THE SIGNAL AVERAGED P WAVE: A NON-INVASIVE MARKER OF ATRIAL ELECTROPHYSIOLOGICAL SUBSTRATE

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By

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LIST OF ABBREVIATIONS

Abbreviation	Full Name
ADC	Analogue to Digital Converter
AERP	Atrial Effective Refractory Period
AF	Atrial Fibrillation
AP	Action Potential
APD	Action Potential Duration
Ca	Calcium
CABG	Coronary Artery Bypass Grafting
CV	Conduction Velocity
Cx	Connexin
DSP	Digital Signal Processing
ECG	Electrocardiogram
EDS	Energy density spectrum
EPS	Electrophysiological Study
ERAF	Early Reinitiation of Atrial Fibrillation
ERP	Effective Refractory Period
FFT	Fast Fourier Transform
HRV	Heart Rate Variability
IRAF	Immediate Reinitiation of Atrial Fibrillation
K	Potassium
MAP	Monophasic action potential
ms	Milliseconds
Na	Sodium
PAF	Paroxysmal Atrial Fibrillation
PDS	Power Density Spectrum
PVI	Segmental Pulmonary Vein Isolation
PWD	P Wave Duration
RMS	Root Mean Square
SA	Sino-Atrial
SAPW	Signal Averaged P Wave
SR	Sinus Rhythm
SEM	Standard Error of the Mean
VCG	Vector Cardiogram
Vmax	Maximum rise of action potential upstroke
WACA	Wide Area Circumferential Ablation

TABLE OF CONTENTS

PREFACE

NON-INVASIVE ASSESSMENT IN CARDIOLOGY

The technological advances made over the last century have afforded the clinician an array of sophisticated tests to aid the diagnostic process. Much of the knowledge gained on the pathophysiology of cardiac disease has been from invasive assessment, often in animals, but also in human subjects. Application of this knowledge to patient care is limited by the need for invasive studies that present some risk of harm to the patient. Non-invasive assessment reduces risk of harm significantly whilst providing information equivalent to invasive assessment. The best example of this is the insight delivered by technological advances in imaging of the heart. Ultrasound echocardiography, radio-isotope imaging, computerised tomography and magnetic resonance imaging have all excelled expectations in delivering accurate anatomic and functional information non-invasively.

Assessment of electrophysiologic function began non-invasively with the recording of surface potentials by Augustus D Waller[1] and the development of the electrocardiogram (ECG) by William Einthoven[2] (who was later awarded the Nobel Prize in 1924 for his endeavours). Recognition of pathology from the surface ECG was hypothesis generating. In order to explore the heart's electrical system further electrophysiological assessment was made invasively to supplement the information obtained from the surface ECG. This information proved favourable and when combined with pacing stimulus protocols provided the clinician with detailed information on conduction properties that could be measured in a reproducible and reliable way to reflect the impact of drugs or disease in detail that the surface ECG could not. Moreover, the invasively measured properties could be linked with changes at the cellular level and thus the effect of changes in ion channel density, for example, on electrophysiologic properties could be predicted.

It would obviously be beneficial to somehow gather the information non-invasively, but this has proved more challenging. Firstly, much of the information obtained invasively is the product of pacing protocols that cannot be reproduced non-invasively. Secondly, the detailed assessment of cardiac electrophysiology from surface electrograms is hampered by multiple factors pertaining to the intervening tissue, i.e. body habitus and electrical interference (noise). Given these factors the expectations of non-invasive assessment of cardiac electrophysiology must be limited and cannot be compared to imaging. The utility of non-invasive tests must be in the 'broad stokes' rather than the fine detail. However it is not beyond expectations to provide useful insights that may be employed in the investigation of disease trends and or the impact of intervention. The trade off for lack of detailed information is the safety, low cost and general applicability to a large patient population.

The difficulty in gathering further information from the surface ECG has been alluded to briefly above. Digital techniques are used to overcome some of the difficulties such as amplification and noise reduction. Digital applications are then often used to analyse the data gathered.

It is useful to be familiar with some of the concepts involved in digital signal processing as it pertains to cardiac signals and thus a brief outline is presented in appendix 1.

This thesis begins with a detailed review of the surface P wave in health and disease, and a review of atrial fibrillation (AF) – the most common arrhythmia encountered in clinical practice.

STATEMENT OF ORIGINALITY

The study concepts, design, data collection, analysis and interpretation for chapters 5, 6 and 7 were entirely my own work. The concept for design of the study in chapter 4 was originally Dr Peter J Stafford and Dr C J Garratt. Dr Kevin Ward recruited two patients to the study. However the subsequent patient recruitment, study execution and analysis were my own.

Damian P Redfearn

6th April 2008

BRIEF THESIS ABSTRACT

Introduction

Investigation of the signal averaged P wave (SAPW) has indicated that change in measures of duration and energy is present in paroxysmal AF and after cardioversion. If evidence of a relationship between change in the SAPW and change in atrial substrate were evident, the SAPW might afford a useful non invasive clinical tool.

Methods

P wave averaging and analysis was performed using either a dedicated standalone system or a digital Holter ECG recording system. Pilot studies were performed in situations where change in atrial substrate would be expected either with drug agents, after cardioversion or after catheter ablation for atrial fibrillation.

Results

Overall 176 subjects were investigated in 5 studies. Reproducibility was assessed in 16 subjects; P wave duration (PWD) was reproducible over 24 hours (Percentage coefficient of reproducibility (%CR) 3.2%); energy less so (%CR 31%). Nine patients were investigated at electrophysiologic study; PWD was associated with change in conduction time during sinus rhythm in the LA ($\rho = 0.49$ ($p < 0.04$)) after flecainide.

Twenty three patients attending cardioversion were randomised to oral verapamil or current medication; verapamil therapy resulted in higher measured P wave energy (Energy within 20-150Hz (P20): 56.8(13.0) vs. 28.0(3.3) (p=0.03)). Early reinitiation occurred in patients with lower P wave energy 19.0(3.4) vs. 45.4 (9.0) (p=0.017).

Segmental pulmonary vein isolation (PVI) was compared with a wide area circumferential approach (WACA). WACA resulted in PWD prolongation (149.0(4.3) ms to 162.1(4.9) ms; p=0.002), a fall in root mean square (RMS) (4.2(0.4) μV to 2.9(0.4); p=0.002) and energy (P30: 19.6(3.4) to 16.6 (2.2); p=0.001). No significant change was seen after PVI. WACA and WACA + isolation (hybrid) was investigated in a cohort of 83 patients (28 and 55 respectively). Clinical success was better with the hybrid approach (p=0.005) and was associated with a reduction in PWD after the procedure (155.2 (2.8) to 149.7 (2.6) p=0.001)

Conclusion

The studies presented support the notion that changes in the atrial substrate might be reflected in the SAPW.

STRUCTURED THESIS ABSTRACT

Introduction

The concepts in the thesis are introduced in chapter 1 and 2. Chapter 2 deals with general methodology of acquisition and analysis of the recordings used in this thesis. Chapter 1 deals with atrial fibrillation (AF), the arrhythmia studied in this thesis. Recent advances in our understanding of the pathogenesis of AF suggest that it is a complex phenomenon comprising a substrate, that may variously involve conduction delay and also changes in atrial refractoriness which is modified by the arrhythmia itself, a process termed remodelling. Moreover, the importance of the interaction between triggers for the arrhythmia, particularly those from the pulmonary veins, and this underlying substrate is increasingly recognised. Various therapeutic advances have increased our ability to offer treatments for AF and these can be broadly defined as drug interventions and catheter ablation.

AF is associated with a number of well-defined electrophysiological abnormalities of the atria. These include a reduction in the refractory period, an increase in the dispersion of the refractory period and a reduction in conduction velocity of the atrial impulse. These parameters combine to reduce the wavelength and to promote re-entry. Antiarrhythmic drug therapy manifests benefit by changing atrial electrophysiology, whereas the benefit from catheter ablation appears to be more a reduction in trigger than alteration of the electrophysiologic substrate. At the same time, investigation of the high-resolution signal averaged P wave has indicated that changes in quantitative measures of its duration and energy content are present in patients with paroxysmal AF and after cardioversion from persistent AF and can predict those individuals at risk of developing the arrhythmia after coronary bypass surgery.

The above implies that there may be a relationship between parameters measured non-invasively from the surface P wave and indices of underlying atrial electrophysiology. This hypothesis is supported by indirect data concerning the effects of drug intervention on signal averaged P wave (SAPW) parameters and by serial evaluations of the SAPW after cardioversion from persistent AF. If evidence of a relationship between the SAPW and changes in underlying atrial electrophysiologic substrate were evident then this technique would afford a useful non invasive clinical method for the serial evaluation of the atria after therapeutic interventions as well as for the identification of subsets of patients with AF that may respond to different interventions or drugs.

In order to determine if this hypothesis can be supported a series of pilot studies were performed. These studies were designed to examine the SAPW in scenarios where change in atrial electrophysiological substrate might be expected from invasive studies or previous observations. The study designs and protocols for chapters 4 and 5 were reviewed by the University of Leicester Higher Degrees Committee and Local Ethical Committee approval was sought and granted for all studies included. The studies in chapter 6 and 7 replaced original work on recommendation from the examiners and local ethics was granted at the various institutions the where the work was performed.

Methods

Collection of SAPWs was made for 10 minutes at each assessment. Derived analogue signals were amplified 10000 times and band pass filtered between 1 and 300Hz. One lead exhibiting the most obvious P wave was then further band pass filtered between 20 and 50Hz and used as a trigger to align subsequent P waves for signal averaging. The error limit was set to allow at least 100 beats to average but signals with excessive noise were excluded. The analogue data was sampled at 1KHz with 12-bit resolution. Filtered P wave duration (milliseconds) and root mean square of the terminal 30ms of the filtered P wave (RMS30) were calculated. P wave energy was determined in frequency range 20-150Hz (P20), 30-150Hz (P30), 40-150Hz (P40), 60-150Hz (P60) and 80-150Hz (P80) and expressed as $K\mu V^2.s$.

Results

The five studies are presented in chapters 3 to 7; the results are summarised for each chapter below.

Chapter 3 –System Reproducibility

The Holter system used in this study (Syneflash, ELA Medical, Paris, France) was examined for immediate and short term (24 hour) reproducibility. Sixteen subjects volunteered for recordings, mean age 40.4 ± 11.8 years (range 18 to 60 years), seven male. When initial and 24 hour recordings were compared the percentage coefficient of reproducibility (%CR) for PWD was 3.2%, for P20 was 31%, for P60 was 46% and for RMS30 23%. Possible biologic and mechanical reasons for poor reproducibility of P wave energy are speculated upon.

The Holter system was validated against the original hand built system employed in previous studies. Twenty one patients were recruited, with a mean age of 50 years; 8 patients were male. Correlation was high between the two systems and Bland Altman plot demonstrated no significant bias.

Normal values for the Holter system are presented from an analysis of 38 subjects (20 male; mean age 38.9±12.5 years), table 8; page 61.

Chapter 4 - High Resolution Analysis of the Surface P Wave as a Measure of Atrial Electrophysiological Substrate

Nine patients were investigated attending for diagnostic electrophysiological studies (EPS) (4 male; mean age 35.7). A 20 pole catheter was positioned in the right atrium; a decapole catheter was placed in the coronary sinus. Atrial effective refractory period (AERP) and conduction times were measured at the lateral and septal right atrium and the left atrium during sinus rhythm (SR) and at pacing cycle lengths of 600, 500 and 400ms. Simultaneous SAPW recordings were taken during SR and pacing at 600ms. Intravenous flecainide (2mg/kg) was given after which the protocol was repeated.

Flecainide slowed conduction time significantly at all sites ($p < 0.05$) in a controlled environment and simultaneously significantly changed all P wave parameters, 12ms for PWD and 11.5μV^2.sec for P20 during sinus rhythm. Change in conduction time was correlated with P wave variables using Spearman's Rank correlation. PWD was associated with change in conduction time during sinus rhythm in the left atrium ($\rho = 0.49$ ($p < 0.04$)). Negative correlation was observed between P wave energies and conduction time.

The SAPW presented a non-invasive marker of change in atrial electrophysiology

Chapter 5 - Signal Averaged P Wave Reflects Change in Atrial Electrophysiological Substrate Afforded by Verapamil Following Cardioversion from Atrial Fibrillation

Detailed analysis of signal averaged P waves (SAPW) can provide insights into atrial electrophysiology. Abbreviated dosing of verapamil prior to cardioversion improves outcome at one week post cardioversion. The mechanism by which verapamil manifests benefit is uncertain. I hypothesised the SAPW would reflect any change in atrial electrophysiologic substrate afforded by verapamil when compared with controls.

Twenty three patients attending external cardioversion of persistent AF (6 female; mean age 68 years) were investigated. Patients were randomized to verapamil 240mgs daily in three divided doses 3 days before cardioversion and 1 week after, or usual medication. SAPW recordings were performed during sinus rhythm (SR) immediately after cardioversion, at 24hours and 1 week.

The groups were comparable in terms of age, gender, left atrial size and duration of AF. 8 of 9 patients prescribed verapamil maintained SR at 1 week post cardioversion compared with 6 of 14 controls ($p=0.027$). SAPW spectral analysis delivered higher energy for patients prescribed verapamil (median (IQ range)); 40.8(33.4-95.1) vs. 25.7(19.0-38.0) for energy within 20 to 150Hz, P20 (KμV^2.sec; $p=0.03$). There was no difference in P wave duration (PWD) or root mean square of the terminal 30ms between the two groups. Early reinitiation occurred in patients with significantly lower P wave energy 19.6(12.9-24.6) vs. 39.9 (24.0-47.0) ($p=0.017$)

Verapamil 240mg daily for 3 days prior to cardioversion and 1 week after reduces early recurrence of AF. The SAPW observations indicate change in atrial electrophysiologic substrate might be responsible for benefit afforded by verapamil.

Chapter 6 – Atrial Substrate Change After Wide Area Circumferential Ablation (WACA): Observations from High Resolution Electrocardiographic Recordings

The WACA approach to atrial fibrillation is thought to result in 'substrate modification' perhaps related to autonomic denervation. This was examined prospectively by comparing WACA and segmental pulmonary vein isolation (PVI) using non-invasive surrogate markers.

Heart rate variability (HRV) and signal averaged P wave (SAPW) data were derived from high-resolution (HR) recordings ('SpiderView' ELA Medical) made in sinus rhythm immediately before and 24 hours after ablation.

Forty patients were recruited (20 WACA; 20 PVI); the cohorts were comparable. WACA resulted in a marked SAPW change: P wave duration (PWD) (149[4.6] ms to 160[5.9] ms; P = 0.003), root mean square (RMS) (4.4[0.4]μV to 2.8[0.4]; P = 0.001) and energy content (30–150 Hz; 20.4 [3.6]KμV^2.s to 13.7[2.4]; P = 0.001). No significant change was seen after PVI. Heart rate increased after WACA and PVI (61.4 to 73.5 [P = 0.001]; 69.5 to 75.0 [P = 0.07], respectively). HRV was significantly influenced after WACA: low frequency power (LF) 5.7(0.4) to 3.6(0.4); P = 0.001), high-frequency power (HF) 4.6(0.4)–3.4(0.3); P = 0.024, and after PVI: LF 5.4(0.3) to 4.3(0.3); P = 0.024. HF: 4.4(0.4) to 3.0(0.4); P = 0.018).

High resolution recordings exhibited change in HRV after WACA and PVI. Marked change in both HRV and SAPW were observed after WACA. SAPW variables provided a measure of atrial substrate change after WACA unrelated to autonomic denervation.

Chapter 7 – Signal Averaged P Wave (SAPW) Duration Change after Wide Area Circumferential Ablation (WACA) is Dependent upon Electrical Isolation

Previous work presented in chapter 6 suggested that a WACA approach without isolation might result in increased SAPW duration post procedure (PWD-P). A trend toward increased clinical recurrence with longer PWD-P was noted. This was examined prospectively in 2 non-randomised cohorts of patients. In the first cohort WACA was performed with further ablation directed to reduce voltage and fractionated signals within the circles but no attempt was made to electrically isolate pulmonary veins and isolation was not tested. In the second cohort WACA was performed with additional pulmonary vein isolation tested formally with a circular mapping catheter (Hybrid).

A 10 min high resolution recording was made prior to ablation and 24 hours after using a digital Holter capable of 1000Hz sampling frequency (SpiderView, ELA Medical). Acute change examined (24 hours) in PWD after atrial fibrillation (AF) ablation.

Data were collected from 83 consecutive cases (28 WACA, 55 Hybrid; mean age 54.3 yrs (29-76) 15 female). Outcome is known in 79, mean FU 10 months (3-24). Pre-procedure PWD was long compared with controls (153.4ms (1.06) vs. 130ms (2.1) p<0.001).

Recurrence was observed in 14 WACA (50%) vs. 11Hybrid (20%) post procedure (AF 7 & 5; Flutter 7 & 6 respectively), p=0.005. PWD-P in those destined for recurrence was 167.5ms (5.5) compared with 148.9 (2.0) (p<0.001); a PWD-P of 157ms had a sensitivity and specificity of 65% and 77% respectively for arrhythmia recurrence (PPV and NPV 54% and 84% respectively). PWD reduced from pre-procedure value in the Hybrid group (155.2 (2.8) to 149.7 (2.6) p=0.001) and increased in the WACA group (152.2 (3.7) to 161.3 (4.7) p=0.009). PWD-P was significantly different between two cohorts (p=0.006). On multivariate logistic regression, PWD-P (OR 2.0 (1.2-3.2) for every 10ms increase, p=0.004) and type of procedure (WACA OR 5.5 (1.4-21.7), p=0.015) were both independent predictors of recurrence.

WACA without attempted isolation yields poorer outcomes and is associated with a longer post procedural PWD. SAPW might present a useful technique to determine PV isolation during follow-up.

Chapter 8 - Discussion and Conclusions

The results of the above studies are discussed in the context of the central theme of the thesis to establish if a hypothesis linking change in P wave parameters to change in atrial electrophysiological substrate might be supported. The limitations of each of the studies are examined and discussed. Future directions are investigated and ongoing work is illustrated.

Despite limitations the data presented within this thesis is consistent with the SAPW presenting a marker of short term change in atrial electrophysiologic substrate.

Appendix 1- General Concepts of Digital Signal Processing

The concepts involved in DSP that are relevant to the methodology used in the thesis are outlined in this appendix.

References

CHAPTER ONE

THE SURFACE P WAVE

THE SURFACE P WAVE IN HEALTH

The anatomical origin of the normal P wave is the sinoatrial (SA) node. The structure of the node and the relationship to its function remains a subject of debate[3]. The anatomical location of the SA node is epicardial situated anteriorly at the superior aspect of the right atrium. This provides the normal P wave with an inferior axis toward the left. Initial experience with the surface electrocardiogram in normal healthy subjects identified changes in P wave morphology associated with autonomic tone and exercise. Intracardiac mapping of the right atrium suggests the SA node is partially insulated from the surrounding atrial tissue and houses a dynamic multicentric origin to the sinus impulse. Extranodal sites of pacemaker activity may be coordinated from within the SA node. The exact method of communication and co-ordination remains an area of research but the dynamic function of the SA node explains some observed changes in normal subjects[4].

The maximum duration of normal atrial activation is 110ms. As the SA node is situated within the right atrium this is excited first with an ascending aspect to the proximal P wave in the frontal plane P wave axis (lead II). The apex of the P wave represents the end of right atrial activation and takes between 20 and 40ms. Left atrial activation begins approximately 30ms after right atrial activation and is represented by a descending distal limb of the P wave in lead II; the duration is between 50 and 60ms. A little notching of the apex of the P wave is an uncommon but normal manifestation due to right atrial activation completing before left activation has commenced. The normal observed P wave is thus the composite summation of right and left atrial activation from the SA node.

The P wave axis may be estimated from the frontal plane vectors created by leads I, II, III and aVF, the summation of the positive and negative deflections in each of these leads will result in a P wave vector with a deducible angle in the frontal plane. This axis is normally directed between +45° to +65°; thus P wave axes >+70° are indicative of right axis deviation and an axis of < +45° usually reflects left axis deviation. This results in the normal P wave being most aligned with lead II and thus is best studied in this lead, however a left axis deviation will result in aVR presenting a prominent negative deflection, further deviation (toward 0°) aligns the maximum deflection with lead I. Right axis deviation will align the P wave with aVF and the morphology is best studied in this lead during right axis deviation.

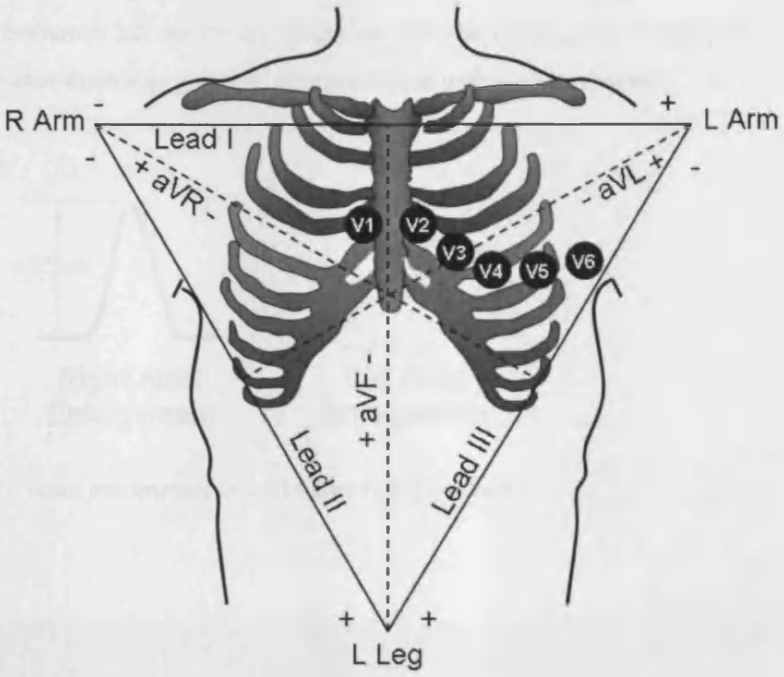

Figure 1: The cardiac vectorgram limb leads and precordial leads.

The normal P wave in lead II has a smooth positive pyramidal deflection with amplitude of 2mm but no greater than 2.5mm. Lead V1 exhibits a biphasic P wave and is thus represented by positive and subsequent negative deflection about the isoelectric line. As the SA node depolarises the surrounding right atrium first, the V1 electrode, positioned at the right parasternal fourth intercostal space, will record an initial positive deflection. As the left atrium is situated posteriorly the left atrial vector recorded by lead V1 assumes a shallow negative deflection. It should be noted however, that the left atrial component of the P wave in V1 might be isoelectric and thus appear incorporated in the PR interval.

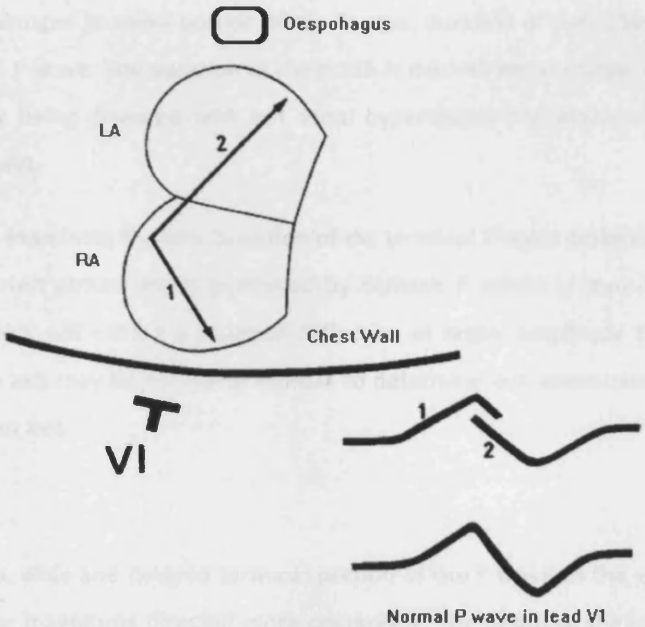

Figure 2: A cross-sectional view is taken with vectors appreciated by lead V1 illustrated together with how they combine to produce the P wave. RA: right atrium; LA: Left atrium.

The normal P wave should therefore remain within the parameters indicated below. Sinus tachycardia will induce a right P wave axis shift of approximately 10° to 15° as compared with the resting ECG. Autonomic influence will also affect the site of pacemaker discharge and thus alter the axis to within a few degrees.

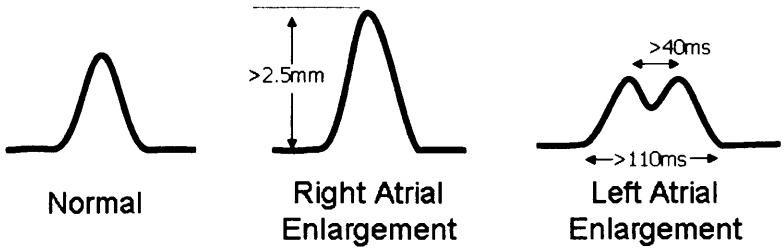

Figure 3. Depicting normal and abnormal P wave parameters in lead II (see text for details).

THE SURFACE P WAVE IN DISEASE

Early reports have linked prolonged P wave duration on ECG with propensity to develop atrial fibrillation or atrial flutter[5]. Increased duration was initially thought to reflect left atrial enlargement; however further study defined inter-atrial conduction disease to be responsible[6]. Atrial arrhythmias following cardiac surgery have been linked to prolonged P wave duration on standard surface ECG; accuracy improved when three leads were recorded simultaneously[7].

LEFT ATRIAL ENLARGEMENT

Left atrial enlargement is manifest by a prolonged terminal portion of the P wave, duration of over 110ms, and a characteristic double peaked or 'notched' P wave. The duration of the notch is over 40 ms as shown in figure 3. Due to the axis of the P wave usually being deviated with left atrial hypertrophy the aforementioned manifestations are best viewed in lead I or aVL.

The P wave axis may be further defined by examining the axis deviation of the terminal P wave deflection. This deflection more accurately represents the left atrium and is portrayed by biphasic P waves in lead III (i.e. a negative terminal deflection). I, aVL and aVR will exhibit a terminal deflection of larger amplitude than the initial deflection. Thus total surface P wave axis may be normal or difficult to determine but assessment of the terminal portion of the P wave will render an axis.

When viewed from lead V1 there is a deep, wide and delayed terminal portion of the P wave as the enlarged left atrium will result in an increased vector magnitude directed more posteriorly. The depth of the left atrial component of the P wave will normally exceed 1mm.

The changes in the surface P wave reflecting underlying atrial pathology are non-specific, reflecting disordered conduction rather than specific structural abnormalities. The abnormalities described are associated with an enlarged left atrium but not left atrial hypertrophy unless there is associated conduction disturbance. A prolonged P wave may be the first electrocardiographic sign of systemic hypertension and is linked with left atrial volume overload (it is thus a transient, but frequent, accompaniment to acute pulmonary oedema).

RIGHT ATRIAL ENLARGEMENT

The initial deflection of the surface P wave reflects right atrial depolarisation and thus may alter as a result of right atrial abnormality. Increased amplitude of the P wave to >2.5mm is a consequence of right atrial enlargement. The duration of the initial right atrial segment of the P wave is also longer but the increased duration is buried within left atrial activation and thus P wave duration is unaltered. Right axis deviation of the P wave will result in a frontal plane P wave axis of +80° or more thus lead III and aVF are best able to represent the P wave.

Lead V1 is of particular interest in the assessment of the P wave in association with pulmonary disease. Chronic airways limitation with an obstructive picture on spirometry may result in negative P waves in leads V1 and V2; this is secondary to hyperinflation, a low diaphragm and displacement of the heart. With right atrial enlargement the P wave in lead V1 will generally become taller with greater symmetry than normal; the amplitude of the P wave may exceed 2.5mm and increase the right atrial component duration to over 40ms. The left atrial component is often lost or attenuated.

