpor, J.R., Borst, C., Keizer, A.M., Nathoe, H.M., Grobbee, D.E., De Jaegere, P.P., Kalkman, C.J., Octopus Study Group, 2002. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. *JAMA : The Journal of the American Medical Association.* **287,** 1405-1412.

288. van Dijk, D., Moons, K.G., Keizer, A.M., Jansen, E.W., Hijman, R., Diephuis, J.C., Borst, C., de Jaegere, P.P., Grobbee, D.E., Kalkman, C.J., Octopus Study Group, 2004. Association between early and three month cognitive outcome after off-pump and on-pump coronary bypass surgery. *Heart (British Cardiac Society).* **90,** 431-434.

289. van Dijk, D., Spoor, M., Hijman, R., Nathoe, H.M., Borst, C., Jansen, E.W., Grobbee, D.E., de Jaegere, P.P., Kalkman, C.J., Octopus Study Group, 2007. Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. *JAMA : The Journal of the American Medical Association.* **297,** 701-708.

290. Vanninen, R., Aikia, M., Kononen, M., Partanen, K., Tulla, H., Hartikainen, P., Paranen, J., Manninen, H., Enberg, P., Hippelainen, M., 1998. Subclinical cerebral complications after coronary artery bypass grafting: prospective analysis with magnetic resonance imaging, quantitative electroencephalography, and neuropsychological assessment. *Archives of Neurology.* **55,** 618-627.

291. Vedin, J., Nyman, H., Ericsson, A., Hylander, S., Vaage, J., 2006. Cognitive function after on or off pump coronary artery bypass grafting. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **30,** 305-310.

292. Videm, V., Fosse, E., Mollnes, T.E., Ellingsen, O., Pedersen, T., Karlsen, H., 1989. Different oxygenators for cardiopulmonary bypass lead to varying degrees of human complement activation in vitro. *The Journal of Thoracic and Cardiovascular Surgery.* **97,** 764-770.

293. Vora, Y.Y., Suarez-Almazor, M., Steinke, D.E., Martin, M.L., Findlay, J.M., 1999. Role of transcranial Doppler monitoring in the diagnosis of cerebral vasospasm after subarachnoid hemorrhage. *Neurosurgery.* **44,** 1237-47; discussion 1247-8.

294. Wang, D., Wu, X., Li, J., Xiao, F., Liu, X., Meng, M., 2002. The effect of lidocaine on early postoperative cognitive dysfunction after coronary artery bypass surgery. *Anesthesia and Analgesia.* **95,** 1134-41, table of contents.

295. Wang, Y., Sands, L.P., Vaurio, L., Mullen, E.A., Leung, J.M., 2007. The effects of postoperative pain and its management on postoperative cognitive dysfunction. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry.* **15,** 50-59.

296. Warach, S., Chien, D., Li, W., Ronthal, M., Edelman, R.R., 1992. Fast magnetic resonance diffusion-weighted imaging of acute human stroke. *Neurology.* **42,** 1717-1723.

297. Watters, M.P., Cohen, A.M., Monk, C.R., Angelini, G.D., Ryder, I.G., 2000. Reduced cerebral embolic signals in beating heart coronary surgery detected by transcranial Doppler ultrasound. *British Journal of Anaesthesia.* **84,** 629-631.

298. Westaby, S., Saatvedt, K., White, S., Katsumata, T., van Oeveren, W., Halligan, P.W., 2001. Is there a relationship between cognitive dysfunction and systemic

inflammatory response after cardiopulmonary bypass? *The Annals of Thoracic Surgery.* **71,** 667-672.

299. Whitaker, D.C., Green, A.J., Stygall, J., Harrison, M.J., Newman, S.P., 2007. Evaluation of an alternative S100b assay for use in cardiac surgery: relationship with microemboli and neuropsychological outcome. *Perfusion.* **22,** 267-272.

300. Whitaker, D.C., Newman, S.P., Stygall, J., Hope-Wynne, C., Harrison, M.J., Walesby, R.K., 2004. The effect of leucocyte-depleting arterial line filters on cerebral microemboli and neuropsychological outcome following coronary artery bypass surgery. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery.* **25,** 267-274.

301. Wimmer-Greinecker, G., Matheis, G., Brieden, M., Dietrich, M., Oremek, G., Westphal, K., Winkelmann, B.R., Moritz, A., 1998. Neuropsychological changes after cardiopulmonary bypass for coronary artery bypass grafting. *The Thoracic and Cardiovascular Surgeon.* **46,** 207-212.

302. Wityk, R.J., Goldsborough, M.A., Hillis, A., Beauchamp, N., Barker, P.B., Borowicz, L.M.,Jr, McKhann, G.M., 2001. Diffusion- and perfusion-weighted brain magnetic resonance imaging in patients with neurologic complications after cardiac surgery. *Archives of Neurology.* **58,** 571-576.

303. Wolman, R.L., Nussmeier, N.A., Aggarwal, A., Kanchuger, M.S., Roach, G.W., Newman, M.F., Mangano, C.M., Marschall, K.E., Ley, C., Boisvert, D.M., Ozanne, G.M., Herskowitz, A., Graham, S.H., Mangano, D.T., 1999. Cerebral injury after cardiac surgery: identification of a group at extraordinary risk. Multicenter Study of Perioperative Ischemia Research Group (McSPI) and the Ischemia Research Education Foundation (IREF) Investigators. *Stroke; a Journal of Cerebral Circulation.* **30,** 514-522.

304. Yin, Y.Q., Luo, A.L., Guo, X.Y., Li, L.H., Huang, Y.G., 2007. Postoperative neuropsychological change and its underlying mechanism in patients undergoing coronary artery bypass grafting. *Chinese Medical Journal.* **120,** 1951-1957.

305. Zamvar, V., Williams, D., Hall, J., Payne, N., Cann, C., Young, K., Karthikeyan, S., Dunne, J., 2002. Assessment of neurocognitive impairment after off-pump and on-pump techniques for coronary artery bypass graft surgery: prospective randomised controlled trial. *BMJ (Clinical Research Ed.).* **325,** 1268.

306. Zhang, Z., Ma, P., Xu, Y., Zhan, M., Zhang, Y., Yao, S., Zhang, S., 2011. Preventive effect of gastrodin on cognitive decline after cardiac surgery with cardiopulmonary bypass: a double-blind, randomized controlled study. *Journal of Huazhong University of Science and Technology.Medical Sciences = Hua Zhong Ke Ji Da Xue Xue Bao.Yi Xue Ying De Wen Ban = Huazhong Keji Daxue Xuebao.Yixue Yingdewen Ban.* **31,** 120-127.

307. Zigmond, A.S. & Snaith, R.P., 1983. The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica.* **67,** 361-370.