Tall P waves with a right axis deviation in acquired heart disease (+90°) are frequently associated with obstructive chronic airways limitation and termed 'P pulmonale'. The P wave in V1 may be positive or negative in chronic obstructive airways limitation but the absence of right atrial deviation is a strong indicator of alternative lung pathology e.g. diffuse pulmonary fibrosis. This would appear to reflect chest hyperinflation changing the P wave axis proportionally. In chronic obstructive airways disease the degree of frontal plane right axis deviation of the P wave, rather than P wave amplitude, correlates well with pulmonary function.

Uncommonly, the manifestation of right atrial enlargement in lead V1 may mimic left atrial enlargement, with a pronounced negative deflection. This may be distinguished from left atrial enlargement by down slope of the P wave at the termination of the positive component. This transitional deflection will not exceed 30ms, whereas in left atrial enlargement the duration of this deflection is always longer than 30 ms (figure 4).

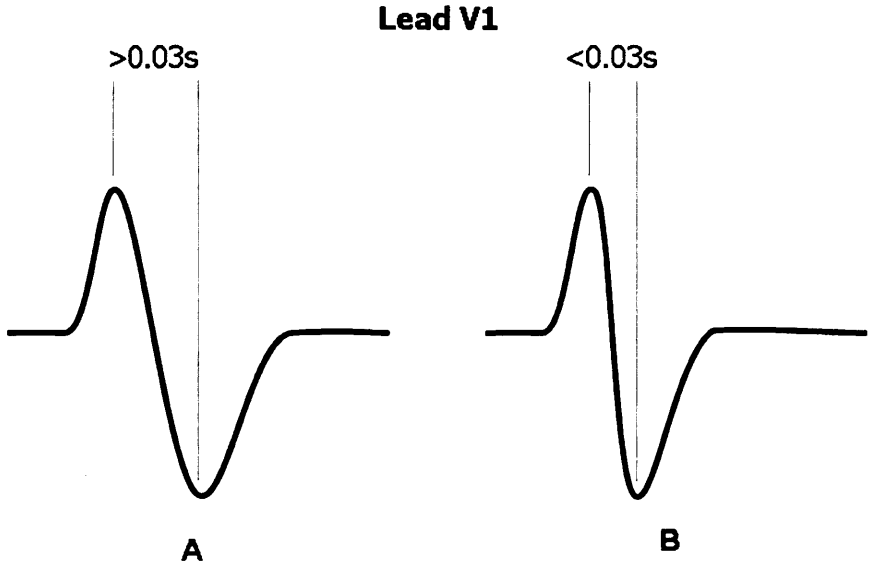

Figure 4: Exhibiting the differing duration of down slope observed from lead V1 in left (A) and right (B) atrial enlargement.

CONGENITAL HEART DISEASE

Tetralogy of Fallot and pulmonary stenosis both result in right atrial enlargement. The surface ECG manifestation of these conditions is different from acquired causes of right atrial enlargement. Tall peaked P waves are present but the mean frontal plane axis is either within the normal range or deviated slightly to the left (+45° to 0°). Marked left axis deviation in association with tall surface P waves is associated with Ebstein's anomaly. The term 'P congenitale' is given to the association of tall P waves of right atrial enlargement and left axis deviation.

COMBINED LEFT AND RIGHT ATRIAL ENLARGEMENT

Mitral stenosis associated with either, marked pulmonary hypertension, tricuspid incompetence or tricuspid stenosis, and atrial septal defect, with or without acquired mitral stenosis (Lutembacher's syndrome), manifests as combined left and right atrial enlargement. Left atrial diameter has correlated well with P wave area ($r = 0.739$, $p = 0.001$) and also with P-wave duration ($r = 0.635$, $p < 0.01$) or P-wave amplitude ($r = 0.683$, $p < 0.01$),measured in lead II[8]. The surface appearance is of a wide notched P wave of increased amplitude. When this P wave has a pronounced initial peak taller than the second (left atrial) peak it is often termed P 'tricuspidale' because of the association with tricuspid valve disease. The appearance of lead V1 reflects the dual pathology with a tall peaked positive initial right atrial component and a terminal deep, wide left atrial component.

Tall peaked narrow, entirely positive P waves in lead V1 may also be a representation of retrograde atrial activation. It is difficult to differentiate this from right atrial enlargement from this lead alone; however examination of the inferior leads will establish the diagnosis as the frontal plane axis is in the region of -80° to -90°, thus the vector is directed toward the negative poles of leads II, III and aVF resulting in negative P wave deflections in all these leads.

THE SURFACE P WAVE IN TACHYCARDIA

Detailed examination of the surface P wave from a standard 12 lead electrocardiogram during tachycardia may provide much information as to the mechanism of the tachycardia. A recent study on atrial tachycardia, examining 31 consecutive patients, compared the surface ECG characteristics with the results of invasive electrophysiological mapping and correlated the results. The investigators found that leads aVL and V1 were useful in predicting the origin of atrial foci. The sensitivity and specificity of using a positive or biphasic P wave in lead aVL to predict a right atrial focus was 88% and 79%, respectively. The sensitivity and specificity of a positive P wave in lead V1 in predicting a left atrial focus was 93% and 88%, respectively. The investigators also demonstrated examination of the inferior lead P waves could help predict a superior or inferior focus[9].

Interatrial block, defined as P wave duration (PWD) over 120ms and biphasic P waves in the inferior leads, in a group of patients with cardiomyopathy or valvular lesions was associated with a 94% chance of developing atrial flutter or fibrillation as oppose to a 24% chance in controls with a similar clinical picture but no ECG evidence of interatrial block[10]. Dilaveris et al developed this further in a study of 60 patients with paroxysmal atrial fibrillation (PAF) compared with 40 healthy controls. The group measured the maximum PWD from a surface 12 lead ECG and also the difference between the maximum and minimum i.e. the P wave dispersion. There were significant differences between the groups with a PWD of 110ms or over and a P wave dispersion of 40ms demonstrating a sensitivity of 88% and 83% and a specificity of 75% and 85%, for PAF patients, respectively[11].

THE SURFACE P WAVE IN PAROXYSMAL ATRIAL FIBRILLATION

The potential for atrial arrhythmia may be reflected in the surface P wave - careful examination of the sinus P wave can provide information on risk of atrial fibrillation. Intra-atrial conduction delay (defined as a single lead P wave or total P wave duration (derived from three simultaneously recorded leads) of over 110ms) provided a sensitive but non-specific marker of post operative atrial fibrillation[7].

The prevalence of prolonged P wave duration on sampling of a general hospital population has been estimated at approximately 40%[12]; this has driven many researchers to refine the analysis of P wave morphology in such a way as to provide a more sensitive and specific marker of arrhythmic potential. P wave dispersion and P wave

variance, the difference between the maximum and minimum measured P wave duration and the variance of P wave duration respectively, have been used to distinguish patients with paroxysmal atrial fibrillation in a variety of clinical settings[13, 14]. Challenges exist in the accurate estimation of P wave duration; when evaluated for intra-observer and inter-observer variability there was poor reproducibility for P wave dispersion and the most accurate method was the use of on-screen digital callipers[15]. Frost et al used the surface P wave as a predictor of atrial fibrillation. The surface P wave duration compared favourably against the signal averaged P wave, but neither method offered an independent predictor of atrial fibrillation[16].

REFERENCE TEXTS ON SURFACE ECG INTERPRETATION

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THE SIGNAL AVERAGED P WAVE

Signal averaging systems have generally been applied to the QRS portion of the ECG examining for late potentials – high frequency electrograms thought to represent fractionated slow conduction through damaged parts of the ventricle[17]. High frequency fractionated electrograms are present during sinus rhythm (SR) in patients with atrial fibrillation and sinus node disease[18, 19] and has been associated with prolonged PWD and intra-atrial conduction time[20]. Thus the techniques used in QRS averaging were employed in a similar fashion for examination of the P wave.

SAPW ANALYSIS

Analysis of the P wave continues to be a debated issue as acquisition varies between investigators[21]. Yamada[22] and Gondo[23] have both published data concentrating on the terminal portion of the P wave; much the same as the work on ventricular late potentials. Yamada concentrated on a 100ms segment starting 75ms prior to the end of the P wave. FFT was performed on this segment in 28 patients with PAF and 34 controls; the results established a greater proportion of patients with PAF had frequency components in the 20-40 Hz range.

Gondo *et al* examined P wave duration and the root-mean-square voltage in the last 10, 20 and 30ms of the P wave. The group found PAF was associated with a prolonged total P wave duration and also a reduced RMS voltage at 20ms (L20). The group concluded that the L20 reflected atrial late potentials and this was responsible for the increased P wave duration and atrial vulnerability; they suggested further work concentrate on the high frequency low amplitude signals at the end of the P wave.

Stafford also looked at the last 30 ms root-mean-square voltages and did not demonstrate pronounced differences compared with a longer P wave duration and a greater peak spatial velocity[24]. Spatial velocity was defined as the rate of change of voltage within the P wave signal in each orthogonal lead and represented the rapidity of directional change of the P wave vector during atrial activation. The investigators concluded that there was little supporting evidence for 'atrial late potentials' and found a low reproducibility of terminal P wave voltage when repeated recordings in the same patient are examined. Of note this study also found the filtered P wave duration was a risk factor for atrial fibrillation and was independent of cardiopulmonary disease or LA size on echo.

Stafford *et al* continued work on the most robust technique for analysis of the P wave postulating that fractionated electrograms from the right atrium are unlikely to be present at the terminal portion of the P wave. A novel method of P wave analysis using the whole P wave, which due to the natural P waves tendency toward zero at beginning and end of the P wave, eliminated the need for windowing and the inherent problems incurred (see page 120), was compared against the standard method of terminal P wave analysis

using a Blackmann Harris window. Both P waves were zero padded to 1,024 points and the techniques compared on test signals and patient data[25]. The results indicated the conventional method proved to be less robust and provided considerable variation in response to test signals on increasing duration. On analysis of patient data the group found a significant difference in absolute energy contained in frequency bands 80 to 150Hz with the novel method but no such difference with the conventional method, a cut-off of 1.4KμV^2.s in P80 conveyed a specificity and sensitivity of around 70% (p=0.01). Power ratios were not significantly different between patient and controls due to the power in the lower frequency range also being increased. The conventional method was also far less reliable and sensitive to changes in the P wave endpoint being sensitive to the relative phase of signals comprising the terminal P wave. Thus this study cast doubt on work using the conventional method of terminal P wave analysis; it also demonstrated efficacy of frequency domain analysis of the entire P wave in assessment of the SAPW.

Steinberg's group also published data on the most robust method of SPAW analysis[26]. The group compared five different methods of signal filtering: unidirectional, bidirectional, finite impulse response, least squares fit and spectral fast Fourier transform, at different frequencies. The recordings were from 15 patients with atrial fibrillation and 15 controls. The group found significant differences in calculated P wave duration dependent upon the type of filter employed. This impacted upon the clinical utility of the SAPW; for example, using the finite impulse response filter with this system detected no difference in PWD between controls and AF patients. The least squares fit filter appeared to show the best discrimination ability with an odds ratio of 26 (p=<0.0001) for association with atrial fibrillation. Such discrepancy serves to highlight the lack of transferability of the results of one system to another and subsequently the general lack of consensus of what constitutes a normal P wave duration.

Most signal averaging algorithms use successive waveforms matched to a template to achieve averaging. It is clear, though, that the P wave morphology changes on a regular basis and these different morphologies exhibit pronounced differences in energy when analysed in the frequency domain[27]. The significance of the number or frequency of change of these different P wave morphologies remains obscure; however the inclusion of these distinct P waves in averaging will lead to significant compromise of the frequency analysis results[28]. The majority of groups use a template matching system adapted from QRS averaging; this does not exclude P waves with an altered morphology, unless this is gross, such as an atrial ectopic beat.

SAPW AND AUTONOMIC VARIABLES

Cheema et al[29] looked at the effect that drug manipulation of the autonomic nervous system would have on the SAPW duration using a conventional template averaging technique. No frequency domain measurements were made. Subjects were administered infusions of epinephrine (50 ng/kg body weight per min) and isoproterenol (50 ng/kg per min) to stimulate the sympathetic nervous system and beta-blocked with propranolol. The following day they were administered atropine (0.04 mg/kg) to effect parasympathetic

blockade. The results revealed a significant shortening of the P wave duration from 141 ± 10 ms to 110 ± 16 ms ($p < 0.001$) with isoproterenol, and epinephrine produced a significant prolongation to 150 ± 10 ms ($p < 0.05$). Beta-adrenergic blockade increased the P wave duration to 153 ± 10 ms ($p < 0.005$), autonomic blockade (propranolol followed by atropine), shortened the P wave duration to 143 ± 16 ms ($p < 0.05$ vs. beta-blockade). Atropine induced parasympathetic blockade effected a shortening of the P wave duration to 136 ±15 ms ($p < 0.1$). The curious disparity between isoproterenol and epinephrine is not fully explained by the authors. Isoproterenol is a pure beta-agonist whereas epinephrine has a more complex action on both alpha and beta receptors perhaps explaining this finding. In addition, isoproterenol resulted in a much faster heart rate than epinephrine (RR interval 489±32 vs. 760±118ms respectively) and this may have affected the accuracy of filtered P wave measurement as the P wave onset may well have been buried within the preceding T wave.

Dilaveris studied the effect of the autonomic nervous system on the different P wave morphologies[30]. Temporal P wave morphology was examined over a 24 hour period and demonstrated a pronounced circadian rhythm. The P wave morphology remained relatively stable from 9 a.m. to 5 p.m. suggesting that this will impact little on high-resolution recordings made within normal working hours.

SAPW AND SINUS NODE DISEASE

Sinus node disease (SND) is associated with atrial fibrillation and presence of fractionated atrial electrograms[19, 20]. Patients with SND are paced using single chamber pacemakers with atrial leads only, unless there is a suspicion of co-existing AV nodal tissue disease when a dual chamber device may be used. To optimise PPM prescription the SAPW was examined in the context of SND, patients with SND alone, combined with PAF and twenty normal controls[31]. The authors looked at the SAPW duration and energy content pre and post pacing. In sinus rhythm, duration and energy were greater in SND-PAF than in SND and normal controls (PWD: 153±4ms; 140±4ms; 134±2ms ($P<0.001$) and P20 76.1±17.6KμV^2.sec; 47.7±6.6KμV^2.sec; 36.3±2.8KμV^2.sec ($P<0.006$)). The P wave in SND-PAF patients was prolonged by 11% on pacing to 170±8ms but the patients with SND alone exhibited a 20% prolongation of P wave duration (to 167±3ms) and a significant increase in P wave energy with atrial pacing. The authors conclude the results indicate an abnormal P wave in sinus rhythm in patients with PAF and SND, changes little on pacing. The patients with SND alone have a relatively normal resting P wave that exhibits marked changes on pacing.

This work is developed further by Gribbin et al study published in abstract form at NASPE in May 2000[32]. This compares SAPW parameters in physiological (AAI, DDD) and non-physiological pacing (VVI/R) in patients with SND. This demonstrated a significant difference in P wave duration and energy in the group paced VVI or VVIR (148±4ms to 157±5ms ($P=0.01$) and 43.6±7.3μV^2.sec to 47.4±6.4μV^2.sec ($P=0.01$)), but no such difference was demonstrated in the atrial paced group during sinus rhythm suggesting the observations from the prior study on P wave parameters did not translate into long term detriment. The authors suggest altered electrophysiological properties are responsible for the SAPW changes seen in the non-physiologic pace group and this in turn is responsible for the greater numbers of individuals who develop AF in the non-physiologically

paced group. Pacing studies suggests that physiological pacing, in particular AAI, may delay the onset of atrial fibrillation in subjects with SND as evidenced by a decrease in frequency of attacks[33].

SAPW IN CORONARY ARTERY DISEASE

Myrianthefs *et al* used a 3–channel Holter system to examine the SAPW in 47 patients during balloon angioplasty of coronary arteries. The SAPW duration appeared to lengthen during acute ischaemia of the left anterior descending artery induced by balloon angioplasty. In the left anterior descending coronary artery group (n = 23), the mean SAPW duration was 122.4±17 ms prolonging to 131.3±16 ms during balloon inflation, ($p<0.005$). Studies of RCA inflation did not produce any significant difference[34].

SAPW IN HEART FAILURE

In a study performed by Faggiano *et al* in 48 patients with congestive cardiac failure and no history of AF, PWD was correlated with measured pulmonary capillary wedge pressure. The investigators found moderate correlation between prolonged PWD and higher wedge pressures which reversed on the administration of sodium nitroprusside[35]. Left atrium diameter also significantly correlated with PWD but not as closely as left atrial pressure ($r = 0.42$, $p=0.005$ and $r =0.62$, $p=0.0001$ respectively).

SAPW FOLLOWING CORONARY BYPASS GRAFTING FOR AF RISK STRATIFICATION

Coronary artery bypass grafting (CABG) is a common procedure for many patients with ischaemic heart disease. The postoperative complication of AF was recognised early, but prediction of the 40%[36] of patients who will develop AF has been elusive. These patients may benefit from pre-operative antiarrhythmic therapy but targeting the population at risk requires a reliable marker of post-operative AF.

Buxton et al published some encouraging early work on the standard surface P wave concluding that P wave duration on three standard leads is a sensitive but not specific marker for AF[7]. The signal averaged P wave was examined for prediction of postoperative risk and many groups studied these patients with varied sometimes conflicting results[16, 36-42] (see table 1).

The studies with the exception of Frost et al demonstrate a significantly longer pre-operative P wave in patients who develop AF. Patients with a normal SAPW were unlikely to develop AF post bypass surgery, but a prolonged P wave duration did not reliably predict post–op AF. The difference in results probably stems from the various ways of analysing the SAPW duration. Frost found that P wave duration in the standard ECG recorded at $50mm.s^{-1}$ was associated with the onset of post-op AF; surprisingly this was not the case with the

filtered P wave duration[16]. None of the results were significant when the age and weight of the patient were accounted for.

Stafford examined standard P wave parameters, echocardiogram and SAPW values within 24hours of coronary artery bypass grafting[40]. SAPW duration proved significantly different in the group developing AF and was better than standard ECG assessment or echocardiographic variables with positive predictive and negative predictive accuracies of 34% and 83% respectively for P wave duration of ≥141ms.

Zaman looked at SAPW duration of >155ms combined with serum magnesium on the first post operative day of <0.7mmol/l as a predictor of post operative AF[43]. The group enrolled 102 patients of which 26% developed AF. The sensitivity was 75% and specificity was 80% when combined with Magnesium.

Most recently, Hayashida et al examined the pre-operative SAPW duration as a marker of risk[44]. The group improved the positive and negative predictive accuracy of duration if combined with age and/or left atrial dimensions to 57% and 88% respectively.

SUMMARY OF TRAILS OF THE PRE-OPERATIVE SAPW AS A PREDICTOR OF POST-OPERATIVE AF

Reference	No.	Duration	Sens%	Spec%	PPA%	NPA%
Steinberg'93	130	>140ms	77	55	37	87
Chelucci'95		>110ms	83	76	86	71
Klein'95	45	>155ms	69	79	65	82
Frost'96	189	-	ns	ns	ns	ns
Dimmer'97	91	>134ms	75	57	28	91
Stafford'97	189	>141ms	73	48	34	83
Hayashida '05	95	>135ms	50	81	52	79
Aytemir'99	53	>122.3ms	68	88	76	83

Table 1: Summary of studies to date examining the predictive accuracy of the SAPW duration for post-operative atrial fibrillation. (No. = total number of patients included in analysis; Sens = sensitivity; Spec = specificity; PPA= positive predictive accuracy; NPA= negative predictive accuracy)

SAPW AND PAROXYSMAL ATRIAL FIBRILLATION

Paroxysmal atrial fibrillation is associated with surface P wave abnormalities visible on the standard 12 lead ECG. By definition, PAF patients enjoy periods of sinus rhythm between episodes, however the risk of embolic stroke remains. Furthermore, diagnosis can be limited by lack of recorded arrhythmia. It is thus an area where detailed examination of the P wave might allow greater prediction of susceptible individuals.

Marconi et al compared 22 patients with documented PAF and 24 controls. The group analysed 300 beats and demonstrated a significantly ($p<0.001$) prolonged P wave duration in the patients with PAF[45]. In the same year Stafford et al also demonstrated a significantly prolonged P wave duration in 9 patients with PAF compared with 15 controls[46]. The group also studied the terminal P wave RMS voltage and spatial velocity. These parameters reflected a significant difference with RMS35 and peak spatial velocity being greater in subjects with PAF ($P<0.05$). The authors suggest the results support fragmentation of atrial conduction rather than atrial late potentials as the pathogenesis of PAF.

Guidera et al looked at 15 patients with AF and 15 disease matched controls without a history of AF[47]. The standard lead P wave duration was not significantly different between the two patient groups; however the filtered P wave duration was significantly longer in patients with a history of AF ($P<0.01$). If a cut off P wave duration of 155ms was used the sensitivity, specificity and positive predictive accuracy were 80%, 93% and 92% respectively.

Stafford looked at 24 patients with documented idiopathic PAF and compared them with 34 control subject recruited from a gastroenterology clinic. The control group had cardiac echocardiography, ECG and history and examination. Each patient had a high resolution P wave recording with the P wave providing a template for averaging using a modulus difference algorithm[25]. Increases in absolute energy were seen to be statistically significant for energy contained within frequency bands 30-150Hz (P30), 60-150Hz (P60) and 80-150Hz (P80). Using a cut off energy of $1.4K\mu V^2.s$ typical sensitivity and specificity values were 70% for P80. Combination analysis with P wave duration using logistic regression analysis calculated a sensitivity of 81% and a specificity of 73%[24]. The authors as with their previous study[46] speculate that the increased total P wave energy reflects slowed or fractionated intra-atrial conduction.

Frequency domain analysis was used to differentiate between high frequency attacks of PAF (>2 attacks per month) or low frequency (2 or less per year) by Mechelucci[48]. The group also demonstrated significant differences in P wave duration and frequency domain parameters between PAF and normal controls.

The normal three bipolar lead positioning has been challenged with 32 unipolar electrodes in a study by Hiraki et al comparing 23 patients with PAF and 19 controls[49]. Frequency analysis was of the whole P wave after FFT was performed using a Blackmann-Harris window. Time domain analysis was performed using a conventional three lead orthogonal configuration (lead I = X, aVF = Y, V1 = Z). The P wave duration was significantly longer in the PAF group as compared with controls ($P<0.01$). The group examined the power spectrum in all 32 unipolar leads and found a wide distribution of values and significance. The area ratio of power spectrum area was significantly higher ($P<0.05$) in leads V12, V13, and V14 as compared with controls. The authors comment the difference was seen because of a decrease in power of high frequency signals. This is contrary to both the work of Yamada[22] and Stafford[25]. However the work done by Stafford confirms increased low and high frequency power thus the power ratios remained unchanged. Both Stafford and Hiraki criticised Yamada's analysis of the terminal portion of the P wave, a less robust technique, as compared with the analysis if the P wave as a whole. It is not clear why Hiraki failed to find an increase in high frequency energies as well as low frequency energies, but the methodology and analysis were very different in the two studies.

Recently Yamada examined the spatial dispersion for the signal averaged P wave duration[50]. In this study 16 unipolar precordial leads were used to measure dispersion and this was compared with a conventional orthogonal method. The maximum and minimum duration was greater in PAF patients than controls. Dispersion in the precordial mapping leads was significantly greater than in the conventional X,Y,Z leads ($P<0.0001$). There was no significant difference in dispersion in the control patients. Sensitivity was greater for the precordial method (93%) as compared with the conventional method (75%), whilst the specificity was comparable (74% vs. 72%). Moreover, when the PAF patients were treated with pilsicainide, a new class 1c drug, freedom of attacks was significantly associated with a decrease in dispersion measured after one oral dose of pilsicainide ($P<0.0001$). Thus a decrease in P wave dispersion might reflect atrial electrophysiologic substrate that might in turn predict drug efficacy.

The only prospective study to assess the SAPW as a predictor of PAF/AF in non-surgical patients was in the study of patients with hypertrophic cardiomyopathy[51]. One hundred and ten subjects with HOCM were recruited and underwent a SAPW recording of approximately 300 beats. The filtered P wave duration was measured and the group followed prospectively. Eighteen patients (16%) developed AF. The P wave duration was significantly greater in these patients compared to the group remaining in sinus rhythm ($P<0.001$). A P wave duration cut off of 140ms generated a sensitivity, specificity and positive predictive accuracy of 56%, 83% and 66% respectively.

Gencel et al investigated twenty patients with cryptogenic embolic stroke without prior evidence of atrial fibrillation with electrophysiological studies (EPS)[52]. The results were correlated with SAPW recordings. The recordings correlated well with atrial vulnerability; a filtered P wave duration of > 125ms combined with a RMS 30 < 3μV had a PPV of 78% a NPV of 88% for the detection of atrial vulnerability at EPS.

SAPW POST CARDIOVERSION

Opolski et al examined 35 patients who had a successful DC cardioversion for atrial fibrillation[53]. The recording was taken soon after cardioversion - the duration and RMS20 were calculated. Eleven patients developed AF during a six-month follow-up period. The filtered P wave duration was significantly longer in the group developing AF (P<0.001); RMS20 was significantly lower in the AF group (P<0.02). A filtered P wave of >137ms combined with RMS20 of <1.9μV had a sensitivity of 73% and a specificity of 71%.

Similar results were obtained recently on a total of 73 patients who were also followed for 6 month with 31 patients reverting to AF. The filtered P wave duration was longer and the root mean square voltages for the last 20 ms of the P wave were lower in patients with recurrence of atrial fibrillation (P = 0.001). A filtered P wave duration of 128 ms or more, associated with a root mean square voltage for the last 20 ms of the P wave of 2.1 μV or less, had a sensitivity of 70% and specificity of 76% for the detection of patients with recurrence of atrial fibrillation. The use of these parameters provided a 4.31 fold increase in likelihood of AF recurring[54].

P wave energy was studied by Stafford et al following cardioversion. SAPW recordings were taken at 3 hrs and 24 hrs following successful cardioversion in 31 patients[55]. There were 75 cardioversions in total and 59 of these were low energy internal cardioversions. Filtered P wave duration and P wave energy from 20, 40 and 60 to 150Hz was examined. Thirty patients returned to AF at one week. No P wave parameter differed significantly at the 3hr recording. Paired 3hr and 24hr data were present in 47 patients. The group remaining in sinus rhythm at one week demonstrated significant reductions in P wave energy (P40 P<0.001) that was not reflected in the group returning to AF. A significant drop in P wave energy only appeared to predict short term SR at 1 week but not at 4 weeks. In addition a lack of fall in energies failed to predict recurrence of AF.

Spurrell et al explored this further in a study of 81 patients requiring cardioversion for persistent AF[56]. All cardioactive drugs were suspended at least five half-lives prior to cardioversion. External cardioversion was performed at electrophysiological study and on attainment of sinus rhythm the atrial effective refractory period (ERP) was assessed at two sites; this was repeated again at 24hrs and 2 weeks. SAPW recordings were taken immediately following completion of the EP study, at 3, 6, 20 and 24 hrs and again at two weeks. Twenty eight of 78 patients remained in sinus rhythm at two weeks. P wave energies fell significantly over 24hrs (p<0.0001). There was no change in P wave duration. In the same time interval a significant (P<0.0001) prolongation of atrial ERP was noted. There was a significant negative correlation between P wave energies and ERP most marked at the mid lateral right atrium. This method did not predict sinus rhythm at two weeks and the continued increase of the atrial ERP at two weeks was not mirrored by changes in P wave energies, which remained similar to the 24hr measurement. P wave duration did show a modest but significant shortening at 2 weeks (157 ± 11 to 153 ± 13ms (p<0.03)).

In another study, Healey and colleagues followed 76 patients after cardioversion from persistent atrial fibrillation and made serial assessment of the SAPW immediately post cardioversion and at 3 days[57]. Thirty six patients had a recurrence of AF at 90 days. Filtered P wave duration did not predict recurrence despite longer P wave duration in patients returning to AF. The authors did note a significant decrease in P wave duration at 3 days in the patients remaining in SR and concluded this was a manifestation of reverse atrial remodelling.

SAPW AND DRUGS

Signal averaged recordings were taken during a double blind crossover trial performed on subjects given caffeine or placebo[58]. No change in heart rate or filtered P wave duration was demonstrated; however the group did show a significant ($p<0.01$) prolongation of filtered QRS complexes.

Early work linked a prolonged filtered P wave with efficacy of propafenone and flecainide in PAF[59], this may appear paradoxical but probably reflected the action of these drugs in prolonging atrial conduction time (see chapter 4). Sotalol has been examined in a longitudinal, within patient, crossover trial involving sixteen patients. SAPW recordings were taken off medication and on sotalol; duration and P wave energies were examined. Significant decreases in high frequency P wave energy (e.g. P60: 4.3 (0.4) v 3.3 (0.3) $\mu V^2.s$, $P = 0.003$) and energy ratio (PR60: 5.6 (0.5) v 4.7 (0.6), $P = 0.03$) were observed during sotalol treatment; these changes were independent of heart rate. There was no difference in P wave duration between the treatment groups[60].

Amiodarone, a potent class III antiarrhythmic agent, has also been examined in the context of P wave signal averaging[61]. Thirty patients with documented coronary heart disease and PAF were enrolled. SAPW recordings were taken prior to and following loading with amiodarone (8 weeks). The patients underwent a 24hr Holter recording to ascertain the efficacy; AF on the tape indicated drug failure, as did presentation with an episode of PAF. In the group with 'effective' therapy the SAPW duration was less and the RMS10 and RMS20 had increased ($P<0.05$). In the group presenting with AF recurrence the P wave parameters were not significantly changed from baseline.

The response of the surface P wave to changes in atrial pathology or electrophysiology are summarised over overleaf.

Parameter	PWD	Frequency	RMS
AF	↑	↑	↓
Isoproterenol	↓		
B-blockers	↑		
Atropine	↓		
Ischaemia	↑		
LA diameter	↑		
LA pressure	↑		
Class 1C	↑		
Sotalol	+/-	↓	
Amiodarone	↓		↑

Table 1. Summary of known effects of various parameters on signal averaged P wave parameters. Frequency refers to parameters derived from frequency domain analysis such as energy and power. Class 1C drugs are sodium channel blockers and evidence exist for effects with flecainide, propafenone and pilsicainide. +/- indicates where the evidence is contradictory and thus unreliable.

ATRIAL FIBRILLATION

The most common atrial arrhythmia requiring investigation is atrial fibrillation (AF) characterised by an irregular ventricular response to an apparently chaotic atrial dysrhythmia. The literature concerning pathogenesis and epidemiology of atrial fibrillation is reviewed in the remainder of this chapter.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice[62]. Recent advances in understanding of the pathophysiology of AF[18] have resulted in a number of therapeutic options including drug therapy and catheter ablation. Clinical management remains controversial and judging which therapy for which patient can be challenging to the clinician.

The existence of AF was discovered in 1874 following experiments with electricity on animal hearts[63]. This was not associated with its clinical counterpart, *arrhythmia perpetua*, until 1909 when the recording of electrocardiographic activity demonstrated the common origin. Intensive investigation into the mechanism of this arrhythmia has continued until the present day. Mechanisms of AF are covered in detail beginning page 32. Original experiments in jellyfish ventricles demonstrated circus movement and this was the dominant theory of AF perpetuation until electrophysiological experiments done between 1948 and 1950 advanced the concept of focal discharge as a mechanism; thus the notion of circus movement lost favour. Subsequent work developed the idea of wavefronts that re-entered a common path, reviving the theory albeit in a more complex form. In 1964 Gordon Moe [64] published a computer model of multiple reentrant wavelets as a probable mechanism, this model relied upon a critical number of wavelets present to sustain AF (23 to 40). In 1968 Moe published a conceptual model of AF discrediting the focal and circus theories in favour of a multiple wavelet hypothesis. Later research supported this by invasive electrophysiological measurements of the atria during induced AF in the dog and human atria[65,66]. Much of this work was performed in the right atrium and only recently has the importance of the left atrium and focal repetitive discharges in the pulmonary veins been demonstrated[67].

EPIDEMIOLOGY OF ATRIAL FIBRILLATION

The classification of AF varies dependant on author but the generally excepted classification is temporal and based upon the time spent in arrhythmia. Paroxysmal AF may be defined as attacks of arrhythmia lasting for <7 days separated by prolonged episodes of sinus rhythm, whereas chronic AF is AF established for >7 days and can be further sub-divided into persistent and permanent. Persistent AF represents a more therapeutic approach to classification identifying individuals who would benefit from attempts at chemical or electrical cardioversion or catheter ablation. In patients classified as permanent AF, attempts at cardioversion would be, or have been futile thus therapeutic options have been limited to anticoagulation and rate control. However catheter ablation of the left atrium is challenging this concept with emerging evidence for maintenance of SR

and objective improvement in quality of life scores and echocardiographic measures[68]. In some cases there is a spectrum of progression from PAF to permanent AF; Levy estimated 30% of PAF patients will develop chronic permanent AF[69], however this figure might be an underestimate. A more recent study from Japan followed a cohort over a mean of 14 years and found 77.2% transition from paroxysmal to permanent[70]. This is higher than previously thought but the fact that 20% of individuals remained paroxysmal might represent a different pathological process, possibly with a genetic basis, protecting against progression to persistent/chronic AF.

The incidence of AF doubles with each successive decade after the age of 50 to approximately 10% of octogenarians[71]. In 1995 Feinberg et al published figures suggesting that since 1968 the prevalence of AF in men aged between 65 and 84 has risen from 3.2% to 9.1%[72]. They also found that significant differences persisted when figures were adjusted for age, valvular disease and prior MI. There was no significant increase in the prevalence of AF in women during the same time period[62].

Persons developing AF were more likely to have diabetes, left ventricular hypertrophy, echocardiograph abnormalities, coronary heart disease, valvular heart disease, left ventricular failure and already have suffered a stroke. There was a significant difference in distribution of these factors according to gender; 33% of women and 20% of men had valvular heart disease, whereas 28% of men had an MI as compared with 14% of women[72].

The more recent ALFA study[73] recorded similar sex differences. The percentage breakdown of all patients revealed hypertension to be the most common condition associated with AF at diagnosis (39.4%). The percentage with valvular heart disease was much lower than one might expect (15.2%) indicating the changing demographic profile in France due to reduction in incidence of Rheumatic fever.

In the Framingham study, smokers were 40% more likely to develop AF; hypertension alone increased risk by 70%, and diabetes resulted in a 2-fold increased risk. ECG evidence of LVH indicated a four-fold increased risk of AF. Alcohol intake did not appear to be a significant independent risk factor[62]. Echocardiographic determinants that proved strong independent risk factors for AF were: left atrial size, a reduction in left ventricular fractional shortening and left ventricular wall thickness[74].

MORTALITY FROM ATRIAL FIBRILLATION

Debate exists as to whether the excess mortality associated with AF (approx. 40%) is directly attributable to the condition or merely increased the risk of coexistent cardiovascular disease. In the Framingham study 23.5% of strokes were attributed to AF; Wolf et al found a fivefold increased risk of stroke in patients with AF and cardiovascular disease compared with healthy controls[75]. A number of studies found no benefit from maintenance of sinus rhythm as oppose to rate control suggesting 'well managed' AF might not be associated

with excess mortality[76]. Many studies have concluded that prevention and treatment of AF will yield benefits in reduction of mortality, stroke, and health care costs[77, 78]. In a non-randomised study of 1171 patients, catheter ablation of AF was associated with a reduction in mortality and morbidity compared with a control group managed with antiarrhythmic medication to maintain SR[79]. However it might be that antiarrhythmic medication resulted in excess morbidity and mortality as there was no rate control comparison group, as suggested in the AFFIRM study of rate vs. rhythm control[80]. Most recently ablation for chronic AF (mean 5.5 years) was associated with favourable outcome compared with a strategy of short term amiodarone and cardioversion. Left ventricular ejection fraction improved and left atrial diameter fell over the year follow-up[68].

GENETICS OF ATRIAL FIBRILLATION

The Framingham study suggested an increased risk of AF developing in the offspring of parents with AF (RR 1.85)[81]. There is evidence to suggest that in some families susceptibility to AF is inherited in a Mendelian fashion; Brugada et al have identified over 100 families with a familial form of AF[82]. Although uncommon there has been some success in mapping an area on chromosome 10q 22-24[83, 84]. Further work has suggested an autosomal dominant inheritance pattern in the same region. In addition, a novel locus has been mapped to chromosome 6q 14-16 and investigation is underway to identify the causative gene[85]. Likely candidates are genes encoding the I(Ks) potassium channel[86]. Of interest the genetic locus of familial dilated cardiomyopathy is within the same region (10q 21-24) as familial AF and may represent a common aetiological genetic mutation[87]. The identification of a new channel disorder or novel cardiac abnormality by examination of the causative genes might provide better models of AF for more focused research.

ION CHANNELS OF THE ATRIAL MYOCYTE

Ion channels are pore forming membrane proteins with a vast diversity in structure and function. The channels are not static, fixed structures as often illustrated in textbooks; they are fluid, changing in number and function in response to changes in local environment and distant signals. They are influenced by altered transcription rates, altered rates of protein translation and post-translational modifications, changes in membrane trafficking and insertion and final phosphorylation of the channel protein. Cardiac rate and rhythm changes as well as cardiac disease can all influence the properties and density of the ion channels by acting at any number of these levels[88].

The normal atrial cell in diastole has a resting negative charge across the cellular membrane (V_r). This resting negative potential is largely due to the predominance of intracellular anions which are non-diffusible proteins and an efflux of positive charge made up of potassium (K^+). The sodium/potassium (Na^+/K^+) pump is responsible for maintaining the negative resting potential by the exchange of two extracellular K^+ for three intracellular Na^+; due to selective permeability, the K^+ ions slowly diffuse out of the cell via inwardly rectifying K^+ channels. The resting negative charge, V_r, is therefore largely determined by the ratio of intracellular to

extracellular K^+ concentrations. There is a small leak of Na^+ from the sodium/calcium (Na^+/Ca^{2+}) exchanger and via other channels and thus the resting potential is slightly more positive than predicted by the Nernst equation[89]. Rises in extracellular K^+ (e.g. secondary to ischaemia) will result in membrane depolarisation.

The terminology associated with ion channels is dictated by convention. Inward currents are the movement of positive charge into the myocyte and are thus depolarising currents. Outward currents are the movement of positive charge out of the cell; this results in repolarisation of the cell and occasionally hyperpolarisation of V_r. Rectification describes the resistance to ion flow in relation to the membrane voltage i.e. currents exhibiting outward rectification increase with progressive membrane depolarisation whereas the conductance of inwardly rectifying currents decreases with progressive depolarisation.

THE CARDIAC ACTION POTENTIAL

The cardiac action potential (figure 5, page 30) is a wave of depolarisation that propagates from cell to cell via connexins and is initiated when an excitatory stimulus depolarises the membrane beyond threshold potential. The action potential upstroke is generated by a large, brief increase in membrane conductance via I_{Na}, the maximum rise of upstroke (V_{max}) reflects the magnitude of I_{Na}. Rapid repolarisation is the result of voltage dependant inactivation of the I_{Na} channels and the activation of the transient outward current channels (I_{to}). These channels are divided into two separate and distinct components. I_{to1} is a voltage dependant rapidly activating K^+ current, displaying outward rectification. This channel is slow to recover and its importance may diminish as heart rate increases and diastolic recovery period shortens. This shortening can be appreciated in figure 5 during atrial flutter when APD shortens.

Influx of Ca^{2+} through L-type calcium channels ($I_{Ca,L}$) triggers calcium release from the sarcoplasmic reticulum via ryanodine; this correlates with activation of I_{to2} and inward flow of chloride ions(Cl^-). $I_{Ca,L}$ is activated at membrane potentials above –40mV, the release of Ca^{2+} from the sarcoplasmic reticulum activates the contractile myofilaments.

The plateau phase (phase 2) is brief and ill defined in the atrial cell reflecting a large I_{to} compared with a relatively small I_{Ca}. The delayed outward rectifier K^+ current, I_k, mediates the slow terminal phase of repolarisation with another potassium channel $I_{k,Ach}$. Activation of this channel by vagal stimulation shortens the atrial action potential duration and refractory period.

The summation of all the individual cell action potential waveforms is manifest as the surface P wave.

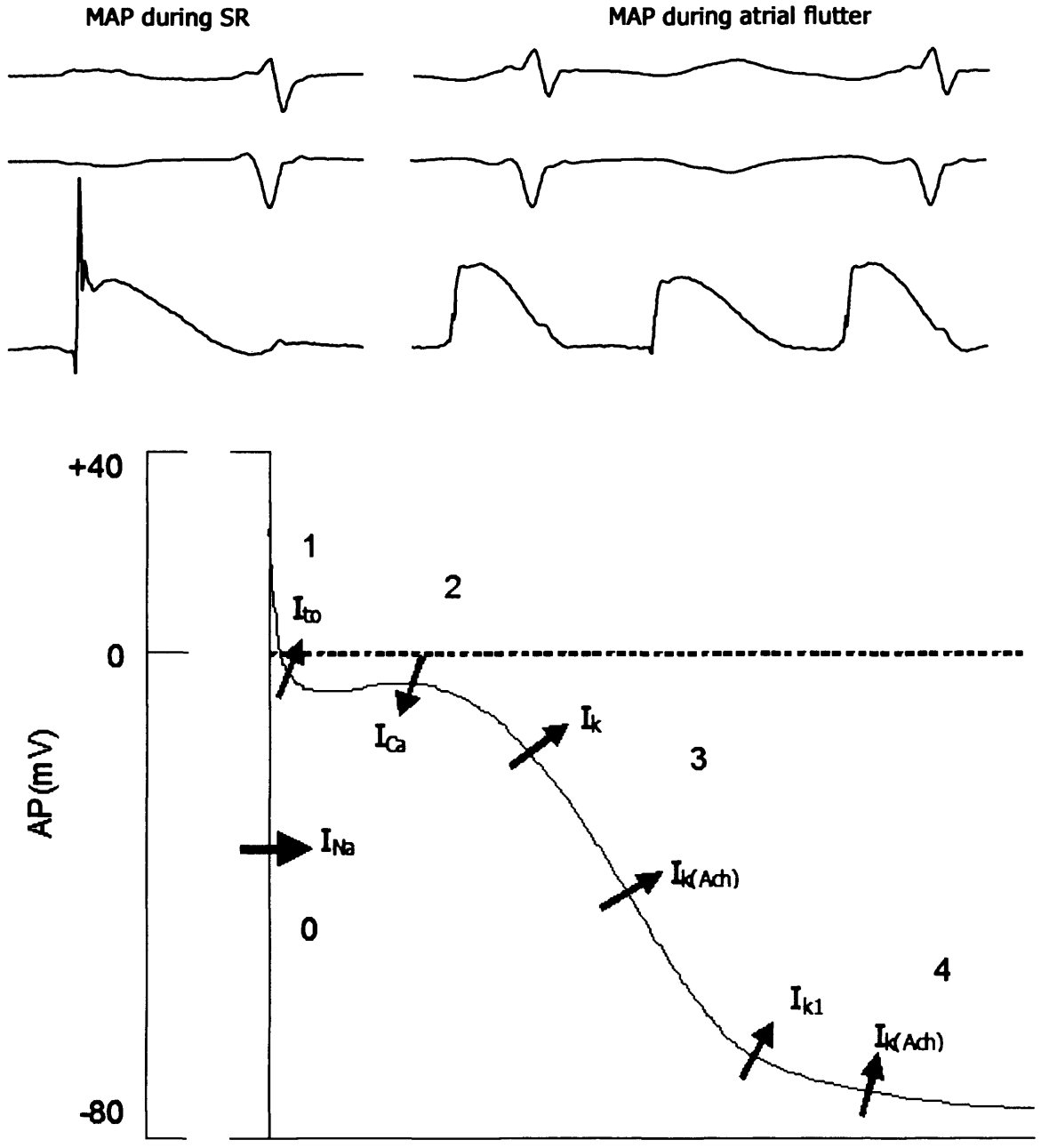


Figure 5. Above: Monophasic action potential (MAP) recording is shown during SR and atrial flutter (note MAP alternans). Below: illustration of atrial cardiac action potential waveform. Phases of activation are represented 0=depolarization; 1=initial repolarisation; 2= plateau phase; 3= late repolarisation; 3= resting (diastolic) phase. I_{Na} =Na^+ current; I_{to} =transient outward current; I_{Ca}= Ca^{2+} current; I_k= delayed outwardly rectifying K^+ current; I_{k1}= inwardly rectifying K^+ current; $I_{k(Ach)}$= acetylcholine activated K^+ current. See text for explanation.

RATE CHANGE

The pacemaker current I_f (also known as the 'funny' current) is a hyper-repolarisation activated current carried by K^+ and Na^+ ions and is activated at about –45mV with a reversal potential of –20mV. It is a slow inward current present in the normal sinus node pacemaker cells.

In order for the heart rate to speed or slow there has to be interaction between the ionic channels and the autonomic nervous system. Vagal stimulation results in a bradycardia via the action of acetylcholine (Ach) on muscarinic 2 receptors. Activation of the inwardly rectifying K+ current, $I_{K(Ach)}$, reduction of I_{Ca} and reduction of I_f, results in hyper-polarisation of the membrane potential and abbreviation of the action potential duration, slowing the rate of diastolic depolarisation. Catecholamines accelerate the sinus rate via alteration of the activation potential of I_f to a more positive potential and increasing I_{Ca} and I_K thus increasing the slope of the pacemaker potential[90].

SIGNAL PROPAGATION

The signal propagation from cell to cell is, in part, via gap junctions between each atrial myocyte. The proteins responsible for the gap junctions are termed connexins (Cx); the phosphoprotein Cx43 is the most abundant cardiac connexin, forming junctions with a mean conductance of 45pS. In the ventricle Cx43 is more abundant in the intercalated disk than in the lateral borders of the cells, partially explaining anisotropic impulse conduction, whereas its distribution in the atrial myocyte is fairly even. Anisotropy is the principle of heterogeneous conduction velocity through tissue dependent upon the direction of impulse propagation. Cx 40 is a phosphoprotein with a mean conductance of 160pS and is co-localised with Cx43 in the atrium contributing equally to impulse conduction. Another connexin, Cx45, has been discovered at protein level but its role in impulse conduction is yet to be established.

Although, as will be examined later, heterogeneity of cardiac electrophysiology is increasingly recognised in cardiac arrhythmia, there is considerable variation in expression and functional repertoire of ion channels under normal physiological conditions. This highlights the responsive nature of ion channels to local environment and can make it difficult to determine if the response is pathological or physiological [91].

THE IONIC BASIS FOR ATRIAL FIBRILLATION

Macroscopic discontinuities in cardiac structure are known to affect membrane channel function. In any situation where the propagating wavefront encounters anatomically discontinuous tissue, the wave becomes curved. The curvature of this wavefront, convex or concave, will alter the ionic current activation accordingly. The difference between excitatory local current upstream and electrical load of non-excited cells downstream,

results in local conduction delay, and localised increase in the amount of depolarising inward current if the wavefront is convex. At a concave wavefront the conduction velocity is increased and inward current reduced. Sodium blocking agents are therefore effective at convex wavefronts, binding the open sodium channels[92]. If there is marked curvature large local conduction delays will result; the Ca^{2+} inward current then becomes essential for propagation and the Ca^{2+} blockers will produce localised conduction block[93].

The expression of connexins is decreased in heart failure and the junctions partially close in response to cardiac ischaemia/ hypoxia. The closure of these junctions results in a decrease in conduction velocity that is much more marked than that produced by inhibition of ion channels. This is associated with disruption of cell-to-cell coupling, which is normally a smooth continuous propagation of the action potential. In advanced uncoupling the membrane sites in single cells are activated almost simultaneously and a long conduction delay exists between cells; thus $I_{Ca(L)}$ is necessary to support propagation. The inward Na^+ current will be inactivated before the downstream cell reaches threshold therefore flow of inward Ca^{2+} current later during the action potential is necessary to assure propagation. The conduction process changes from being solely Na^+ dependant to Na^+ and Ca^{2+} inward current dependant. Uncoupled tissue allows reentrant arrhythmias to occur more readily due to the very small dimensions allowed in the reentrant circuit because of conduction delay.

The expression of various ion channels has been extensively studied in AF and animal models. The expression of I_f has been shown to be increased in clinical AF and also with increased left atrial filling pressure[94]. However the expected changes in K^+ flow were not seen, instead there were significant reductions in the I_{to} and I_K outward K^+ current densities in atrial myocytes[95, 96]. The down regulation of the $I_{Ca(L)}$ and sarcoplasmic reticular Ca^{2+}-ATPase gene has been demonstrated in AF[97] together with direct evidence of sarcoplasmic reticulum Ca^{2+} regulatory protein abnormalities[98]. These changes in gene expression and consequent ion channel function are currently implicated in the development of atrial remodelling. Nattel's laboratory in Montreal examined this in detail by the rapid (400bpm) atrial pacing of dogs for 7 and 42 days[99]. They examined the mRNA encoding I_{to}, $I_{Ca2+(L)}$, and I_{Na}. For 7 and 42 days the mRNA encoding for I_{to} (Kv4.3) was reduced by 60% and 74% respectively ($P<0.01$ & P0.001); for $I_{Ca2+(L)}$, 57% and 72% ($P<0.01$) and for I_{Na} , 18% and 42% (p=NS & $P<0.01$). The changes in ion channel current density paralleled the mRNA levels. The delayed inward rectifier K^+ current and the Na^+/Ca^{2+} exchanger ion current densities and mRNA levels were unchanged by tachycardia. Thus fast atrial rates result in changes in ion current densities via altered mRNA transcription. These changes may be related to the self-perpetuating nature of AF.

MECHANISM OF ATRIAL FIBRILLATION

Recently the importance of the posterior left atrium, in particular the pulmonary veins has been recognised in AF leading to catheter ablation procedures targeting this region[79, 100, 101]. However the suggestion that a small number of periodic repetitive reentrant sites is required to maintain chronic AF[102] has led many to revisit the circus movement concept first postulated by Sir Thomas Lewis in 1925[103].

WAVELETS

The phenomenon of wavelet formation is analogous to the formation of eddies when a wave meets an obstacle in water. The obstacle may be structural such as scar or fibrous tissue, or functional e.g. longer refractory period relative to surrounding tissue. As the wavefront passes the obstacle it is split, the free ends begin to curl and spiral into two counter rotating waves; these in turn meet obstacles and repeat the sequence. In Moe's hypothesis a single early premature response in irregularly excitable tissue may produce fractionation of the premature wavefront as it encounters areas of non-excitable (refractory) tissue within the atria. As the wavefront divides around the refractory tissue each 'daughter' wavelet may be considered an independent wavefront capable of accelerating, decelerating, combining with or producing further wavelets. Thus in mature AF many wavelets spawn discrete areas of refractory tissue and therefore induce more wavelets in an entirely random fashion. Moe suggested that given certain criteria this mechanism could be self-sustaining and demonstrated this with a simple computer model[64].

Support for this hypothesis was provided by high density mapping of the atria of both animals and humans[65, 66, 104]. Additional support was found in the work of Wang et al that demonstrated a reduction in number of wavelets in response to sodium channel blocking drugs and termination of AF[105, 106]. The creation of multiple surgical lines within both atria (MAZE procedure) was associated with a reduction in AF recurrence by reducing available tissue to spawn wavelets with multiple surgical lesions placed in the atria[107].

This idea neatly explained the self sustaining nature of AF and provided an explanation for the observation that the arrhythmia can persist for many years. This was the main reason that Moe and co-workers discredited the notion of ectopic focus or circus movement re-entry. Yet this theory alone did not answer some fundamental questions about the origin of the activity required to give rise to these wavelets. In addition the work of Allesie et al found fewer wavelets than predicted by Moe's theory in the fibrillating dog atria[65].

MOTHER ROTORS

The difference between a local cycle length and the refractory period is the excitable gap; the time when the tissue is once again excitable and may be depolarised by an advancing wavefront or pacing stimulus. Thomas Lewis postulated the circus movement in fibrillation was short and the irregularity of AF was based on a shorter excitable gap, the re-entrant wavefront was interdigitated with its wake leading to heterogeneous propagation and wavefront fractionation (Figure 6). If the mechanism of AF were purely random re-entry there would be no excitable gap. Work in animals and later in humans confirmed the presence of an excitable gap during atrial fibrillation suggesting that there may be a driving 'mother' rotor continuously producing 'daughter' wavelets[108]. Capucci demonstrated local capture in the right atrium at pacing cycle lengths of 129.2±9.2ms with transient acceleration of AF at shorter cycle lengths.

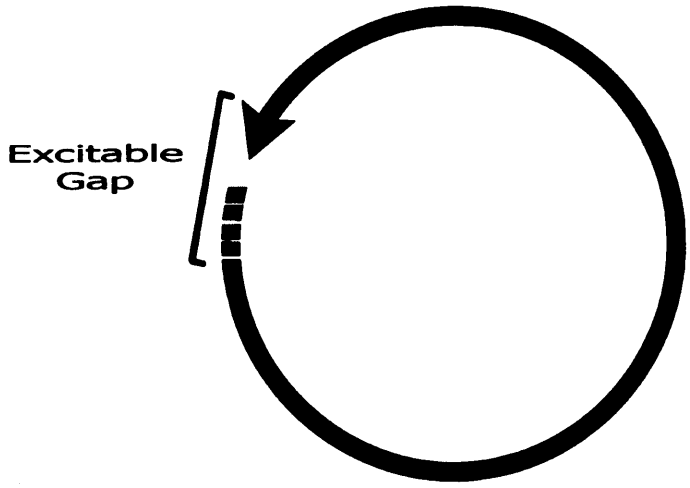


Figure 6. Graphic representation of a reentrant rotor. The cycle length is the time taken to for the circuit to come full circle; the solid line represents the time when tissue is refractory (non-excitable). The excitable gap is the space at the tail of the circuit when the tissue becomes excitable and may be captured with pacing. Thomas Lewis postulated the tail of the circuit was interdigitated with the leading wavefront, i.e. the arrow was beyond the dashed line. This would divide the wavefront as it encountered refractory tissue and lead to fractionation and random reentry.

The work of Schuessler et al indicated that stable reentrant circuits could be identified with production of 'daughter' wavelets[109]. In 1998 Jalife et al proposed the following mechanism: "Sustained AF depends on the uninterrupted periodic activity of discrete reentrant sites. The shorter reentrant circuits act as dominant frequency sources that maintain the overall activity. The rapidly succeeding wavefronts emanating from these sources propagate through both atria and interact with anatomical and/or functional obstacles leading to fragmentation and wavelet formation"[102].

Good evidence for anatomic obstacles is presented for structures such as the branch sites of pectinate musculature and the crista terminalis in the right atrium. Pacing Bachmann's bundle at a frequency higher than 6.5Hz results in fragmentation and fibrillation[110]. This is reminiscent of the theory of Thomas Lewis who postulated a single reentrant source driving the chaotic activity within the atria. The activation of the right atrium in atrial fibrillation may be seen to be slower than the left[111] and this has led to the idea that the right atrium is 'enslaved' to the left[102] and that the 'driving' source is anchored in the left atrium .

Mandapati et al published an optical mapping experiment in the Langendorff perfused sheep heart[112]. The investigators used bipolar electrodes at specific sites to map the atria. Power spectral analysis was employed to determine the dominant frequency. Activity recorded at bi-atrial sites and right atrial areas were irregular, with multiple peaks on spectral analysis. However at sites closer to the pulmonary veins the electrograms appeared more organised with more rapid activity and higher dominant frequency. The electrogram recorded from the

bottom of the left atrial appendage was rapid and regular with a frequency higher than that recorded elsewhere. Isochrone optical mapping of the atria confirmed the mechanism of this episode of AF. A vortex rotating with a frequency identical to the electrogram recording was observed to emanate from the left atrial appendage providing evidence that this high frequency rotor was responsible for maintenance of the AF. Other studies have identified certain specific triggers such as the stable anatomical circuit that underlies atrial flutter or ectopic foci of rapidly discharging pacemaker cells in the pulmonary veins[95, 113, 114].

These studies have taken elements from Moe and Lewis and constructed an evidence base for a theory of AF driven by a high frequency source either ectopic or rotor, that propagates with increased heterogeneity throughout the atria masking the organised driving mechanism.

Addressing this driving mechanism can potentially improve paroxysmal AF and thus attention has focused on whether a driving mechanism in chronic AF can be interrupted providing a substrate for curative ablation[115]. Attempts at pulmonary vein isolation in persistent or chronic AF have not been encouraging[101]. Compartmentalisation of the pulmonary vein ostia incorporating most posterior left atrial tissue has perhaps yielded better results in AF associated with structural heart disease and persistent AF and this may be because of reduction of left atrial tissue available to participate in propagation of arrhythmia[68, 79]. Such substrate modification over and above the electrical isolation of pulmonary veins (PVI) might be more effective for a number of reasons. First, the area of tissue involved is simply larger than PVI and reduces the amount of tissue required for perpetuation according to Moe's theory and there is some experimental evidence to support this[116]. Second the area around the venous ostia is considered a likely point of rotor formation and encompassing this area disrupts rotor formation. Third, and possibly in combination, is vagal denervation by ablation of vagal afferents situated around the pulmonary veins[117]. Patients with a wide area ablation for atrial fibrillation demonstrating attenuation of heart rate variability have been observed to be at reduced risk of recurrence[118].

The areas targeted for catheter ablation in AF share common anatomical landmarks to postganglionic vagal innervation. Vagal stimulation shortens action potential duration and increases vulnerability to AF, although the exact mechanism remains to be elucidated. It is postulated that the areas outside pulmonary veins, rich in vagal innervation, act as anchors for rotors and encouraging repetitive depolarisations[119]. Targeting these sites specifically improves the success of AF ablation in some laboratories[117, 118]. This dysautonomia probably relates to the concept of atrial remodelling when the electrophysiological properties of the atrial substrate change with sustained AF and the importance of the driving engine in the maintenance of the arrhythmia may be less[18].

ATRIAL ELECTROPHYSIOLOGICAL REMODELLING

In 1995 Wijffels et al advanced the term "AF begets AF" to describe the concept of atrial electrophysiological remodelling as a mechanism for sustained AF[120]. Two separate groups published in 1995: Morillo et al demonstrated that rapid (400bpm) atrial pacing in dogs for 6 weeks allowed sustained AF (>15 min) to be easily induced in 11 out of 22 dogs, whereas none could be induced at baseline[111]. Echocardiographic examination exhibited marked bilateral atrial enlargement and the right atrial endocardial refractory period was significantly reduced from 150 +/- 8 to 127 +/- 10 ms. Electron microscopy of the atrial tissue showed an increase in number and size of mitochondria, enlarged nuclei and disruption of the sarcoplasmic reticulum.

The study performed by Wijffels et al and published one month later involved chronically instrumented goats; multiple electrodes sutured to the left and right atrium measured the refractory period at these sites (figure 7, page 37). An external pacemaker was used to deliver a burst of rapid stimuli (1s, 50Hz) to the atria whenever sinus rhythm was detected. Normal caprine hearts do not sustain AF for more than a few seconds but within the first 24 hours of repetitive re-initiation of AF the duration and rate of AF increased significantly. A marked shortening of the median AF cycle length (AFCL) was noted that was uniform throughout the goats. Once the AFCL had dropped below 120msec there was an exponential increase in AF duration.

Mapping of the atrium in chronic and paroxysmal AF has revealed that the normal adaptive shortening of refractory period as rate increases is paradoxically reversed in AF with refractory period much shorter at all heart rates and longer as heart rate slows, i.e. an inverse relationship. Furthermore the normal distribution of atrial effective refractory period (i.e. distal coronary sinus > high right atrium > low right atrium) documented in normal controls and patients with paroxysmal atrial fibrillation is reversed in patients with chronic atrial fibrillation.[121, 122]

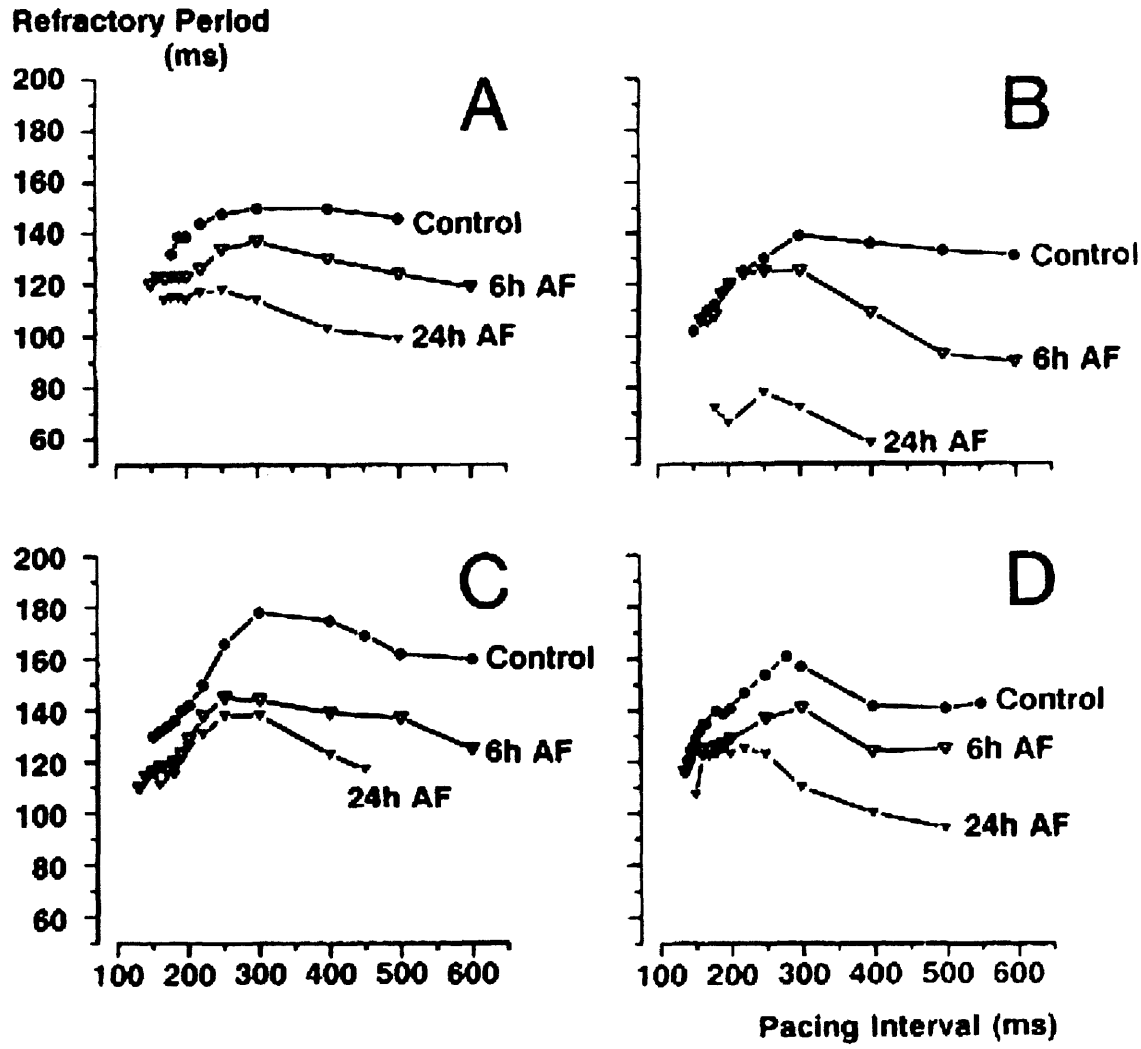


Figure 7. Adapted from Wijffels et al. The atrial refractory period in 4 carpine hearts (A-D) at different pacing cycle lengths. After 24hrs of AF the refractory period curve is shifted downward indicating shortening of the AERP at all cycle lengths. The degree of shortening is more pronounced at slower pacing rates and the physiological rate adaptation is blunted.

CALCIUM LOADING DURING AF

With observation of reduced activity of L-type calcium channels, Goette et al demonstrated how the electrophysiological changes induced by persistent rapid pacing of dogs could be blocked by pre-treatment with verapamil and accentuated by hypercalcaemia[123]. Tieleman et al also demonstrated that the electrophysiological remodelling of the atrium caused by atrial fibrillation may be blunted with verapamil[124]. Piot et al demonstrated that the high frequency depolarisation of atrial myocytes induced upregulation of calcium currents resulting in an 80% increase in calcium influx[125]. Work examining the atrial contractile dysfunction following a short episode of AF in porcine hearts demonstrated a reduction in dysfunction with verapamil pre-treatment, but the calcium agonist BAY K8644 increased dysfunction[126]. A marked attenuation of AF related refractory period shortening of the atrium in humans[127]and goats[124] has also been demonstrated with verapamil use (figure 8).

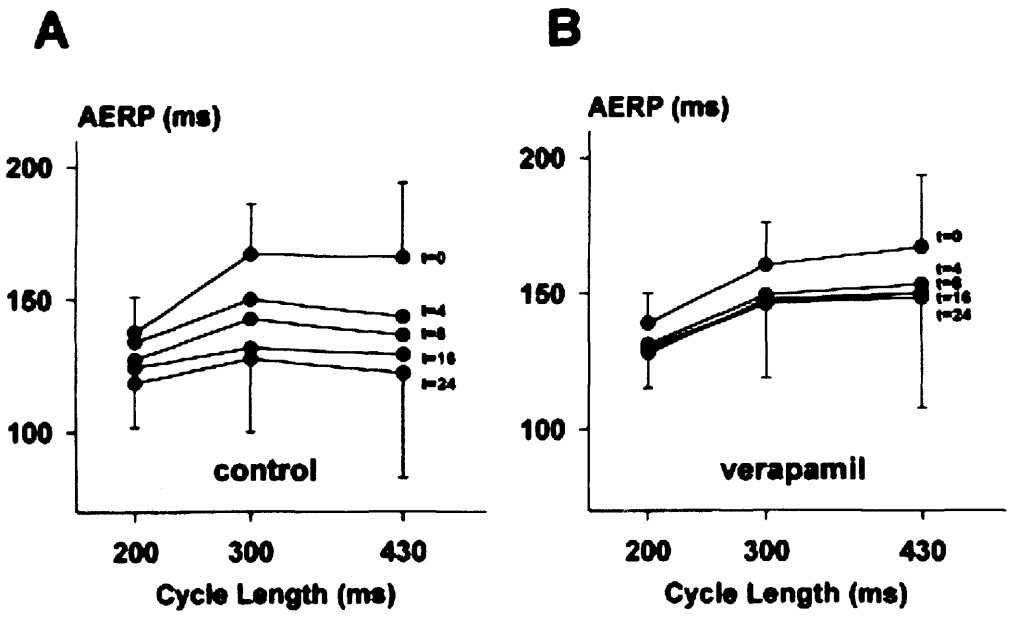


Figure 8. From Teileman et al. Shortening of refractory period on 38 electrodes in five goats during 24 hours of rapid atrial pacing during saline infusion (A) and continuous verapamil infusion (B). Refractory period shortened significantly less during verapamil infusion[124].

Work on rat ventricular myocytes directly links intracellular calcium loading with a decrease in expression of mRNA encoding sodium channels providing a possible explanation for the slowed conduction velocity documented in AF. Verapamil reduced the levels of intracellular calcium and restored membrane sodium channel density[128, 129].

Data on the long term effects of verapamil are lacking; however Lee et al found the benefit observed at 1 day was short term with no difference in AERP shortening or dispersion at 1 week or 6 weeks in dogs pre-treated with 120mg slow release verapamil compared with controls[130]. Similarly there was no significant difference in the inducibility of AF at 1 and 6 weeks; however the duration of induced AF at 6 weeks proved to be significantly longer in the verapamil group. The expected differences were documented at 1 day and thus the authors conclude the effects of verapamil are short term.

Unlike I_{CaL}, which is down regulated in AF, the T- type calcium current, I_{CaT} is not reduced[99]. Fareh et al investigated the effect of a specific T-type calcium channel blocker, mibefradil, on tachycardia induced electrical remodelling in dogs. The study was performed after 7 days of rapid atrial pacing; AERP shortening and increased dispersion accompanied by increased vulnerability to AF induction and longer AF duration was demonstrated in the controls. Contrary to the findings of Lee et al using slow release verapamil, the dogs administered mibefradil exhibited a marked attenuation of the effects of rapid atrial pacing. AF duration in placebo treated dogs was 414+/-232 seconds compared with 3+/-1 seconds for the mibefradil group[131]. The

authors postulate that whilst down regulation of I_{CaL} protects from calcium overload there is a continuing influx of Ca^{2+} from I_{CaT} and the attenuation of this influx by mibefradil accounts for the observed benefits. Mibefradil was never studied in human AF because of adverse drug reactions related to CYP 3A4 inhibition.

Amiodarone has multiple channel blocking properties, including T-type Ca^{2+}- channels, and has been shown to inhibit electrical remodelling in the atrial tachycardia dog model[132]. The study demonstrated that amiodarone prevented tachycardia induced changes in atrial ERP and expression of the L-type Ca^{2+} channel $alpha_{1c}$ subunit. The study also examined the ability of amiodarone to reverse already established electrical remodelling. Addition of amiodarone restored ERP, ERP rate adaptation, and AF duration to their control values. This study suggests the efficacy of amiodarone is secondary to prevention of Ca^{2+} -channel down regulation and can reverse established electrical remodelling.

REVERSE REMODELLING

The process of reverse remodelling has been studied in goats and humans[120, 133]. The time course of electrical reverse remodelling, i.e. the normalisation of refractory period and rate adaptation, is within 3 days of sinus rhythm even after several months of AF[133]. In the goat model of AF the reverse electrical remodelling and contractile dysfunction were studied after 5 days of AF. The recovery of atrial contractility followed the same time course as reverse electrical remodelling[134]. As electrical remodelling is known to be secondary to a reduction of I_{CaL} the contractile dysfunction is probably related to a reduced Ca^{2+} inward current. However in humans although the electrical reverse remodelling after prolonged episodes of AF is relatively rapid; the recovery of atrial contractility can take several months[135, 136]. This suggests additional, as yet unknown factors, are responsible for the delay in recovery[120, 137]. Furthermore the recurrence of atrial fibrillation a week or more after cardioversion cannot be explained by abnormal electrophysiology due to remodelling. Experiments to investigate the possibility of a second factor in the development of persistent AF in the goat have been performed[138, 139]. In one study AF was maintained by burst pacing for 5 days on three successive occasions. Each episode was separated by 2 days of sinus rhythm during which electrical remodelling was completely reversed. There was no difference in the time required to sustain AF between the first and the second 5 day episode. This suggested that if a second factor existed it required longer episodes of AF[138]. The study was repeated with the duration of the consecutive episodes increased to 1 month[139]. Following cardioversion, electrical remodelling was allowed to completely reverse. On this occasion the duration of burst pacing required for AF to become sustained was reduced from 12 days to 4 days ($p<0.01$). This was supported with further work on efficacy of chemical cardioversion that decreased with duration of AF[140]. Thus the evidence is strong that a second factor, separate from electrical remodelling, is complicit in the development of sustained persistent atrial fibrillation. The most likely candidates are associated with structural remodelling of the atria[141].

ATRIAL STRUCTURAL CHANGES ASSOCIATED WITH ATRIAL FIBRILLATION

Little is known of the structural changes associated with lone AF in humans over any period of time. Most work has been performed on animal models of AF obtained from goat and dog models. Following sustained AF for a period of 9 to 23 weeks in the goat, a variety of structural changes can be observed[142]. Electron microscopy of atrial tissue exhibits marked myolysis; there is a loss of sarcomeres from the cell that is most pronounced around the nucleus; the space occupied by the sarcomeres is replaced with glycogen. In addition there is an increase in myocyte size with networks of disorganised membrane observed together with changes in the size and shape of the mitochondria. Heterochromatin, normally in small clumps in the nucleus, is dispersed uniformly throughout the nucleoplasm. The typical changes of cell degeneration, such as cytoplasmic vacuolisation, mitochondrial swelling or membrane disruption, are absent. There is no observed difference in the amount of connective tissue between goats maintained in AF and controls; of particular note there is no atrophy of cells, in fact the degree of myolysis correlates well with the increase in size of the cell with no alteration in the extracellular matrix. Gap junction remodelling consists of a loss of connexin 40[143]. There are differences within species however with an increase in connexin 43 described in the dog that reverses with cessation of AF[144].

The histological observations are that of dedifferentiation of the atrial myocyte to an embryonic state. This has a remarkable similarity to 'hibernating' myocardium described in the ischaemic ventricle[145]. Human studies on structural change in response to AF remain limited but the changes observed of dedifferentiation in animal models are confirmed[146]. In addition however, unlike animal models, there is also evidence of degenerative changes and increased interstitial fibrosis in patients with chronic AF. In the dog model of heart failure similar structural changes are observed and are related to an increased propensity to AF in the absence of electrical remodelling; this is due to heterogeneity of conduction secondary to discrete regions of slow conduction[141]. The changes observed may explain the poor contractility of atrial tissue following cardioversion[147].

Reversibility of structural remodelling has been investigated in both the dog model and goat model of atrial fibrillation[148, 149]. The myocyte changes persist several months after electrical remodelling has taken place, and increased vulnerability to AF remains. Thus, complete reversal of structural remodelling has not been demonstrated, and it remains to be seen to what extent the process is reversible.

SUMMARY

The causal relationship between known risk factors and AF development remains uncertain but the prevalence of severe valvular heart disease as a co-morbidity is declining. Once initiated, AF is a self perpetuating arrhythmia that in some cases may initially be reliant upon a driving mechanism. The reliance on this driver

lessens as electrical and structural remodelling occurs until it may no longer present a therapeutic target. Electrical remodelling is responsible for early reinitiation of AF after cardioversion but reverses within a few days. Structural remodelling takes longer to occur but once established it may not be fully reversible and is partially responsible, with the original pathology, for long-term vulnerability to AF. The dog model of heart failure also suggests that AF can occur without electrical remodelling with the implication that some cases of AF associated with structural heart disease have a different mechanism perhaps less dependent on driving rotors[141].

Underpinning these changes are significant and complex changes in cellular function and ion channel density and distribution. The ionic changes are likely to be initially adaptive to calcium loading but thereafter may participate in arrhythmia perpetuation.

DISCUSSION

The electromechanical manifestations of remodelling are discernible from inspection of the surface electrocardiogram. The interval of fibrillatory waves during AF can provide insights into the atrial effective refractory period[150]. Change in atrial electrophysiology is apparent in the action potential and as the P wave is the summation of atrial action potentials it might possess the ability to assess these changes non-invasively. During sinus rhythm the surface P wave can reflect abnormality of the underlying atria, and it is this potential for non-invasive assessment that forms the basis of a hypothesis for investigation of surface markers of atrial electrophysiology. The electrophysiologic changes associated with atrial fibrillation are:

- Structural changes consisting of increased left atrial size, reduction in left atrial function and cellular changes with alterations in gap junction expression, cellular dedifferentiation and possibly fibrosis in the chronic state.
- Ionic changes with a reduction in expression of sodium channels in response to increased intracellular calcium and consequent altered calcium homeostasis.
- The electrophysiologic manifestation of these changes are a shortened, heterogeneous atrial refractory period and reduced conduction velocity.

The electrophysiologic changes associated with AF are now well described as are the P wave changes (Chapter 1, Table 1, page 25). Data is lacking on the causal and temporal relationship between P wave changes and AF; however there is a circumstantial evidence to invite speculation on a link between changes in surface P wave indices and changes in atrial electrophysiology.

- Paroxysmal AF is associated with a significant increase in filtered P wave duration and energy. PWD has long been thought to reflect inter atrial conduction time and increased left atrial diameter. Both LA size is

increased and conduction velocity slowed in PAF patients. Fractionation present in the sinus beat produce high frequency signals and energy is notably higher in patients with PAF. Increases in left atrial size will be reflected in P wave amplitude and area under the P wave[8] – power, this is directly related to energy.

- The SAPW variables are subject to influence from the autonomic nervous system. The APD is subject to major influence from autonomic input.
- Filtered P wave parameters appear to reflect sodium channel blocking drugs in clinical studies. As sodium channels are the major contributor to Vmax , a reduction of sodium channel activity will reduce Vmax and conduction velocity. The changes in the action potential may be appreciable from the surface P wave.

HYPOTHESIS

The studies presented above of the signal averaged P wave in PAF, post cardioversion, and with antiarrhythmic medication suggest detailed analysis of the P wave might reflect change in atrial electrophysiological substrate. This apparent ability of the signal averaged P wave to reflect underlying changes in atrial electrophysiology in a predictable manner invites speculation on the role of the SAPW as a non-invasive marker of atrial substrate.

In order to determine if this hypothesis can be supported a series of pilot studies are presented. These studies are designed to examine the SAPW in scenarios where change in atrial electrophysiological substrate might be expected from invasive studies or previous observations.

All study designs and protocols were reviewed by the University of Leicester Higher Degrees Committee (except chapter 6 and 7) and Local Ethical Committee approval was sought and granted for all studies included.

CHAPTER TWO

GENERAL METHODOLOGY

INTRODUCTION

The majority of this chapter is devoted to describing the methods by which all the high resolution electrocardiograms in the subsequent studies were recorded and analysed. Included is the validation of a digital commercial Holter system for high resolution signal acquisition and the accompanying specially developed software for the analysis of the P wave.

ACQUISITION HARDWARE

The equipment used for signal acquisition varied in the studies. A purpose built acquisition system was used for recordings in chapters 4 and 5. Chapter 6 employed the digital Holter acquisition system validated in chapter 3. For chapters 4 and 5 the hardware comprised: three bipolar leads referenced to isolated ground lead; Amplicon PC26A7 analogue to digital converter; amplifier; a laptop computer (Toshiba) connected to a Zip drive (Iomega) and final analysis on a desktop personal computer.

PATIENT PREPARATION

No specific electrical shielding was used during experiments. Recordings were taken with the subject lying supine, on a bed, or couch, on the ward, or in outpatients. The subject was prepared by shaving the area, if necessary, prior to skin preparation with standard abrasive tape (Red dot). The area was cleaned with alcohol and allowed to dry prior to the application of electrodes (Blue Sensor; R-00S) according to a modified Frank's lead (Ernest Frank, 1956) orthogonal arrangement[25] (illustrated in figure 1).

SIGNAL AVERAGED P WAVE RECORDING

Following preparation as outlined above, signal averaged P wave recordings were performed with the patient relaxed and supine for a period not less than 5 minutes. Analogue signals were amplified between 4000 and 20,000 times and band pass filtered between 1 and 300Hz. A trigger signal derived from one of the orthogonal leads was band pass filtered between 20 and 50Hz. The analogue signals were then digitised at 1kHz with 12 bit resolution and stored on the laptop hard drive. These files were transferred to Zip and stored for later processing.

The Holter system recordings were made using an ELA Medical digital Holter device (Spiderview) and recorded on SD cards with study codes. The data was transferred to a password protected PC and stored on the hard drive. During high-resolution recording the device sampling rate was 1000Hz at an amplitude resolution of 2.5µV. The common mode rejection was 80 dB.

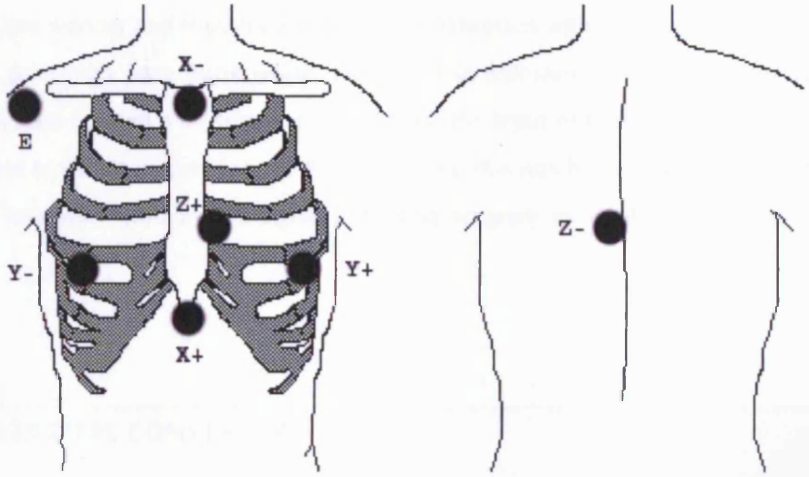
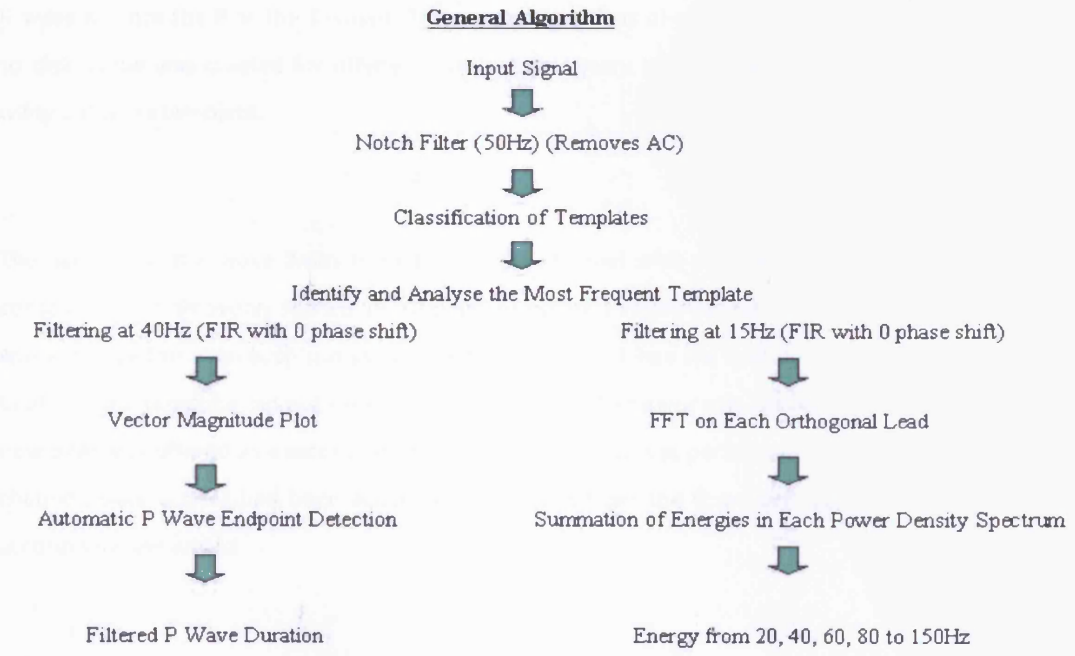


Figure 1. Modified Frank's lead orthogonal lead placement. X: Manubrium positive, Xiphisternum negative; Y: V4 positive, V4R negative; Z: V2 positive, position directly opposite on posterior chest wall.

P WAVE ANALYSIS



ANALOGUE PRECONDITIONING

Signals from the patient were presented to a high gain, high impedance three channel amplifier with the following features: overall gain X 10, common mode rejection –170dB at 60Hz (balanced source impedance), frequency response DC to 1KHz. Signals underwent further amplification in two stages to total gain of 10000x and filtered with a high pass Butterworth filter at 0.2Hz and a low pass Bessel Filter at 300Hz.

To eliminate baseline wander and thus allow maximal amplification without saturation of the amplifiers, there was a second 3 pole high pass Butterworth filter at 1Hz followed by DC offset for each channel. The preconditioning system created a 4^{th} trigger channel from the input of the lead displaying the largest P wave and clear difference in amplitude between R, P and T waves; this was further bandpass filtered between 20 to 50Hz. This signal was later used by the signal averaging program to identify the fiducial point for P wave alignment.

ANALOGUE TO DIGITAL CONVERTER

Amplicon PC26AT. Output from above consisted of 4 signals presented to a 12 bit ADC with voltage range of ± 2V.

SIGNAL AVERAGING

The 4 signals were sampled at 1KHz and displayed on screen. Triggering from the R wave of the trigger channel identified each electrocardiographic cycle. The user defined the voltage threshold that detected the peak of the R wave but not the P or the T waves. The preceding 400ms of each channel containing the P wave was stored to disk. A file was created for offline analysis. Subsequent offline analysis aligned successive 400ms sections using a P wave template.

The user defined P wave limits from the trigger channel with on-screen callipers; this was followed by the construction of an evenly spaced 15-30 point template between these limits. A modulus difference algorithm was employed to align each successive P wave and accept into the average if the difference between the new beat and the template did not exceed a preset value. If this error was exceeded the beat was rejected and this new beat was offered as a second template and so on. This was performed on the signal comprising the trigger channel, once a beat had been accepted the signals from the three orthogonal channels were time shifted accordingly and added.

Once averaging was complete the mean value of each data point was calculated and each lead normalised to an overall amplification of 10000 times. Subsequent to this a 100 beat sample of the recording was used to establish the relative frequency of each template. This enabled a template to be selected that best matched the majority of the morphologies contained within that recording.

TIME-DOMAIN FILTERING

After averaging, P waves were high pass filtered using a 30-term finite impulse response filter (40 to 300Hz) and a vector magnitude plot constructed. The impulse response of the filter was windowed using a Kaiser Bessel window with the coefficients chosen to give the first null at DC.

DISPLAY

After filtering of each lead separately, the signals were combined to produce a single vector magnitude display from which the P wave limits were defined. An algorithm identified the beginning of the P wave as the point at which the voltage was raised three standard deviations above the mean isoelectric voltage. The P wave end was given when the vector magnitude voltage fell to within 3 standard deviations of the baseline value of the minimum PR segment magnitude. The user was presented with this information and could alter the limits after inspection of the signal.

FAST FOURIER TRANSFORM

The signal was high pass filtered a 15Hz to remove the DC offset and zero padded to 1024 points to smooth the frequency spectrum and aid banding of the frequencies for analysis. Unfiltered signals were processed separately between the limits of the P wave defined on the vector magnitude plot. The resultant energy output for each orthogonal lead was then summed to give estimates of the total energy per band and presented as an energy density spectrum. The absolute powers in each frequency band (V^2) within the P wave limits (seconds) were then summed algebraically to give total energy values for frequencies contained within 20 to 150Hz (P20) or 30 to 150Hz (P30), etc. The values were expressed as $K\mu V^2.sec$.

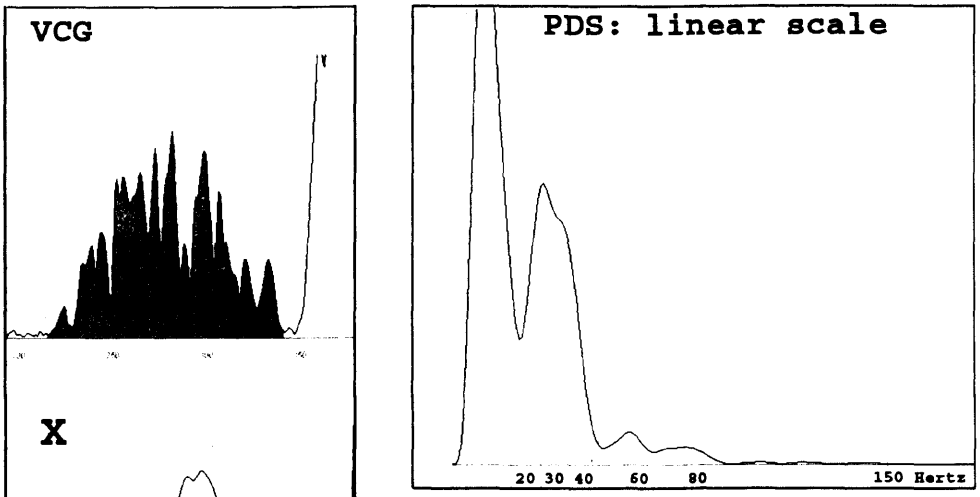
POWER DENSITY SPECTRUM

The resultant energy spectrum is illustrated in figure 2 right hand panel. It can be appreciated that numerically the lower frequency energy dominates. Energy was not windowed to deliver a value for a narrow spectrum e.g. 20 to 30 Hz or 60 to 80Hz as this would have introduced noise into the adjacent bands and contaminated the signal, rendering the higher energy in particular unworkable. This does mean however that the value of P20

includes P30, P40 etc. In practice the small value of the higher frequency energy will impact little upon the lower energy and for analytical purposes is negligible.

STATISTICAL ANALYSIS

Normal distribution of data was determined with Anderson-Darling test of normality. Frequency domain derived data does not display a normal distribution; the data tends toward a positive skew with unequal variances. Thus all analysis of P wave energy employed non-parametric tests. Wilcoxon Signed Rank test was used to analyse within patient data; Mann-Whitney was used to examine data within two separate groups. MINITAB™ Release 13.31 statistical software was used exclusively for all the analysis. For data demonstrating normal distribution Students T or Paired T was employed. Reference to specific statistical tests is found in the chapters.



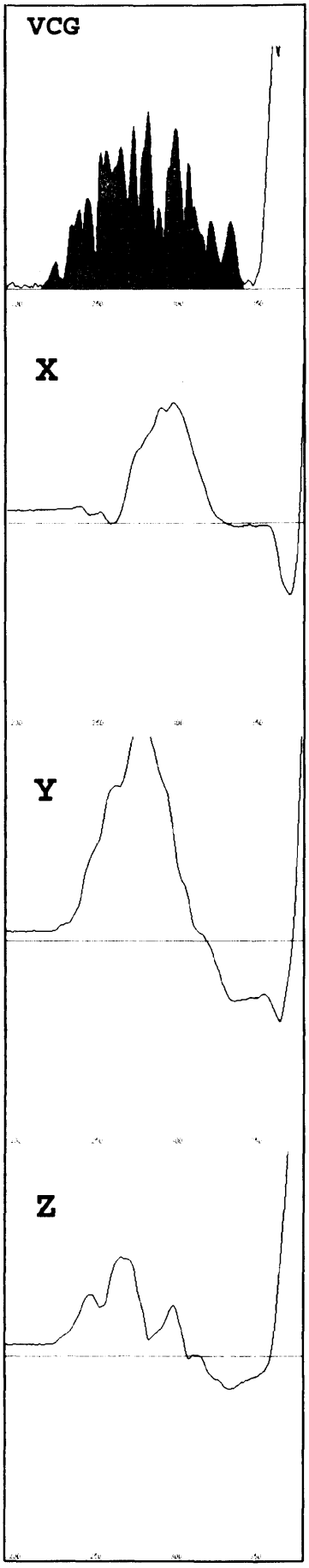


Figure 2.

SAPW from a normal adult male.

Left panel shows a vectorcardiogram (VCG) from which the p wave duration is calculated. The individual signal from each orthogonal lead is shown below.

The right hand panel is a power density spectrum (PDS) constructed from the summation of power in each lead. The frequency scale is highlighted on the X axis (power in μV^2 is the Y axis). The energy contained within a frequency band can then be calculated. P20 will represent total energy ($K\mu V^2.sec$) contained within frequencies 20 to 150Hz, P60: 60 to 150Hz etc.

CHAPTER THREE

SYSTEM REPRODUCIBILITY

INTRODUCTION

The reproducibility of the system used in two of the studies included in this thesis had been assessed previously[28]; however chapters 6 and 7 employed a digital Holter acquisition system and software adapted for use with this system. The purpose of this chapter is to first review the data previously published on reproducibility of P wave parameters and in particular the data published on the system used for chapters 4 and 5; second, present data on reproducibility of the Holter system and validation against the original system; finally, using the data acquired estimate the sample sizes needed to detect significant difference in measured parameters.

SIGNAL AVERAGED P WAVE REPRODUCIBILITY

Several studies have examined reproducibility of the signal averaged P wave[28, 151-154]. The study from Steinberg measured the immediate and 4-5 day reproducibility of a P wave template averaging system in 28 subjects[152]. Immediate and short term PWD and root mean square voltage demonstrated good reproducibility (r =0.94 for PWD); however the terminal P wave voltages were less reproducible in the subjects with cardiac disease or history of AF (r = 0.84). Similar results have been found for reproducibility of filtered PWD by Dhala et al in 280 subjects, (r=0.96 for PWD)[151]. Both studies used linear regression analysis which has been criticised as inappropriate for accurate assessment of reproducibility[155, 156].

The study of Savelieva et al examined reproducibility of PWD and terminal voltage at 5 minutes, 1 day, 1 week and 1 month[154]. The authors used relative errors of pairs of recordings to estimate reproducibility. The group found excellent reproducibility for PWD but noted poor reproducibility for terminal voltages.

SYSTEM REPRODUCIBILITY

There is limited data on reproducibility of frequency domain parameters for the signal averaged P wave, most of the literature on short term frequency domain recordings concerns heart rate variability analysis. For the system employed in chapters 4 and 5 the system reproducibility had been studied previously in 20 subjects, 10 normal volunteers and 10 cardiac patients[28]. The relevant details of this study are presented overleaf.

STUDY DESIGN

To assess reproducibility, 20 subjects were studied: 10 normal controls and 10 patients with paroxysmal AF documented on Holter recordings. Analysis of recordings made back-to-back without change in electrodes and at 1 week was made. Reproducibility was presented as a coefficient of reproducibility calculated from the standard deviation of the difference between two means[155].

RESULTS

Tables 1 and 2 show the immediate and 1 week reproducibility published in this study, respectively.

	Mean 1 (SEM)	Mean 2 (SEM)	CR	%CR
PWD	139 (3)	140 (2)	15.9	11.4
P20	43.82 (5.25)	43.58 (5.33)	10.68	24.6*
P30	29.80 (3.86)	28.93 (3.86)	6.00	20.1*
P60	3.57 (0.36)	3.71 (0.37)	1.34	37.7*

*Table 1. Immediate reproducibility. Mean values (standard error of the mean). CR: coefficient of reproducibility; %CR: CR expressed as a percentage of the mean of the two values of that variable. PWD: P wave duration in milliseconds, P20, P30, P60: energy contained in frequency bands from 20, 30 or 60 to 150Hz expressed as $K\mu V^2$.sec. * statistical significant difference between variables as assessed by Wilcoxon rank sum test.*

	Mean 1 (SEM)	Mean 2 (SEM)	CR	%CR
PWD	139 (3)	139 (3)	18.2	13.1
P20	43.82 (5.25)	44.27 (7.77)	32.54	74.1*
P30	29.80 (3.86)	28.54 (4.48)	20.96	70.3*
P60	3.57 (0.36)	3.89 (0.51)	3.33	93.4*

Table 2. One week reproducibility. Data definitions as per table 1.

P wave duration proved to be the most reproducible parameter with a coefficient of reproducibility of 10%. Thus a second recording would have a 95% probability of being within 10% of the original; for example a second recording of a PWD originally 140ms would lie between 126ms and 154ms. Frequency domain parameters were much less reproducible with a coefficient of reproducibility for P20, P30 and P60 being 74%, 70% and 93% respectively for paired initial and 1 week recordings. Inspection of the recordings noted major differences in the P wave morphology in some patients. A repeat analysis was performed with these subjects removed. Reproducibility improved with the exclusion of subjects with extreme differences in P wave morphology (see tables below) but remain higher than for PWD (18%, 28% and 62% respectively). No difference in reproducibility was found when data was analysed separately for normal subjects and subjects with AF.

		Mean 1 (SEM)	Mean 2 (SEM)	CR	%CR
Immediate	PWD	140 (3)	140 (3)	12.5	8.9
	P20	43.63 (6.33)	43.01 (6.33)	5.59	12.8
	P30	29.21 (4.61)	28.56 (4.56)	5.04	17.3
	P60	3.67 (0.43)	3.58 (0.41)	0.57	15.5*
1 week	PWD	137 (5)	140 (7)	18.9	13.8
	P20	36.41 (3.59)	34.67 (3.36)	6.66	18.3
	P30	24.30 (1.75)	23.42 (1.33)	6.78	27.9
	P60	3.25 (0.68)	3.27 (0.39)	2.02	62.4

Table 3. Reproducibility assessed immediately and at 1 week with exclusion of subject with P wave morphology change (see text). Data definitions as per table 1.

The authors studied the reproducibility of the signal averaging algorithms on the same series of P waves and found the reproducibility to be high (data not shown) and concluded that the change in P wave morphology rather than inconsistencies in the P wave averaging system was responsible for the poor reproducibility. The template system of averaging (described in chapter 2) enhanced these differences as it matched the morphology of the most frequent P wave recorded at that time. The authors speculated that a less selective approach might be used but it was unlikely to have improved reproducibility as the most prevalent morphology at that time would still dominate and influence the results accordingly. This paper concluded that P wave duration was reproducible but energy was less reproducible because of normal biological variation. Such variation limits the value in prediction of atrial arrhythmia in individual patients.

The following study was performed prospectively as part of this thesis to demonstrate the reproducibility of the digital Holter acquisition system employed in chapter 6.

REPRODUCIBILITY OF HOLTER HIGH RESOLUTION RECORDINGS FOR P WAVE SIGNAL AVERAGING

INTRODUCTION

Methodology for acquisition of high resolution recordings used subsequently for signal averaging of P waves differs between authors[22, 23, 28, 49]. The ideal recording device would possess the following qualities: portable, light, easy to use, require minimal shielding and deliver good quality, reproducible recordings. Additional desirable qualities would be digital acquisition, analysis and the ability to incorporate information about rate and rhythm. A contemporary Holter device might deliver many of the qualities listed and offers the prospect of recordings taken in the context of the ambient rhythm.

The objective of this study was to investigate the utility of a commercially available Holter device (Syneflash, ELA Medical, Paris, France) for the purpose of acquiring high resolution recordings for signal averaged P wave analysis.

METHODS

Normal volunteers from staff at a large tertiary hospital comprised the study cohort. Recordings were made with subjects supine, warm and relaxed in quiet room. No additional shielding was used. Each recording was of ten minute duration. The first two recordings were made back to back for immediate reproducibility and a further recording was acquired at 24 hours to evaluate short term reproducibility. The data was analysed in a random order using study codes and blinded to the subject's identity and order of recording.

The software employed was based upon previously validated software incorporated into a Windows format for PC. The algorithms have been described in detail earlier in the chapter, page 43.

STATISTICAL ANALYSIS

An absolute coefficient of reproducibility (CR) was calculated between recording pairs, 1st and 2nd, 1st and 3rd, according to the formula:

$$CR_{A,B} = 2 \times SD(A-B)$$

Additionally the CR was expressed as a percentage of the mean value for the two measurements A and B as follows:

$$\%CR_{A,B} = \frac{2 \times SD(A-B)}{Mean\ (A,B)} \times 100$$

RESULTS

Sixteen subjects volunteered for recordings, mean age 40.4 ± 11.8 years (range 18 to 60 years), seven male. Subjects reported good health with no past medical history of note. The data for all patients is presented in table 4. Analysis of variance is presented as P value between the recordings; no difference was found.

	PWD	P20	P30	P40	P60	P80	RMS30	Noise
1	133.9(1.8)	29.0(2.2)	20.5(1.8)	10.5(1.2)	3.0(0.4)	1.2(0.2)	4.3(0.5)	0.07(0.00)
2	134.1(2.1)	28.2(2.2)	19.4(1.6)	10.0(1.1)	2.9(0.3)	1.2(0.2)	4.5(0.5)	0.07(0.00)
3	134.1(2.0)	28.4(2.2)	19.8(1.8)	9.9(0.9)	3.0(0.3)	1.2(0.2)	4.5(0.5)	0.08(0.00)
P=	0.995	0.868	0.933	0.998	0.974	0.967	0.977	0.647

Table 4. Mean (SEM) for all 16 subjetcs with results of Kruskall-Wallis analysis of the three recordings in each column delivered as a P value.

REPRODUCIBILITY OF FIRST AND SECOND RECORDINGS

The results of reproducibility between the first and second recordings are presented in table 5. PWD was the most reproducible variable with spectral parameters being less reproducible.

REPRODUCIBILITY OF FIRST AND THIRD RECORDINGS

Similar findings were present when the first and third recordings were examined. PWD remained a highly reproducible parameter but energy proved to be poorly reproducible with a notable trend toward lower reproducibility with ascending frequency bands. On inspection of the raw data, the recordings for several individuals showed a difference in P wave amplitude that was reflected in energy.

	Mean 1 (SEM)	Mean 2 (SEM)	CR	%CR	P=
PWD	133.9(1.8)	134.1(2.1)	4.7	3.5	0.861
P20	29.0(2.2)	28.2(2.2)	5.3	18.5	0.518
P30	20.5(1.8)	19.4(1.6)	6.0	30.0	0.453
P40	10.5(1.2)	10.0(1.1)	3.2	30.4	0.423
P60	3.0(0.4)	2.9(0.3)	0.9	31.2	0.518
P80	1.2(0.2)	1.2(0.2)	0.42	34.9	0.776
RMS30	4.3(0.5)	4.5(0.5)	1.0	23.2	0.394

Table 5. Reproducibility between first and second recordings - immediate reproducibility. Statistical difference between variables examined by Wilcoxan Rank sum and paired T test (for PWD).

	Mean 1 (SEM)	Mean 3 (SEM)	CR	%CR	P=
PWD	133.9(1.8)	134.1(2.0)	4.3	3.2[*3.4*]	0.842
P20	29.0(2.2)	28.4(2.2)	8.9	30.9[*22.6*]	0.266
P30	20.5(1.8)	19.8(1.8)	7.5	37.4[*25.9*]	0.171
P40	10.5(1.2)	9.9(0.9)	5.0	49.4[*43.0*]	0.289
P60	3.0(0.4)	3.0(0.3)	1.4	45.9[*40.7*]	0.897
P80	1.2(0.2)	1.2(0.2)	0.8	64.5[*56.5*]	0.856
RMS30	4.3(0.5)	4.4(0.5)	1.0	22.9[*20.9*]	0.423

Table 6. Reproducibility between 1st and 3rd recording – 24 hour reproducibility. %CR is presented for all 16 subjects. Below is the value on exclusion of 1 subject (see text and figure 1)

This was not necessarily associated with a significant change in dominant morphology. Figure 1 shows the first and third recordings from a 31 year old male. The P wave morphology appears to show only minor change between the recordings however the filtered P wave amplitude is considerably greater in the 24 hour recording (right panel) than on the initial recording. This was reflected in a difference in P20 of 11.4KμV².s. Reanalysis after exclusion of this recording is shown in table 6 in square brackets for illustration only.

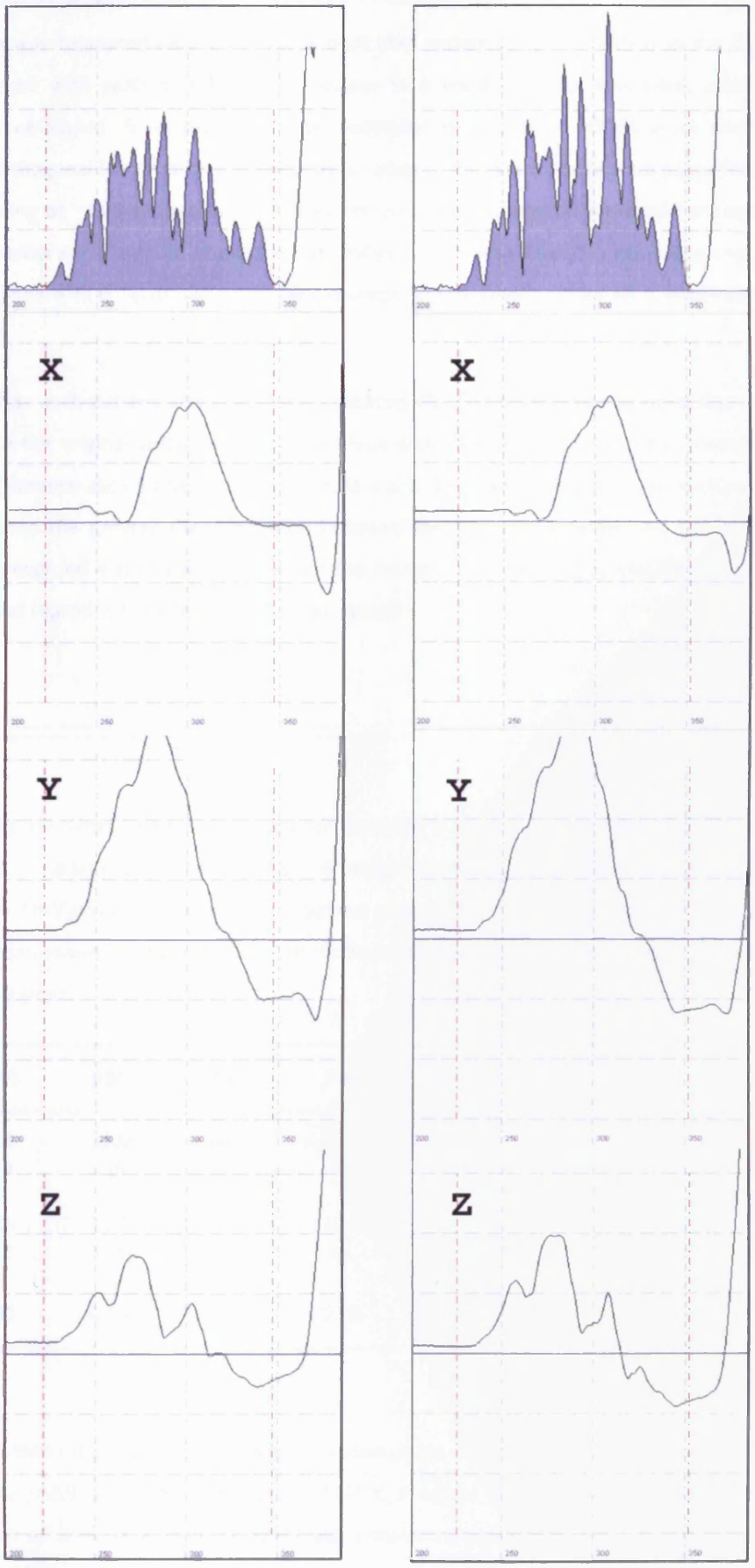
Figure 1

Vector magnitude plots are at the top of each panel with P wave morphology from each orthogonal lead below.

The recordings are from the same subject; first in the left panel and 24 hour in the right.

Note the similar morphology in the presence of increased amplitude in the vector magnitude plot.

This resulted in a change in total energy from baseline in the presence of unchanged P wave duration.



VALIDATION AGAINST ORIGINAL SYSTEM

The digital Holter system was compared with the original dedicated system described earlier in the chapter. Recordings were performed with patients relaxed and supine in a ward or outpatient clinic setting, no additional shielding was employed. Silver-silver chloride electrodes (Blue Sensor R00-S) were positioned according to a modified orthogonal lead system following preparation of the skin with abrasive paper (Red Dot) and alcohol. Initial recording of ~ 600 sequential beats were taken using the original standard hardware and technique[25]. Immediately afterward, without change in electrodes, a recording was obtained using the digital Holter employing the standard ECG leads used for 24hr recording. The device obtained a high-resolution recording for ten minutes.

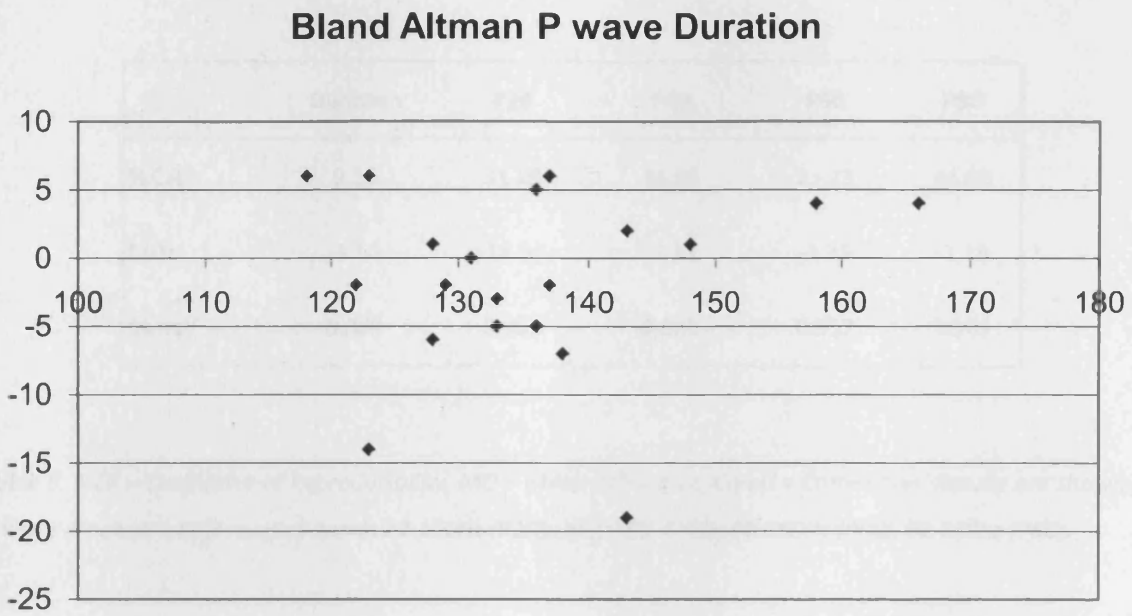
Data was downloaded after each patient and stored on a desktop PC. The data obtained using the original system was analysed with the original software. The comparison was standardised further by increasing the error limit (percentage difference allowed between the template and the P wave) to allow a maximum of 100 beats. The higher the error the greater the difference between the included P wave and the reference template. The error was recorded and compared between the two systems (table 7). Correlation and 'Bland Altman' analysis[155] assessed reproducibility between the two systems.

RESULTS

Twenty one patients were recruited, with a mean age of 50 years; 8 patients were male; 7 patients had documented atrioventricular nodal reentrant tachycardia, 6 patients atrioventricular reentrant tachycardia, 4 patients paroxysmal atrial fibrillation, 3 controls and 1 patient was averaged following ablation for isthmus dependent flutter. The mean values for each method are displayed below in Table 7. There was no significant difference in the values obtained.

	PWD	P20	P30	P40	P60	P80	Error
Holter	133 ±14	31.0 ±19	18.6 ±11	9.2 ±5	2.7 ±1.5	1.1 ±0.6	12.6 ±3.5
Original	135 ±12	32.5 ±18	20.0 ±11	10.0 ±5	3.1 ±1.5	1.3 ±0.7	9.6 ±4.2
P=	0.49	0.68	0.56	0.35	0.39	0.58	0.01

Table 7. Mean values (± standard deviation) for P wave duration in ms and P wave energy contained within frequency bands 20-150Hz (P20); 30–150Hz (P30) etc in KμV².s. P values are for Mann-Whitney statistical analysis between each set of data, a p value of <0.05 was considered significant. Error is expressed as a percentage (see text for details).



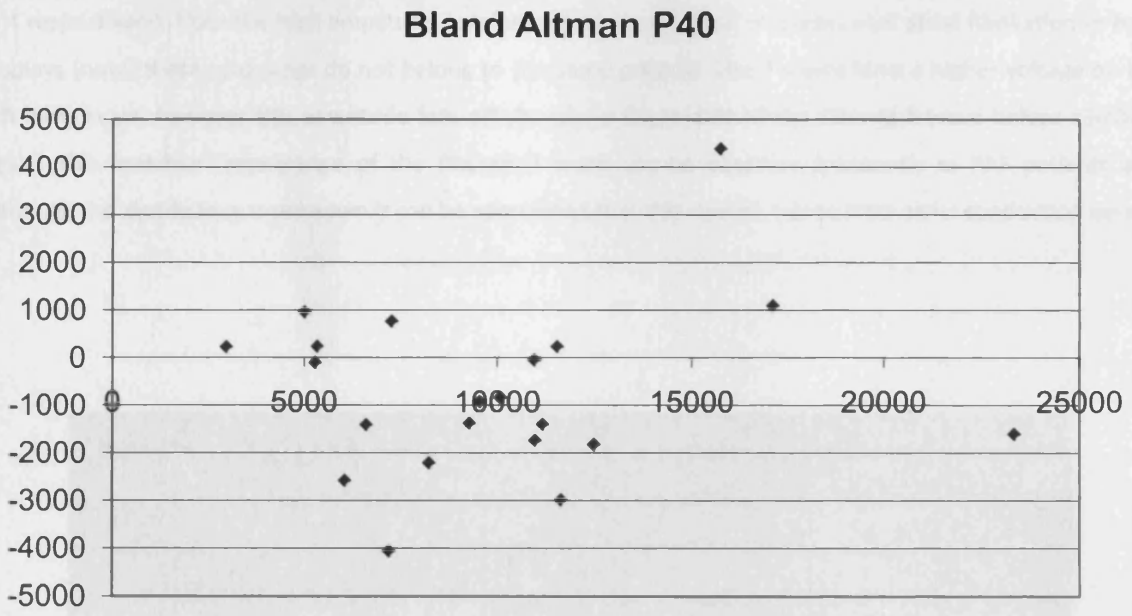


Figure 2. Bland Altman plots for P wave duration and P40 respectively. An even scatter is noted about the mean suggesting no significant bias.

P wave duration and energies demonstrated good reproducibility between the two techniques, but with a significantly higher error for the 'Syneflash' data recordings: 9.6 (± 4.2) vs. 12.6 (± 3.5) (p = 0.014).

Correlation coefficient and coefficient of reproducibility for the two sets of data are presented in table 8. There was good correlation between the two results and minimal variability in the time domain. However the frequency domain did show an increased coefficient of reproducibility with higher frequencies. The correlation results are presented in table 8, with corresponding Bland Altman plots presented in figure 2 above.

	Duration	P20	P40	P60	P80
%CR	9.58	31.29	36.25	29.23	44.88
MD	-1.52	-14.57	-7.26	-3.35	-1.18
Correl	0.889	0.965	0.940	0.957	0.909

Table 8. %CR = Coefficient of Reproducibility, MD = Mean Difference, Correl = Correlation. Results are shown for P wave duration and frequency bands 20-150Hz (P20); 40-150hz (P40); 60-150Hz (P60); 80-150hz (P80).

Representative displays of a vector magnitude plot are provided for the original and developed software (Fig 3 & 4 respectively). Note the high amplitude notched appearance typical of paroxysmal atrial fibrillation in both displays (note: these recordings do not belong to the same patient). The P waves have a higher voltage on the left hand scale; however this amplitude falls off sharply in the middle of the filtered P wave before climbing again. This 'notched' appearance of the filtered P wave can be observed frequently in PAF patients and although the significance is unknown it can be speculated that this may be due to intra-atrial conduction delay.

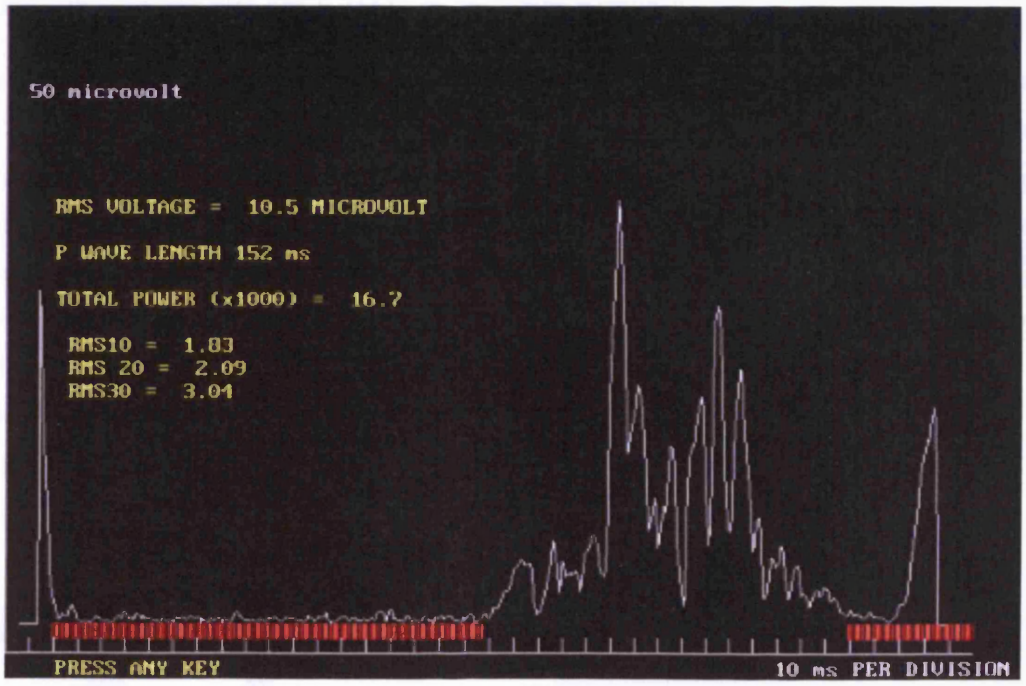


Figure 3. Representative signal averaged P wave from original system

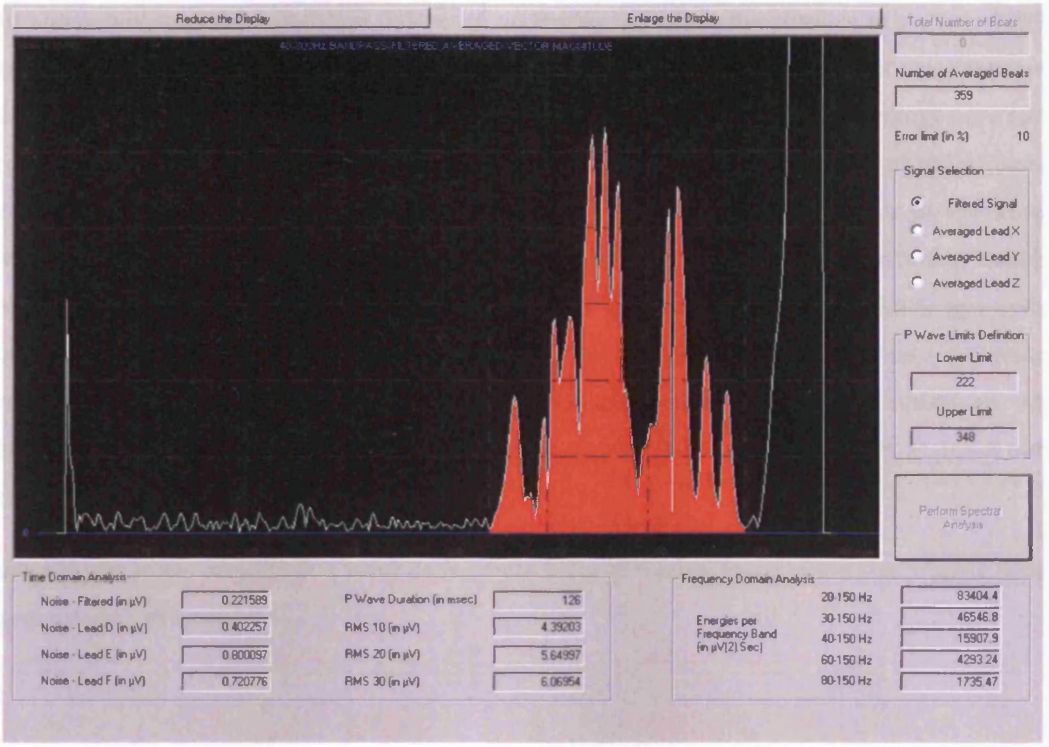


Figure 4. Representative SAPW display from the Windows based software.

DISCUSSION

REPRODUCIBILITY OF THE ORIGINAL

Stafford et al described a coefficient of reproducibility (%CR) in the order of 10% for PWD but for the frequency domain variables the %CR was 74.3% at 1 week for P20 [28]. On close inspection of the raw data the group concluded the reproducibility might be improved by exclusion of individuals with major change in dominant P wave morphology. In practical terms such exclusion is not feasible as the change in morphology may be due to the process under investigation and thus cannot be reliably excluded. Furthermore, minor change in P wave morphology can accompany a change in amplitude of the P wave that is reflected in energy as demonstrated in Figure 2. Thus repeat assessment of energy values might be investigated in a short term setting such as after cardioversion or at electrophysiological study but repeated measures at 1 week using this technology may be less reliable and require large sample sizes.

REPRODUCIBILITY OF THE NEW SYSTEM

The study cohort consisted of healthy adults with no prior history of cardiac pathology and no regular medication that would be expected to perturb cardiac electrophysiology. The data presented in table 5 are the mean values (SEM) for each of the three recordings from the Holter monitor. The values did not appear

different and demonstrated no statistical difference on testing. However, the absence of statistical difference between tests does not quantify reliability of repeated measures[155]. Closer inspection of the data revealed a marked difference in reproducibility of SAPW parameters. When initial and 24 hour recordings were compared the percentage coefficient of reproducibility (%CR) for PWD was 3.2%, thus for a duration of 100ms there was a 95% probability of a second recording delivering a result between 96.8 and 103.2ms in the absence of intervention. However the %CR for P20 was 30% thus for a P20 of 30 $K\mu V^2$.sec a repeat recording would have a 95% probability of delivering a value between 21 and 39 $K\mu V^2$.sec. Immediate reproducibility was better than 24 hours and the difference probably reflected the normal biological variation between recordings. The frequency domain appeared sensitive to the biological variations present in normal individuals. Although tangible differences existed in P wave morphology in several subjects (illustrated in figure 2), these data were not excluded from analysis.

This study did not assess subjects at 1 week as reproducibility of P wave energy from the original system had been demonstrated to be poor.

VALIDATION

A validation of the new system against the old was performed. Twenty one patients had repeated measures with the old system and then the new system. The data differed between the two systems but correlation was high and there was no significant bias in any direction suggesting any difference between the two systems was randomly distributed. The data demonstrated the Holter system was more or less equivalent to the dedicated original system and could be used for the same purpose.

REPRODUCIBILITY OF FREQUENCY DOMAIN PARAMETERS

The frequency domain appears sensitive to the biological variations present in normal individuals. This is difficult to control for and thus the interpretation of spectral parameters requires some caution. This is true of spectral analysis of heart rate variability (HRV) where more data exists. The results recorded above on reproducibility of energy are typical of non-parametric data in the frequency domain, reproducibility of HRV variables derived from frequency domain analysis have reported coefficients of reproducibility of between 4-30%[156]. Some authors report values of 30% or less as representing 'good' reproducibility[157]. Such heterogeneity results in confusion as to the acceptable levels of reproducibility of tests. This is, in part, also confounded by the different statistical methods employed to examine for differences. In a recent review Sandercock recommended researchers make qualitative decisions on whether the accuracy of the measurements taken are suitable for the proposed purpose[156]. Moreover, assessments of reproducibility should be made in the clinical scenario to be studied prior to estimation of sample size.

CONCLUSIONS

In both the original and new systems P wave duration appeared a reliably reproducible measure. Frequency domain analysis is less reproducible. The above studies support and validate the high-resolution recording of the P wave using a Holter based system. This affords a convenient method for assessing the SAPW that is equivalent to a dedicated high-resolution system and will allow this methodology to be used more easily in the investigation of atrial pathology.

SAPW NORMAL VALUES

Introduction

It would be useful to determine values for the parameters measured in the SAPW that might be expected in normal subjects without significant past medical history.

Methods

High resolution recordings were made as described earlier in normal volunteers. No subject had a history of cardiac illness or hypertension or was taking any medication other than the oral contraceptive pill. Cardiac physical examination was normal.

Results

Thirty eight subjects were recruited, 20 male. Mean age was 38.9±12.5 years (males 34.8±10.4 years and females 43.4±13.4). Uneventful recordings for 10 minutes were obtained in all using old and new systems. Age, gender and SAPW variables are represented in table 8.

	Male	Female	All
PWD	133.5 (2.34)	131.6 (2.45)	132.61 (1.68)
P20	40.98 (3.59)	31.49 (3.26)	36.48 (2.53)
P30	29.15 (3.15)	22.39 (2.62)	25.95 (2.12)
P40	13.68 (1.91)	11.17 (1.16)	12.49 (1.15)
P60	3.79 (0.36)	3.35 (0.40)	3.58 (0.26)
P80	1.56 (0.21)	1.47 (0.21)	1.52 (0.15)

Table 8. Mean values and standard error of the mean (SEM) are presented for 38 normal subjects.

There were no significant differences between male and female values although the trend was for higher energy in males. Correlation was sought between P wave variables and age, an inverse relationship was established between P80 and age (Spearman's correlation coefficient -0.36, p=0.026). The association was stronger with male subjects -0.51 p=0.021 for P80.

SAMPLE SIZE ESTIMATION

We can use the data to estimate sample size based upon the standard deviations determined in the study cohorts. The variables derived from frequency domain analysis do not follow a normal distribution, thus non-parametric tests are used and sample size estimation is more difficult.

The table below illustrates the sample sizes required to identify difference in P wave variables based upon 2 sample Students T test. It must be emphasised however, that only P wave duration follows a normal distribution.

	Standard Dev	Sample Size	Power	Difference
PWD	7.7	14	90	10 ms
P20	8.6	17	90	10 $\mu V^2.s$
P60	1.3	32	85	1 $\mu V^2.s$

Table 9. Sample sizes calculated for each variable with the power to detect the difference in value shown. PWD = P wave duration; P20 = energy contained within the frequency band 20 to 150Hz; P60 = energy contained within 60 to 150Hz. Samples sizes are calculated based on 2 sample T test at alpha value of 0.05.

CHAPTER FOUR

HIGH RESOLUTION ANALYSIS OF THE SURFACE P WAVE AS A MEASURE OF ATRIAL ELECTROPHYSIOLOGICAL SUBSTRATE

INTRODUCTION

On review of chapter 1, AF is associated with a number of well-defined electrophysiological abnormalities of the atria. These include a reduction in the refractory period, an increase in the dispersion of the refractory period and a reduction in conduction velocity of the atrial impulse[114, 158, 159]. These parameters combine to reduce the wavelength and to promote reentry. At the same time, investigation of the high-resolution signal averaged P wave has indicated that changes in quantitative measures of its duration and energy content are present in patients with paroxysmal AF and after cardioversion from persistent AF and can predict those individuals at risk of developing the arrhythmia after coronary bypass surgery[24, 36, 39, 47, 53-55, 160].

It is intriguing to speculate that there might be a relationship between parameters measured non-invasively from the surface P wave and indices of underlying atrial electrophysiology. This hypothesis is supported by indirect data concerning the effects of drug intervention on signal averaged P wave parameters and by serial evaluations of the signal averaged P wave after cardioversion from persistent AF[56, 160]. If direct evidence of a relationship between the signal averaged P wave and changes in underlying atrial electrophysiology were evident then this technique would afford a useful non invasive clinical method for the serial evaluation of the atria after therapeutic interventions as well as for the identification of subsets of patients with AF that may respond to different interventions or drugs.

The following study therefore sought to correlate variables measured by invasive electrophysiological testing with those measured simultaneously from the SAPW and to record the effects of an acute change in atrial electrophysiology on both invasive and non invasive measurements.

METHODS

PATIENT SELECTION:

Consecutive patients attending for diagnostic electrophysiological studies (EPS) without planned progression to radiofrequency ablation were screened. Patients were excluded if they had a history of ventricular dysrhythmia, ischaemic heart disease, antegrade conducting accessory pathway or a structurally abnormal

heart. Of 18 eligible patients 3 wished to proceed to radiofrequency ablation directly following diagnostic studies, 3 developed AF during the diagnostic study, in 2 the diagnostic study exceeded the time allowed for the research protocol and in 1 the research protocol was abandoned at the patient's request. The characteristics of the remaining 9 patients are presented in table 1.

Table 1. Demographic of patient population

Gender	Age	Diagnosis
Male	34	Left sided concealed accessory pathway
Female	30	Dual AV nodal physiology
Male	48	Left sided concealed accessory pathway
Female	30	Left atrial tachycardia
Female	42	Normal study
Female	45	Normal study
Male	44	Normal study
Male	28	Normal study
Female	20	Atrioventricular Nodal Reentrant Tachycardia

ELECTROPHYSIOLOGICAL STUDY:

Antiarrhythmic drugs were stopped at least 5 half-lives before EPS. None of the patients had received amiodarone. Diagnostic EPS was undertaken in a non-sedated post- absorptive state after written informed consent was obtained. The studies were not performed under conditions of autonomic blockade. Following local anaesthesia four catheters were passed via the right femoral vein under fluoroscopic guidance to the heart. Quadrapole diagnostic catheters (Cordis-Webster, Inc) were positioned in the high right atrium, right ventricular apex and His-bundle position. A deflectable decapole catheter (C. R. Bard, Inc.) was positioned in the coronary sinus. Following a standard diagnostic study the high right atrial catheter was removed and a 20-pole halo catheter (Irvine Biomedical, Inc. (H-21)) introduced to lie around the tricuspid valve annulus. Intra cardiac stimulation was achieved with a programmable stimulator (EPMedical Co.,Ltd. (EP3)) using a pulse width of 2ms and amplitude of twice the diastolic threshold.

MEASUREMENT OF CONDUCTION TIMES: Conduction times were measured from intra cardiac signals recorded during sinus rhythm or constant atrial pacing. The earliest signal on the Halo catheter during sinus rhythm was determined and the conduction time measured to the lateral right atrium (Halo poles 1 and 2), the septum (Halo poles 19 and 20) and the left atrium (from coronary sinus poles 9 and 10 to poles 1 and 2). Similar

measurements were made during constant atrial pacing from the Halo poles exhibiting the earliest signal during sinus rhythm.

MEASUREMENT OF AERP: During sinus rhythm AERP was measured at the lateral right atrium (Halo poles 1 and 2), the septum (Halo poles 19 and 20) and left atrium (coronary sinus poles 1 and 2). Sensed extra stimuli were introduced at an initial coupling interval of 160ms at an amplitude of twice the diastolic threshold. The coupling interval was increased initially in 5 ms and subsequently 2ms increments until atrial capture was accomplished. AERP for the site in question was the longest coupling interval of an atrial premature stimulus that failed to capture. Constant atrial pacing was performed as described above using a second stimulator and AERP measurements repeated. Each AERP measurement was performed three times and the average taken.

SIGNAL AVERAGED P WAVE RECORDING: This methodology is described in chapter 3. AERP and conduction time were measured during sinus rhythm and during constant atrial pacing at cycle lengths of 600, 500, and 400ms. Simultaneous SAPW recordings were made during sinus rhythm and during constant atrial pacing at 600ms. The experimental protocol was repeated after intravenous administration of flecainide acetate (3M Health Care) at a dose of 2mg per kg or 140mgs, whichever was the lesser value, at rate of 10mgs per minute.

STATISTICAL ANALYSIS

The Anderson-Darling normality test was used to inspect the data. Data with a normal distribution were analysed by a paired students t test. Data that were not normally distributed were analysed by the Wilcoxon signed rank test. Multiple variables were analysed using a one-way ANOVA for normal data and Kruskal-Wallis test for non-parametric data. A stepwise linear regression analysis was employed to examine for predictors of change in SAPW variables. A P value of <0.05 (2 tailed) was considered significant. As each parameter was tested with a single test the alpha level was not adjusted with Bonferroni correction.

RESULTS

CONDUCTION TIMES

Conduction times during sinus rhythm and during constant atrial pacing, before and after flecainide administration, are demonstrated in table 2. There was no significant change in conduction times with decreasing pacing cycle length. Flecainide induced a significant slowing of conduction during SR, at all pacing cycle lengths, and at all sites measured. No use dependence was observed.

	BEFORE FLECAINIDE			AFTER FLECAINIDE		
	Lateral	Septal	LA	Lateral	Septal	LA
SR	46.56 4.07	31.36 4.87	24.89 2.03	64.72* 6.01	37.83 6.06	31.06* 2.61
600	56.89 4.00	44.00 5.71	26.69 2.57	62.33* 4.86	51.78* 7.54	29.78* 3.02
500	54.39 4.43	44.11 6.15	26.06 2.54	63.67* 4.8	52.72* 7.77	28.72* 2.82
400	52.67 7.31	48.6 8.6	22.67 2.83	60.08* 8.79	57.5* 10.5	26.67* 3.63
P (column)	0.42	0.28	0.88	0.97	0.28	0.82

*Table 2. Conduction Times Before and After Flecainide Administration. Mean values for conduction times measured during sinus rhythm and at different pacing cycle lengths to lateral right atrium, Septal right atrium and left atrium (SEM is represented below conduction time in ms). The one-way Anova test was employed to identify significant row and column differences. *=p<0.05 compared to value before flecainide using Paired t-test.*

REFRACTORY PERIODS

At baseline normal rate-adaptation of refractory periods was observed at all three sites; however this only reached significance at the septum (table 3). After flecainide administration rate-adaptation was attenuated somewhat with relative lengthening of the refractory period at 500ms cycle length. This effect of flecainide was evident at all sites; adaptation returned at 400ms pacing cycle length. Flecainide administration resulted in a modest prolongation of AERP at all pacing cycle lengths at the lateral right atrium ($p < 0.05$). The data was examined for a change in dispersion of refractoriness following flecainide; no significant change was evident, the distribution of left atrium > right atrial lateral wall > right atrial septum persisted after flecainide.

	BEFORE FLECAINIDE				AFTER FLECAINIDE			
	Lateral	Septal	LA	p (row)	Lateral	Septal	LA	p (row)
SR	215.2 7.5	206.3 12.1	283.9 13.5	0.000	237.8 10.8	201.6 13.9	291.1 19.8	0.002
600	200.6 10.4	183.4 9.7	271.6 9.4	0.000	217.7* 9.9	185.1 12.6	273.4 13.3	0.000
500	190.2 11.1	171.5 7.7	262.0 10.4	0.000	218.6* 8.9	191.9 17.1	276.4 18.1	0.002
400	175.3 19.2	155.8 11.6	247.9 17.9	0.005	205.9* 15.6	155.1 11.7	255.7 19.7	0.002
P (column)	0.147	0.014	0.322		0.266	0.306	0.748	

*Table 3: Refractory Periods Before and After Administration Of Flecainide: Mean atrial effective refractory periods measured during sinus rhythm and at different pacing cycle lengths at lateral right atrium, septal right atrium and left atrium (SEM is represented below AERP in ms). The One-way Anova test was employed to identify significant row and column differences. *=p<0.05 compared to value before flecainide using paired T test.*

SIGNAL AVERAGED P WAVE

Values for P wave duration and energy were similar when measured during sinus rhythm and during constant atrial pacing at 600ms cycle length. During sinus rhythm flecainide induced significant lengthening of P wave duration and a significant fall in P wave energy (see figure 1). Similar findings were evident during constant atrial pacing (table 4).

CORRELATION

Both conduction times and refractory periods appeared to change after administration of flecainide. To determine if these changes were independent of each other a correlation matrix was constructed of change in conduction time and change in refractory period. Parameters measured at the left atrium appeared to correlate. A Pearson correlation coefficient of 0.755 (p=0.0001) was calculated for ERP and conduction time measured at the left atrium during pacing at a 600ms cycle length. However no significant correlation was observed during sinus rhythm. Modest correlation was observed at the lateral wall during pacing.

	Sinus Rhythm						High Right Atrial Pacing at 600ms					
	PWD	P20	P30	P40	P60	P80	PWD	P20	P30	P40	P60	P80
Pre	**137** 3.7	**38.0** 11.4	**23.4** 6.6	**11.2** 3.4	**4.0** 0.9	**1.9** 0.40	**142** 6.5	**44.1** 11.0	**26.0** 6.7	**10.3** 1.5	**4.1** 0.8	**1.9** 0.2
Post	**149** 3.8	**26.5** 5.7	**16.2** 4.1	**8.1** 1.0	**2.3** 0.5	**0.8** 0.2	**149** 10.2	**34.8** 6.2	**17.9** 4.4	**8.5** 1.6	**2.3** 0.4	**1.0** 0.2
Δ	12	11.5	7.2	3.1	1.7	1.1	7	9.3	8.1	1.8	1.8	0.9
P (column)	0.04	0.024	0.009	0.044	0.024	0.024	0.320	0.009	0.013	0.193	0.009	0.042

Table 4: P wave duration (milliseconds) and energies ($K\mu V^2.s$) during sinus rhythm and constant atrial pacing at a cycle length of 600ms. P20 represents energy contained within frequency band 20Hz to 150Hz; P30, between 30Hz and 150Hz etc. Significance between values measured before and after flecainide administration is assessed by the Wilcoxon rank sum test. Mean values are shown with SEM displayed below. Δ: absolute difference in values before and after flecainide.

	Sinus Rhythm			Pacing 600ms CL		
	ERP sep	ERP lat	ERP LA*	ERP sep*	ERP lat	ERP LA
CT sep*	0.039 (0.880)	-0.050 (0.845)	0.124 (0.625)	-0.084 (0.756)	-0.318 (0.199)	0.063 (0.803)
CT lat	-0.465 (0.060)	0.047 (0.852)	0.232 (0.355)	-0.205 (0.447)	0.499 (0.035)	-0.314 (0.204)
CT LA	0.037 (0.888)	0.446 (0.064)	0.325 (0.188)	0.303 (0.255)	0.121 (0.631)	0.755 (0.0001)

*Table :. Correlation matrix. During pacing significant correlation is found between left atrial conduction velocity and effective refractory period. *denotes skewed data. Skewed data compared Spearman's Rank Correlation, normally distributed data compared with Pearsons correlation.*

During sinus rhythm modest negative correlation was observed between P wave frequency bands and conduction times in the left atrium (for P80 $\rho = -0.54$ ($p = 0.02$), P60 $\rho = -0.49$ ($p < 0.04$) and P20 $\rho = -0.47$($p=<0.05$)). PWD was positively correlated with conduction time in the left atrium ($\rho = 0.49$ ($p < 0.04$)).

Inverse correlation was observed between lateral wall refractory periods and high frequency P wave energy bands (for P80 $\rho = -0.55$ ($p < 0.02$)). During constant atrial pacing a similar pattern of correlation was observed between P wave variables and indices derived from the left atrium (for LA AERP and P80 $\rho = -0.51$ ($p < 0.03$)). During pacing no significant correlation with conduction times was observed.

DISCUSSION

In this study change in surface P wave parameters was examined in the context of atrial electrophysiologic parameters derived simultaneously. Significant change in P wave parameters during sinus and paced rhythms in response to flecainide were demonstrated. During both rhythms flecainide administration resulted in a prolongation of filtered P wave duration and a fall in measured P wave energy. Simultaneous invasive observations demonstrated the expected slowing of atrial conduction times at all sites measured and a modest prolongation of AERP observed at the lateral wall of right atrium. Direct correlation sought between P wave variables and the electrophysiological changes induced by flecainide raised the possibility of:

1) a positive correlation between conduction times and filtered P wave duration,

2) a negative correlation between right lateral wall effective refractory period and high frequency energy content and,

3) a negative correlation between low frequency energy content and conduction times.

Although the above correlation is speculative it is generally accepted that the surface electrogram can in some way reflect the electrophysiologic properties of the myocardium[161]. This ability has been utilized in the examination of ventricular late potentials; small amplitude, high frequency signals located at the terminal portion of the QRS complex[162]. Low frequency components of the filtered electrogram have been linked to conduction velocity in the atrium and ventricle[160, 163, 164]. A number of studies demonstrate high frequency components of the electrogram are increased with fractionation within the myocardium[17, 161, 165]; however it does not follow that it is necessary to have fractionation to produce high frequency components in surface potentials. Smith et al elegantly demonstrated the presence of relative high frequency content of signal averaged ECG waveforms in the healthy myocardium of patients with the Wolff-Parkinson-White syndrome[166]. In addition they demonstrated relatively more high frequency components in the WPW patients compared to a control group with ventricular dysrhythmia. The authors point to complexities in the activation sequence to explain their findings, suggesting that high frequency content reflects the amount of time that multiple complex wavefronts are present.

Thus, conduction velocity may be reflected in low frequency signals, complexity of activation sequences reflected in high frequency signals. Previous studies examining the frequency spectra of the signal averaged P wave in a population of patients with paroxysmal atrial fibrillation have demonstrated marked differences in

the high frequency components of the P wave when compared with controls with normal atria[11, 46]. Sotalol, a drug known to effect action potential duration (APD) but not conduction velocity, resulted in a relative decrease in high frequency energy components of the SAPW without change in low frequency energy; this is consistent with the lack of effect on conduction velocity[160]. Increasing APD prolongs refractoriness raising the possibility that high frequency energy is a marker of refractoriness of the atria. Studies post cardioversion have linked high frequency energy to refractoriness but as conduction velocity is not known to change after cardioversion this parameter was not examined[55, 56].

The action of flecainide on sodium and potassium channels results in marked conduction slowing and APD prolongation respectively, this has been associated with increased refractoriness[167]; however the action of flecainide on AERP is thought to be minimal[168-170]. A significant and consistent change in conduction times with flecainide was observed in this study, therefore we would expect a change in low frequency energy (in contrast to the effects described with sotalol) and a possible change in the high frequency components consistent with the altered refractoriness of the atria observed at the lateral right atrium and the previous data derived from sotalol[160]. The results show change in all frequency bands during sinus rhythm and pacing which would support low frequency energy reflecting change in conduction velocity but the meaning of a change in high frequency content is less clear given the absence of change in refractoriness in the remainder of the atrium.

HOW MAY REFRACTORINESS BE REFLECTED IN HIGH FREQUENCY CONTENT?

The work of Smith et al have shown that high frequency signals are present in normal myocardium and postulate this reflects the complexity of signals in the ventricle[166]. One may expect to find such complexity in the atria with structures such as Bachmann's Bundle, the Crista Terminalis and the posterior triangle of Koch[171] presenting pivot points for activation wavefront collision and sources for such complex signals[110]. Prolongation of the APD and depression of conduction by flecainide has been shown to increase the conduction times around such pivot points[172, 173]; this would reduce the number of multiple complex wavefronts present in the atrium and in turn reduce the number of high frequency signals produced from these right atrial structures. In the atria of subjects with sinus node disease or PAF we would expect areas of heterogeneous conduction and distribution of refractoriness resulting in a greater degree of complexity of activation wavefronts and fractionated potentials, this in turn would increase the high frequency energy content of the SAPW. This has been observed in previous studies of this technique in paroxysmal atrial fibrillation[24, 46, 160].

STUDY LIMITATIONS

We used a drug that appeared to change both conduction times and AERP. Therefore we cannot be entirely sure as to the relative contributions of each to change in P wave derived parameters. Moreover the conduction time and ERP did correlate at the right atrial lateral wall suggesting confounding of intracardiac variables.

The population studied did not have atrial fibrillation; the effect on refractory period may be more pronounced in remodelled atria and more closely resemble the changes observed in clinical studies of the SAPW[56]. Further studies using pure class III agents appear warranted to confirm these observations.

The study cohort is small with multiple comparisons made raising the possibility of a type II error, but the observed data are consistent within the group and appear to correspond with findings from other studies[56].

CONCLUSIONS

In subjects undergoing diagnostic electrophysiological study, flecainide slowed atrial conduction time and prolonged AERP at the lateral right atrial wall. Differences in SAPW variables appeared to reflect these changes in atrial electrophysiology.

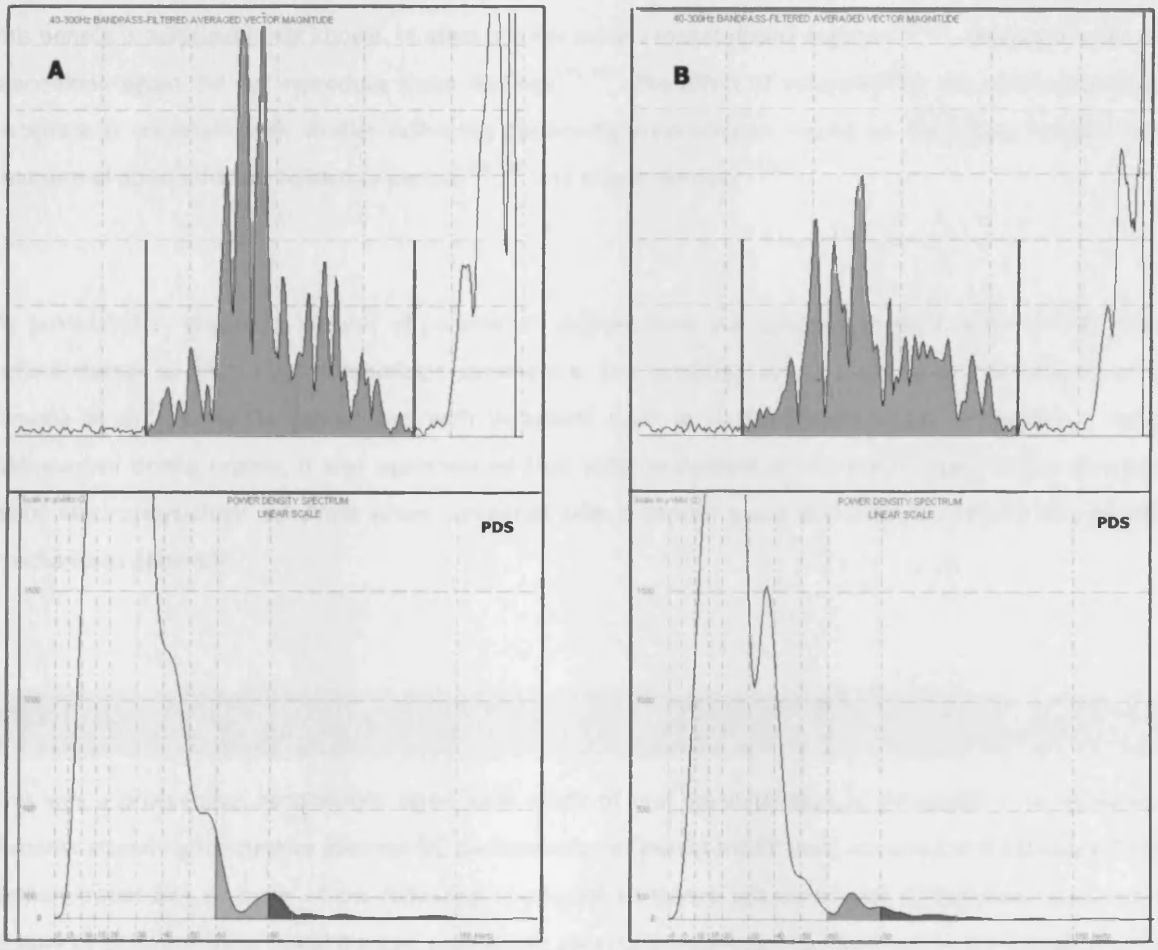


Figure 1: Power density spectrum (PDS) and filtered P wave before (A) and after (B) administration of flecainide. The shading serves to highlight the change in spectral distribution of energy content. See text for details.

CHAPTER FIVE

SIGNAL AVERAGED P WAVE REFLECTS CHANGE IN ATRIAL ELECTROPHYSIOLOGICAL SUBSTRATE AFFORDED BY VERAPAMIL FOLLOWING CARDIOVERSION FROM ATRIAL FIBRILLATION

INTRODUCTION

Pre-treatment with verapamil, an L-type calcium channel blocker, has been observed to attenuate the remodelling effects of atrial fibrillation (AF) on atrial electrophysiologic substrate[174]. An abbreviated dosing regimen around the time of electrical cardioversion has been shown to improve maintenance of sinus rhythm (SR) at 3 month follow-up when combined with propafenone[175] and amiodarone[176]. The mechanism by which this benefit is achieved is not known. In other studies using a longer dosing regimen[177-179], verapamil used as a standalone agent did not reproduce these findings[175, 176]. The effect of verapamil on the electrophysiologic substrate is uncertain with studies delivering apparently contradictory results on fibrillatory interval (as a measure of atrial effective refractory period)[150, 180] and trigger burden[177, 181].

As postulated in chapter 1 analysis of parameters derived from the signal averaged P wave (SAPW) might reflect change in atrial electrophysiologic parameters. The objective was to determine if the results of De Simone et al[175] could be reproduced with verapamil used as a stand alone agent employing a similar abbreviated dosing regime. It was hypothesised that serial evaluation of the SAPW might reflect change in atrial electrophysiologic substrate when compared with a control group and provide insights into possible mechanisms of benefit.

METHODS

This was a prospective, randomised, open label study of oral administration of verapamil in cardioversion. Patients attending for elective external DC cardioversion of persistent AF were screened and excluded if they demonstrated one or more of the following: moderate to severe left ventricular dysfunction; evidence or history of atrioventricular nodal disease; permanent pacemaker; amiodarone treatment in the last six months; concurrent treatment with β-blockers, calcium channel blockers or class 1 antiarrhythmic; history of sensitivity to verapamil.

The study design and protocol was approved by the Leicester Research Ethics Committee. After informed written consent patients were randomised to receive a prescription of verapamil 240mgs daily in three divided

doses or continue with usual medication. The drug was taken three days prior to DC cardioversion and seven days following. Patients not assigned verapamil formed the control group.

External cardioversion was performed with propofol general anaesthetic; successful cardioversion was defined as one or more sinus beats. Patients were monitored on the ward prior to discharge the same day. A resting 12-lead ECG at the end of one week provided the primary end point.

Signal averaged P wave recordings were made using the conventional system described in chapter 2 at one hour (baseline), 24hrs and one-week post cardioversion provided the patient remained in SR.

STATISTICAL ANALYSIS

Kruskal-Wallis was used to examine data over the week; Wilcoxon signed rank test compared changes within patients and Mann-Whitney U test was used to compare data between groups. Categorical variables were compared by the Chi square table.

RESULTS

Twenty eight consecutive patients were randomised, 11 received verapamil. Five patients were not included in the analysis. Two patients, one in each group, failed to cardiovert; one presented with sub-therapeutic INR; another spontaneously cardioverted to SR. One female patient in the verapamil cohort was excluded from the analysis of SAPW data because of signal noise during the recording. Demographic data for the patients included in the analysis are presented in table 1. The groups did not differ significantly.

	Control	Verapamil	P
Gender	2 of 14 female	4 of 9 female	0.108
Age	69.9±8.1	63.9±13.7	0.263
LA Size	4.49±0.6	4.39±0.5	0.65
AF Duration	11.2±12.9	9.13±3.94	0.616
SR at 1 week	6	8	0.027

Table 1. Demographics of both cohorts are presented. There were no significant differences with regard to gender, age, left atrial (LA) diameter or atrial fibrillation (AF) duration prior to cardioversion (months). There was a significant difference in maintenance of sinus rhythm (SR) at one week post cardioversion.

SINUS RHYTHM AT 1 WEEK

Eight of nine patients prescribed verapamil maintained SR at 1 week post cardioversion compared with 6 of 14 controls (p=0.027). Three patients in the control group reverted to AF within 24 hours that persisted at 1 week.

SIGNAL AVERAGED P WAVE ANALYSIS

Initial P wave duration (PWD) recorded was prolonged (when compared to normal values, page 61 and table 5) in both patients prescribed verapamil and controls (175.3±26ms for verapamil and 180.5±18ms for controls). PWD was not different in patients maintaining SR and patients reverting to AF by 1 week (177.2±23.7 vs. 180.6±17.7) (table 2 and 3).

	Verapamil					**Controls**				
	PWD	P20	P30	P60	P80	PWD	P20	P30	P60	P80
Imm	175.3 (9.3)	56.8 (13)	31.4† (6.0)	4.0 (0.8)	1.5 (0.3)	180.6 (4.9)	28.0 (3.3)	13.9 (1.8)	2.1 (0.3)	0.91 (0.1)
24hr	163.1 (4.7)	45.3 (10)	21.4 (2.8)	3.0 (0.4)	1.4 (0.3)	181.0 (6.7)	27.5 (4.5)	13.1 (1.6)	2.3 (0.3)	0.9 (0.1)
Week	161.7 (7.5)	31.6 (7.0)	21.0 (2.3)	2.9† (0.3)	1.4 (0.2)	162.8 (7.0)	25.4 (4.5)	12.4 (2.5)	1.7 (0.7)	0.9 (0.4)
P=	0.39	0.68	0.26	0.62	0.95	0.14	0.73	0.57	0.02	0.32

Table 2. Signal averaged P wave derived values are presented for verapamil treated patients and controls, immediately following cardioversion to sinus rhythm (Imm); at 24 hours after cardioversion (24hr), and at 1 week. Mean (standard error of the mean) are presented for P wave duration (PWD) in milliseconds and P wave energy in KμV².sec. P20 represents power between frequencies of 20 to 150Hz; P30 represents power between frequencies of 30 to 150Hz etc. Underlined values denote p=<0.03 for comparisons between verapamil and controls. † denotes p=<0.01.

SPECTRAL ANALYSIS

Analysis of frequencies between 20 and 150Hz (P20) delivered higher total energy for patients prescribed verapamil; 56.8(13.0) vs. 28.0(3.3) (mean (SEM) p=0.02) at baseline. Representative examples are shown in figure 1. For energy in the higher frequency range (60 to 150Hz) the values remained higher with verapamil use; 4.0(0.8) vs. 2.1(0.3) (p=0.03). Table 2 documents total energy values for ascending frequencies. The higher energy with verapamil persisted at 24 hours and one week post cardioversion.

	Sinus Rhythm				
	PWD	P20	P30	P60	P80
Imm	177.2 (6.6)	45.4 (9.0)	24.2 (4.7)	3.2 (0.6)	1.3 (0.2)
24hr	169.8 (5.1)	36.1 (7.5)	17.0 (2.4)	2.6 (0.4)	1.2 (0.2)
1week	162.2 (5.0)	34.1 (4.7)	17.0 (2.0)	2.4 (0.4)	1.13 (0.2)
P=	0.007	0.025	0.028	0.084	0.290

Table 3. Signal averaged P wave variables from the three recordings in patients remaining in sinus rhythm at 1 week (13 patients, 7 prescribed verapamil).

MAINTENANCE OF SINUS RHYTHM

Patients remaining in SR at 1 week had a non-significant trend toward higher energies in all energy bands than patients reverting to AF regardless of verapamil use; 45.4(9.0) vs. 34.1(4.7) at baseline. PWD was observed to reduce significantly over the week from 177.2 (6.6)ms to 162.2 (5.0)ms at 1 week (p=0.007) (table 3). Spectral energy also fell in the cohort remaining in SR at 1 week (table 3). Reversion to AF at 24 hours occurred in 3 patients. These individuals had substantially and significantly lower energy on spectral analysis compared with patients demonstrating SR at 1 week (table 4). Univariate analysis identified only verapamil use to be associated with maintenance of SR (p=0.027).

Table 4: Immediate recordings grouped according to maintenance of SR. N= number of patients. The first row maintained SR at 1 week, the second row were in SR at 24 hours but AF at 1 week, and the last row returned to AF at 24 hours. P value for comparison between row 1 and row 3. No statistical significance between row 1 and row 2.

			Immediate				
Row	N=		PWD	P20	P30	P60	P80
1	14	SR 1 week	177.2 (6.6)	45.4 (9.0)	24.2 (4.7)	3.3 (0.6)	1.3 (0.2)
2	9	AF 1 week	187.0 (6.6)	33.4 (4.4)	16.5 (2.2)	2.6 (0.3)	1.1 (0.2)
3	3	AF 24 hours	167.7 (2.7)	19.0 (3.4)	11.9 (2.4)	1.3 (0.2)	0.5 (0.1)
		P=	0.202	0.017	0.025	0.009	0.009

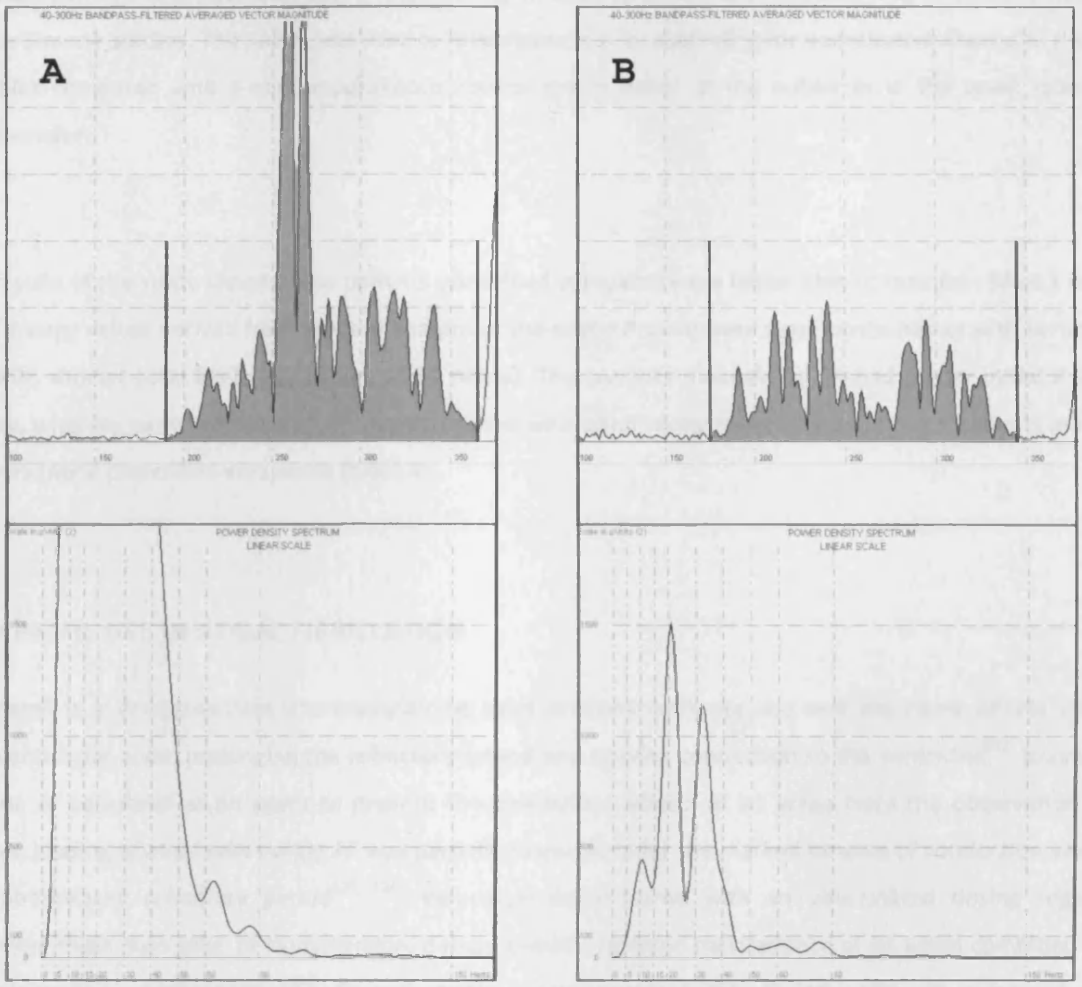


Figure 1. Representative data from patients prescribed verapamil (A) and remaining in sinus rhythm and controls reverting to atrial fibrillation. The patients are matched for age, gender and atrial fibrillation duration and have similar PWD (175ms (A) and 173ms (B)). The difference in vector magnitude is reflected in the linear scale power density spectrum displayed below the respective patient's filtered P wave.

DISCUSSION

The use of verapamil in atrial fibrillation, other than for rate control, is poorly understood with several studies postulating a benefit through the action of verapamil on intracellular calcium handling. However several clinical trials have failed to demonstrate any significant effect of the drug on long term maintenance of SR.

De Simone et al[175] combined an abbreviated dosing regimen of verapamil with conventional antiarrhythmics and demonstrated a reduction in early reinitiation of atrial fibrillation with addition of verapamil. It remains unclear whether verapamil alone confers benefit, and by what mechanism.

It is likely that the mechanism of benefit seen in the studies of De Simone were related to an effect on atrial electrophysiologic substrate with abbreviated dosing as most of the benefit was observed in the first week of the De Simone studies. The SAPW was used to investigate this by examining for quantitative change in P wave variables compared with a contemporaneous control group either at the outset or in the week following cardioversion.

The results of the study showed that patients prescribed verapamil were better able to maintain SR at 1 week. Total energy values derived from spectral analysis of the entire P wave were significantly higher with verapamil use with shorter total PWD (significant at 24 hours). The patients maintaining SR had higher initial P wave energy, whereas early reversion to AF was associated with significantly lower energy in the 3 patients in AF at 24hours (none prescribed verapamil) (table 4).

VERAPAMIL USE IN ATRIAL FIBRILLATION

Verapamil is a cardioselective phenylalkylamine used predominantly for the well described effects on the atrioventricular node, prolonging the refractory period and slowing conduction to the ventricles[182]. Interest in the use of verapamil as an agent to prevent the deleterious effects of AF arose from the observation that calcium loading of atrial cells during AF was partially responsible for the marked slowing of conduction velocity and abbreviated refractory period[123, 124]. Verapamil administered with an abbreviated dosing regimen, beginning three days prior to cardioversion, demonstrated improved maintenance of SR when combined with propafenone[175] or amiodarone[176]. Several studies have examined the clinical utility of verapamil as a standalone agent in prevention of AF recurrences[177-179]. All of the studies used a longer dosing schedule to that of De Simone and none found a sustained improvement over the period of follow-up (1 to 3 months); however even with pre-treatment, the beneficial effects of verapamil are short lived and are absent by 1 week[183]. Thus timing of verapamil dosing may be important and this study elected to reproduce the abbreviated dosing outlined by De Simone.

SIGNAL AVERAGED P WAVE CHANGE WITH VERAPAMIL

Evidence of reverse remodelling was appreciated by a reduction in PWD over the week following cardioversion (table 3 and figure 2). This observation has been made in other studies[57, 111, 133] and reverse remodelling, reflected by shortening of PWD and a fall in energies, has previously correlated with freedom from atrial fibrillation[55]. The time course of these observations is consistent with previous studies of reverse remodelling after restoration of sinus rhythm[57, 133].

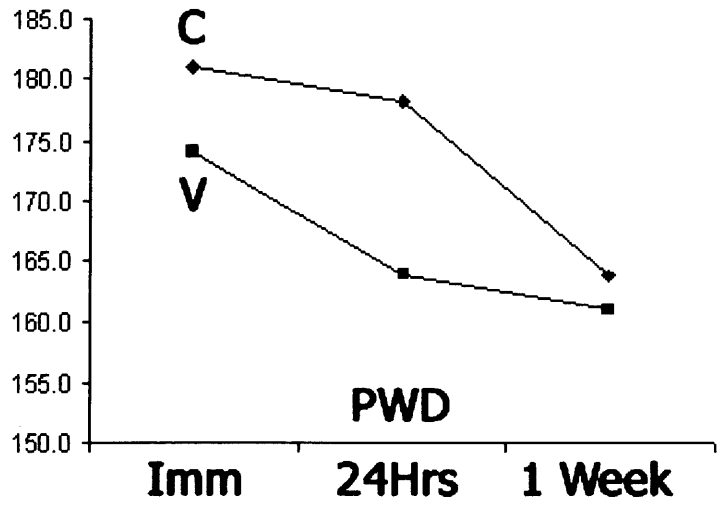


Figure 2. Data presented in table 3 presented according to verapamil use. Mean P wave duration is plotted for the same patients. See text for further discussion.

The high P wave energies associated with clinical benefit appeared at odds with the previous work on P wave energy considered in Chapter 1. Moreover energy appeared to fall in both groups over the week after cardioversion bringing the P wave parameters back into a range believed to be associated with health and away from values previously considered to be associated with atrial arrhythmia.

If the P wave changes of higher energy are considered to be unrelated to the clinical effect of verapamil then either the benefit outweighed the detrimental effect on the P wave or the effect was via another mechanism not examined. Such a mechanism may be reduction in trigger burden as suggested by some[181] or related to conduction velocity.

Experimental evidence in dogs has shown verapamil prevented conduction velocity changes after rapid atrial pacing compared with controls[184]. The sodium channel is the major contributor to the action potential upstroke and amplitude[89] (chapter 1, figure 5; page 30). Experiments have established the relationship between the maximum rate of rise of the action potential and conduction velocity squared[185]. Intracellular calcium overload from rapid depolarisation during AF reduces sodium channel expression and density, slowing conduction velocity, a manifestation of atrial remodelling[186]. This can be appreciated by prolongation of the P wave[47, 111] and is prevented by pre-treatment with verapamil in some experimental studies[174, 187]. The observed higher energy and short PWD with verapamil might have reflected preservation of atrial conduction velocity by intracellular calcium unloading and a restoration of sodium channel function. Should this be the case we might expect that the SAPW variables obtained in the verapamil cohort to be similar to age/ sex matched controls whereas the values derived from the patients not prescribed verapamil would demonstrate lower energy and longer P waves.

Although the cohorts are not age matched the table below does appear to support this line of reasoning with little difference in energy values in patients prescribed verapamil compared with gender matched controls. PWD was significantly longer in the patients compared with healthy controls. The subsequent fall in energies and shortening of P wave duration should be considered separately and were likely due to a complex interplay of factors consisting reverse remodelling such as lengthening of refractory period and further reductions in atrial conduction time and electromechanical function.

	Verapamil Patients (9)					**Control Patients (14)**				
	PWD	P20	P30	P60	P80	PWD	P20	P30	P60	P80
PT	175.3 (9.3)	56.8 (13)	31.4 (6.0)	4.0 (0.8)	1.5 (0.3)	180.6 (4.9)	28.0 (3.3)	13.9 (1.8)	2.1 (0.3)	0.91 (0.1)
HC	134.8 (3.7)	36.1 (1.7)	21.6 (1.8)	3.9 (0.6)	1.8 (0.4)	133.3 (2.9)	37.8 (4.2)	28.2 (3.3)	3.8 (0.5)	1.6 (0.2)
P=	0.003	0.27	0.31	0.79	0.46	0.000	0.07	0.001	0.01	0.06

Table 5. Baseline P wave variables derived from patients (PT) are compared with gender matched healthy controls (HC). Healthy controls were significantly younger 39±11 years vs. 69.9±8 (p=0.0001) for control patients and 45.6±15 years vs. 63.4±14.6 (p=0.032) for verapamil treated patients.

LIMITATIONS

The anaesthetic agents and cardioversion may have altered autonomic tone at the baseline recording but the P wave changes observed persisted through all three recordings and thus are not likely confounded by short term change in autonomic tone.

Episodes of asymptomatic atrial fibrillation may have occurred in the group with SR at 1 week and may confound the serial analysis for reverse remodelling; however it would be unusual for previously persistent patients to become paroxysmal after cardioversion.

The number of patients included was small and representative of a pilot study. Nonetheless, this was a hypothesis driven, mechanistic study. The results are intriguing and hypothesis generating but cannot support the use of verapamil particularly in the light if larger trials with longer follow-up suggesting no benefit[179, 188]. Further trials are required using the same abbreviated dosing regimen.

AF recurrence and four separate P wave parameters were measured as outcomes and given the small numbers the results are vulnerable to type 1 error.

CONCLUSIONS

An acute dosing regimen of verapamil 240mg daily in divided doses, for 3 days prior to cardioversion and 1 week after, reduces risk of AF recurrence. Frequency domain analysis of the signal averaged P wave shows an increase in P wave total energy afforded by verapamil when compared with controls over the week following cardioversion. Reverse remodelling can be appreciated from serial analysis of the SAPW in those patients remaining in SR at 1 week.

Verapamil is known to affect atrial electrophysiologic substrate in AF and a clear clinical benefit was observed supporting an action on the atrium in this cohort. The SAPW appeared to reflect this benefit in atrial substrate afforded by verapamil; however the mechanism can only be speculated upon and requires further investigation.

CHAPTER SIX

ATRIAL SUBSTRATE CHANGE AFTER WIDE AREA CIRCUMFERENTIAL ABLATION (WACA): OBSERVATIONS FROM HIGH RESOLUTION ELECTROCARDIOGRAPHIC RECORDINGS

INTRODUCTION

Catheter ablation procedures for atrial fibrillation (AF) increasingly encompass more atrial tissue with or without electrical isolation of the pulmonary veins from the body of the left atrium[79, 189]. Procedural efficacy is arguably better with wide area circumferential ablation of the pulmonary veins (WACA) compared to a segmental ostial approach (PVI)[190]. Since electrical isolation of the pulmonary veins is rarely the endpoint of a WACA procedure the perceived benefit is from the loosely defined concept of 'substrate modification'[18]. Substrate modification appears to represent a reduction in excitable, possibly fractionated atrial tissue, slowed conduction into ablation circles (figure 1) and autonomic effects from ablation of ganglionated plexi[118]. If this hypothesis were true WACA should result in substrate modification independent of electrical isolation of the pulmonary veins. Moreover this effect may be separate to the neurally mediated effects of ablation[191]. Given the loose definition of substrate modification in this context there is no method described to measure any such change in atrial substrate other than HRV to assess the neurally mediated substrate change[191].

The objective of this study was to examine the signal averaged P wave (SAPW) after AF ablation and determine if atrial substrate change could be reflected in the P wave. The concepts outlined above were also investigated prospectively by comparing PVI and WACA and determining the relative contribution of vagal denervation to substrate change as might be reflected in the SAPW.

METHODS

The protocol was reviewed and passed by the University of Western Ontario Research Ethics Board for Health Sciences Research involving Human Subjects and the South Birmingham Research Ethics Committee. Written and verbal informed consent was obtained before all procedures. Patients undergoing radiofrequency ablation (RF) by either WACA or PVI for AF were invited to participate. The study group was not randomised and comprised consecutive patients attending for left atrial procedures described below. However the cohorts themselves were not consecutive and procedures were performed at different institutions. The strategy for segmental pulmonary vein isolation (PVI) and wide area circumferential pulmonary vein ablation (WACA) are outlined below. SAPW methodology is covered in chapter 2.

HEART RATE VARIABILITY

The use of heart rate variability (HRV) to assess change in autonomic tone is well established. Heart rate change is mediated by autonomic nervous system via efferent vagal and sympathetic nerve traffic. At rest vagal tone predominates and is well reflected in high frequency cyclical fluctuations derived from HRV analysis[192]. Time domain analysis provides a measure of change in RR intervals and is usually expressed as a standard deviation (SD) or the root mean square of the standard deviations (RMSSD). Fast Fourier transform is used to quantify cyclical fluctuations of RR intervals. The total and ultra-low frequencies are best derived from 24 hour recordings; low frequency and high frequency measures are commonly derived from 5 minute recordings in controlled conditions[192]. The 10 minute high resolution recordings obtained for SAPW analysis were used to derive the HRV parameters in controlled conditions with the patients resting supine the morning of the procedure and a similar time the morning after the procedure, approximately 24 hours later. Standard definitions were used for frequency bands and the results were expressed as a log normal value[193].

PULMONARY VEIN ISOLATION

Segmental pulmonary vein isolation was performed as previously described[100, 101]. Pulmonary vein angiograms were obtained before an appropriately sized multipole catheter (LASSO, Biosense Webster, Diamond Bar, California) was introduced to the left atrium together with an ablation catheter (Cool-tip, Biosense Webster, Diamond Bar, California). Ablation was performed during coronary sinus pacing or sinus rhythm after external cardioversion if necessary. No antiarrhythmics were used to facilitate sinus rhythm. Ablation was delivered just proximal to the pulmonary vein ostia until pulmonary vein potentials were absent from the LASSO catheter. No additional ablation lines were drawn and a cavotricuspid ablation line was performed only if clinical evidence of typical atrial flutter existed.

WIDE AREA CIRCUMFERENTIAL PULMONARY VEIN ABLATION

The CARTO electroanatomic mapping system (Biosense Webster, Diamond Bar, California) was used in all procedures. Linear ablation was performed with an 8mm ablation catheter (power 50 - 60 watts and temperature to 55 degrees). Impedance and oesophageal temperature was monitored throughout each RF application[194]. RF was delivered at discrete sites based on electrograms and/or electroanatomic maps; energy was continued for 20 seconds or 30 seconds if the amplitude of the ablation catheter electrogram had failed to diminish by 50% or more. Absence of inducible atrial fibrillation despite aggressive atrial burst pacing and voltage reduction within the ablation circles was considered a satisfactory endpoint. The lesion set is shown in figure 1. Wide area ablation was performed around left and right common ostia with a line across the roof of the left atrium created. Mitral isthmus line was not routinely performed. Ablation of the cavotricuspid isthmus resulting in bidirectional block was routinely performed[195].

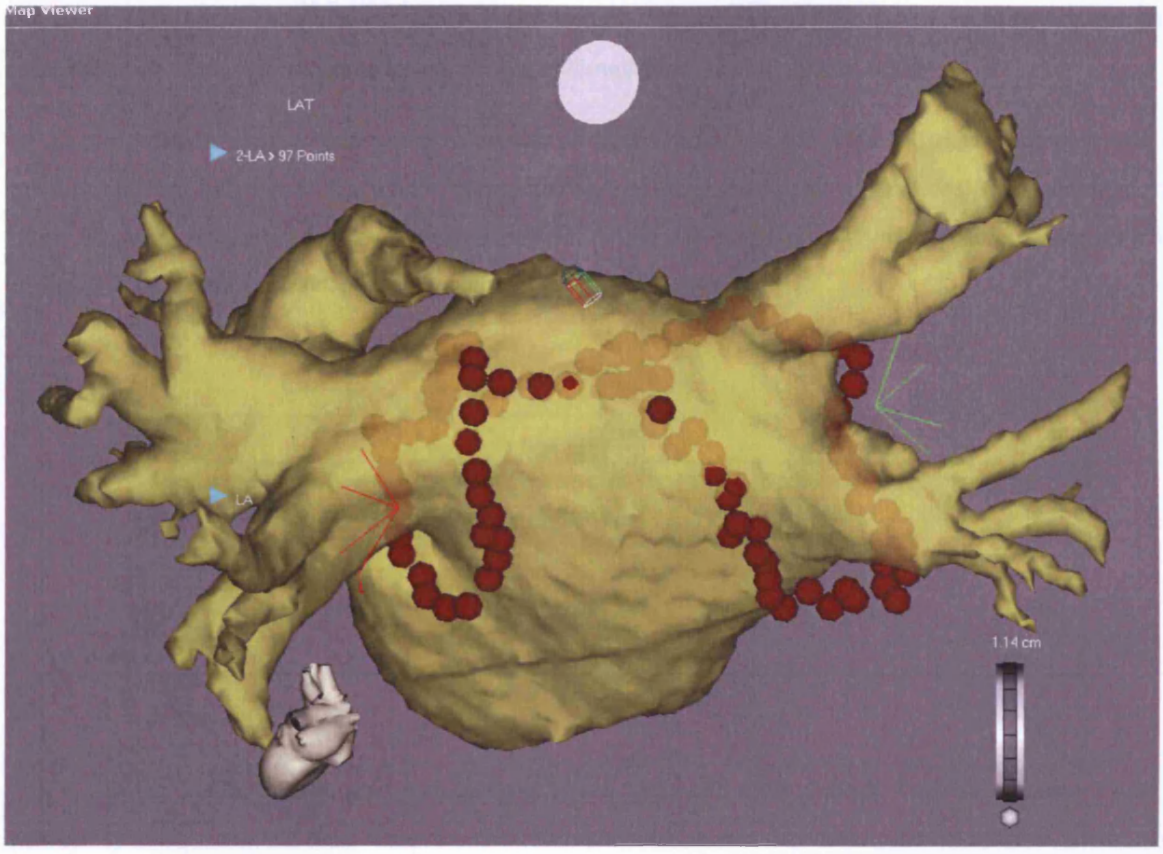


Figure 1. 64 slice CT registered to an electroanatomic map (CARTO). A lesion arrangement is shown with ablation lines circling the right and left pulmonary veins separately. A roof line joins both circles. The shaded area within the circles represents low voltage tissue on completion of the ablation lines.

STATISTICAL ANALYSIS

Data was inspected for normality using an Anderson- Darling test. Within patient data was analysed using paired students t-test or Wilcoxon signed rank. Students T test or Mann-Whitney was used for unpaired data. Categorical variables were analysed using Chi-Square tests. Two- tailed P value <0.05 was considered significant.

RESULTS

DEMOGRAPHICS

Forty patients were recruited (20 WACA and 20 PVI) with follow up over 6 months. Procedural endpoints were accomplished in all patients. There were no complications recorded in either group. The characteristics of patients grouped by procedure are presented in table 1. There were 15 male in the WACA group and 10 in the

PVI (p=0.146). The mean age in the WACA group was 53.7±9.44 years and 52.9±11.2 years in the PVI group (p=0.796). Left atrial size was comparable, 39±8.3 millimetres vs. 42±0.4 millimetres (p=0.64).

Of the 20 patients in the WACA group, 4 presented in persistent AF and thus a P wave recording was not possible and data was lost on one patient after ablation and one patient prior to ablation, leaving paired data in 14 of 20. Atrial fibrillation was present in 1 patient in the PVI group prior to the procedure and data was missing on 7 patients after ablation, thus paired data is available on 13 of 20.

	PVI [20]	WACA [15]	P=
Procedure Duration time (minutes)	215 (14.6)	340.9 (27.6)	0.014
Procedure Ablation time (seconds)	1942.5 (303.4)*	2416 (623)	<0.001

*Table 1. Mean (standard deviation) for total procedure times and total ablation times in seconds. * only the number of ablation lesions were recorded, therefore each lesion was assumed to be 60 seconds. Data from 5 patients in the WACA cohort was not recorded. Fluoroscopy times were not available for the PVI cohort.*

HEART RATE AND HEART RATE VARIABILITY

Table 2 summarises the data derived from HRV analysis. Mean heart rate rose in both groups combined with a fall in time domain and frequency domain HRV variables. Change in both the high and low frequencies after PVI and WACA were observed without significant change in the HF/LF ratio.

SIGNAL AVERAGED P WAVE VARIABLES

SAPW VARIABLES AFTER ABLATION FOR ATRIAL FIBRILLATION ACCORDING TO TECHNIQUE

Table 3 summarises data derived from analysis of the SAPW. Baseline data was comparable. P wave power was higher in the group presenting for PVI (significant for 30-150Hz only). P wave duration (PWD) prolonged significantly after WACA but not PVI. WACA was associated with a fall in voltage contained in the root mean square of the terminal 30 milliseconds (RMS) and a marked reduction in amplitude of the P wave reflected in energy values for all frequencies considered, depicted in figure 2. P wave duration, RMS and energy did not change after PVI.

	WACA [14]				Segmental PVI [13]			
	Pre AF ablation	Post AF ablation	Δ	P=	Pre AF ablation	Post AF ablation	Δ	P=
Heart Rate	61.4 (2.6)	73.5 (2.4)	12.1	0.001	69.5 (2.5)	75.1 (4.3)	5.6	0.072
SD	42.6 (6.1)	20.3 (2.1)	26.3	0.003	43.2 (6.7)	28.2 (4.4)	15.0	0.072
LF Ln(P)	5.7 (0.4)	3.6 (0.4)	2.1	0.001	5.4 (0.3)	4.3 (0.3)	1.1	0.026
HF Ln(P)	4.6 (0.4)	3.4 (0.3)	1.2	0.024	4.4 (0.4)	3.0 (0.4)	1.4	0.018
HF/LF†	4.5 (1.2)	3.0 (0.9)	1.5	0.093	4.6 (1.1)	5.4 (1.2)	0.8	0.460

Table 2. Heart rate variability derived values are presented for wide area circumferential ablation (WACA) and pulmonary vein isolation (PVI), before and after ablation. []: number of patients analysed. HR: heart rate; SD: standard deviation of the RR intervals. LF Ln(P): Napierian Log of low frequency; HF Ln(P): Napierian Log of high frequency; LF/HF: ratio of low to high frequencies. Note significant increase in HR after ablation with falls observed in both HF and LF for PVI and WACA without change in ratio. Data presented as mean (standard error of the mean). Δ: change in value between recordings.

PROCEDURAL OUTCOMES

Data is available on outcomes at a median of 6 months in the WACA group (range 1 to 7 months) and at 6 months in the PVI group. For WACA, 4 of 20 patients had documented recurrence of AF; 1 controlled with medication, 3 had a repeat procedure. Two further patients presented with an atypical atrial flutter presumed left atrial in origin. One persisted at 6 months and was listed for repeat ablation which was successful. Of the remainder follow-up at 6 months documented sinus rhythm in all 14 patients. For PVI, 13 of 20 patients had no recurrence of AF at 6 months (1 patient continued antiarrhythmics), 5 further patients remain free of arrhythmia after a repeat procedure. Atrial flutter was not seen in this cohort. Two patients are lost to follow-up and outcome is unknown at 6 months.

PREDICTORS OF RESPONSE

No candidate variables were identified in the PVI group. In the WACA group univariate variables associated with an adverse outcome were age, presence of AF pre procedure and heart rate post procedure (table 4). Binary logistic regression did not identify an independent predictor.

	WACA [14]				Segmental PVI [13]			
	Pre AF ablation	Post AF ablation	Δ	P=	Pre AF ablation	Post AF ablation	Δ	P=
PWD	149 (4.6)	160 (5.9)	11	0.003	143 (3.3)	140 (3.2)	3	0.97
P20	34.2 (5.2)	28.3 (3.9)	5.9	0.020	52.0 (7.1)	48.9 (7.1)	3.1	0.54
P30	20.4 (3.6)	13.7 (2.4)	6.7	0.001	29.8 (3.6)	28.4 (4.7)	1.4	0.67
P40	9.6 (1.8)	7.0 (0.8)	2.6	0.001	13.3 (2.0)	11.7 (2.1)	1.6	0.91
P60	2.4 (0.4)	1.7 (0.2)	0.7	0.05	3.5 (0.7)	3.7 (0.8)	0.2	0.33
P80	1.1 (0.2)	0.8 (0.1)	0.3	0.79	1.5 (0.2)	1.4 (0.3)	0.1	0.97
RMS	4.4 (0.4)	2.8 (0.4)	1.6	0.001	5.6 (0.7)	5.4 (0.6)	0.2	0.94

Table 3. Signal averaged P wave derived values are presented for wide area circumferential ablation (WACA) and pulmonary vein isolation (PVI), before and 24 hours after ablation. []: number of patients analysed. Mean (standard error of the mean) are presented for P wave duration (PWD) in milliseconds and root mean square for the terminal 30 milliseconds (RMS) in μV. Median (standard error of the mean) are presented for P wave energy in KμV².s. P30 represents energy between frequencies of 30 to 150Hz; P60 represents energy between frequencies of 60 to 150Hz etc. Δ: change in value between recordings.

	Age	HR	PWD	P30	HF	AF	RMS
Sinus Rhythm (13)	49.2 (2.6)	76.7 (2.7)	155.1 (2.4)	18.25 (0.9)	3.30 (0.4)	1	3.0 (0.5)
Recurrence (7)	60.9 (2.1)	65.03 (3.3)	173.4 (12.6)	13.77 (1.4)	3.5 (0.6)	3	2.7 (0.8)
P=	0.003	0.019	0.179	0.267	0.710	0.061	0.58

*Table 4. Candidate predictors of recurrence in the WACA group. High resolution variables recorded **after** ablation. Age in years; HR = heart rate (bpm); HF = Log normal of high frequency power heart rate variability;*

SAPW variables as previously defined; AF refers to number of patients with AF on day of procedure. Age, heart rate and AF pre-procedure were univariate associations with outcome.

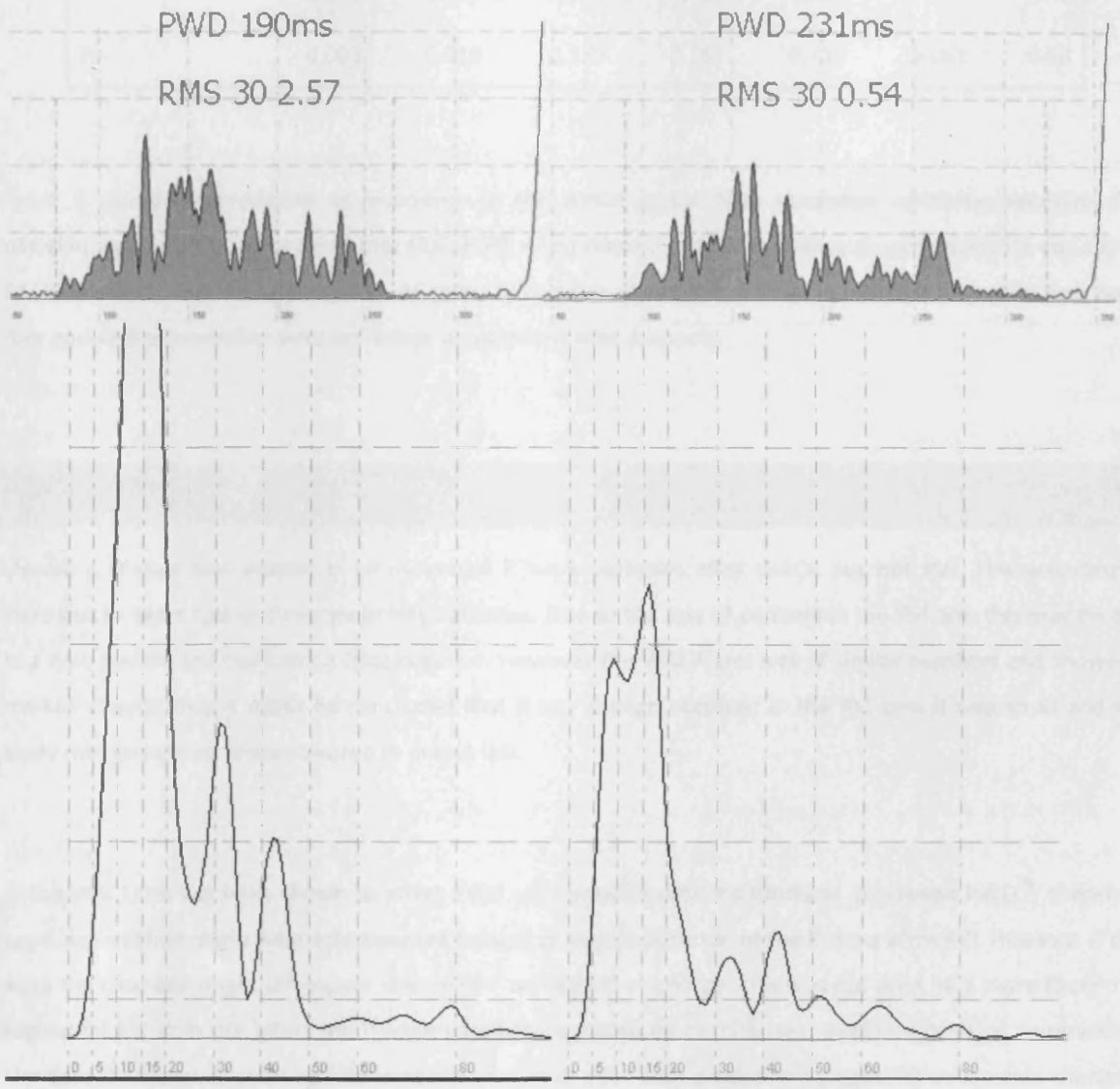


Figure 2.

Representative sample of time domain and frequency domain results before and after wide area circumferential ablation as shown in figure 1. The filtered P wave is shown at the top of the figure before (left) and after (right) WACA. P wave duration increases and overall magnitude decreases after ablation. This is better appreciated in the frequency domain (beneath). The power within the spectrum can be seen to be reduced after ablation. This is quantified into energy bands.

	Age	HR	PWD	P30	HF	AF	RMS
Sinus Rhythm (13)	49.2 (2.6)	76.7 (2.7)	155.1 (2.4)	18.25 (0.9)	3.30 (0.4)	1	3.0 (0.5)
Recurrence (7)	60.9 (2.1)	65.03 (3.3)	173.4 (12.6)	13.77 (1.4)	3.5 (0.6)	3	2.7 (0.8)
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*Table 4. Candidate predictors of recurrence in the WACA group. High resolution variables recorded **after** ablation. Age in years; HR = heart rate (bpm); HF = Log normal of high frequency power heart rate variability; SAPW variables as previously defined; AF refers to number of patients with AF on day of procedure. Age, heart rate and AF pre-procedure were univariate associations with outcome.*

DISCUSSION

Overall a change was evident in all measured P wave variables after WACA but not PVI. This was despite increases in heart rate and change in HRV variables. Due to the loss of patients in the PVI arm this may be due to a type II error and represent a false negative. However the WACA arm was of similar numbers and showed a marked change thus it might be concluded that if any change occurred in the PVI arm it was small and the study may have been underpowered to detect this.

Autonomic tone has been shown to affect PWD with parasympathetic blockade shortened PWD[29]; therefore vagal denervation might have compensated for any change in duration of the P wave after PVI. However if this were the case one might still expect change in P wave RMS or energy. This was not seen. It is more likely that segmental PVI does not affect the P wave parameters measured despite clear evidence of vagal denervation. The data is consistent with vagal denervation occurring after both procedures suggesting autonomic change is not responsible for the change observed in P wave parameters after WACA.

The changes after WACA are discussed in more detail below.

ATRIAL SUBSTRATE CHANGE

P WAVE DURATION

The prolongation of P wave duration after WACA might have reflected delay in conduction times across the atria. This could have been achieved by a number of mechanisms. First, the ablation lines described upon the atrium did not require complete lines of block and it is likely that delay was generated as electrical isolation

was not an end point in these procedures. Second, ablation at the right upper vein to create a roof line and complete the anatomic right circle might also interrupt conduction to the left atrium via Bachmann's bundle further prolonging P wave duration.

P WAVE ENERGY

Absolute P wave energy is reduced uniformly throughout the measured frequencies ranges (figure 2). This most likely reflects a reduction in depolarised tissue, as suggested by a reduction in amplitude of the P wave, meaning tissue contained within the ablation lines is now low voltage compared with the remainder of the atrium (illustrated in figure 1). However previous studies using frequency analysis have documented higher powers in patients with atrial fibrillation and this has been linked with recurrence of AF[22, 55] and fractionated electrograms in sinus rhythm[20, 160]. The frequencies examined have been thought to reflect fractionated electrograms and ablation lines are known to reduce fragmented electrograms found at the junction of the pulmonary veins which are felt to be proarrhythmic. A reduction in these fractionated high frequency electrograms might have also contributed to a reduction in energy, especially at higher frequencies.

NEURALLY BASED SUBSTRATE CHANGE

HEART RATE AND HRV

HRV variables have been shown to change after WACA procedures with a loss of vagal efferent tone and correlate with success[118]. The change observed in this study supports the effect upon vagal tone. The results also suggested a less pronounced effect with a segmental PVI approach (table 2) presumably due to ablation of vagal afferents situated at and around the pulmonary vein ostia[196].

Heart rate variability has been observed to change in a similar fashion after right sided ablations, notably slow pathway modification[197]. Interestingly left sided ablations for accessory pathways have not been associated with change in autonomic balance[198]. Most studies performed the HRV analysis immediately after ablation and in some the effects were absent by 24 hours while in other studies they persisted for up to 6 months[191]. The more marked effect with WACA compared with PVI supports the hypothesis that WACA is generating change in neurally mediated substrate and this is not simply a confounding variable, nevertheless, serial assessment and correlation with response should be made.

CLINICAL IMPLICATIONS

Of the variables that changed significantly after WACA, an increase in heart rate appeared most strongly associated with outcome. A greater prolongation of the P wave and less reduction in energy was associated with recurrence (table 4). The data invites speculation that increases in PWD may be proarrhythmic but the

numbers are too small to make a definitive interpretation. The following chapter further defines the WACA population and provides more insight into associations with recurrence.

LIMITATIONS

Although the recruitment was good the loss of data resulted in exclusion of some patients and thus the predictive analysis had small numbers and interpretation should be cautious and requires further study. Patients were not part of a randomised controlled trial and thus direct statistical comparison concerning the degree of changes was not made. The groups were non-consecutive cohorts with procedures performed at different centres, however patient characteristics were similar.

Direct anatomic correlates are inferred and but cannot be confirmed from this study. Evaluation of patients undergoing lasso guided WACA would make a better measure as discussed above.

CONCLUSIONS

Time and frequency domain parameters of the P wave change significantly after WACA procedures and provide a measure of atrial substrate change. The observed changes are independent of neurally mediated substrate change. The marked change in both atrial and neurally based substrate might explain the improved efficacy observed with WACA compared with PVI. Serial evaluation of patients with this measure should be done to establish if the change after WACA is sustained, dependent upon isolation and can be correlated with recovery of conduction into veins leading to symptomatic recurrence.

CHAPTER SEVEN

SIGNAL AVERAGED P WAVE (SAPW) DURATION CHANGE AFTER WIDE AREA CIRCUMFERENTIAL ABLATION (WACA) IS DEPENDENT UPON ELECTRICAL ISOLATION

INTRODUCTION

As discussed in chapter 6 WACA perhaps achieves better procedural success via substrate modification. However, it remains to be determined if a wide area substrate approach combined with electrical isolation of the pulmonary vein antra would improve outcomes further. The aim of this study was to determine if there were clinical or SAPW derived variables that would correlate with atrial substrate change and could be linked with success.

METHODS

These data were collected between January 2005 and June 2007 using the methodology described in chapter 6 and with ethics approval from the University of Western Ontario Research Ethics Board for Health Sciences Research involving Human Subjects and the Queen's University Research Ethics Board. Patients were followed for at least 12 months with an office appointment at 3 months. Recurrence was any arrhythmia persisting beyond a 3 month blanking period. Recurrence was defined as either atrial fibrillation (AF) or atrial flutter (considered iatrogenic left atrial flutter). Documentation was not necessary and the opinion of the arrhythmia physician was sufficient to report recurrence or success. Patients with recurrence but no documentation were considered AF recurrence. Success was defined as absence of symptoms and evidence of AF off medication.

WIDE AREA CIRCUMFERENTIAL ABLATION

This procedure has been described in chapter 6, page 82. Briefly, radiofrequency ablation was delivered to the left atrial endocardium to describe a circle of ablation around the common ostia of ipsilateral pulmonary veins (Figure 1, page 83). Electrical isolation was not an endpoint and no attempt to demonstrate electrical disconnection of the pulmonary veins during the procedure was made.

HYBRID

This procedure was similar to the WACA but after initial creation of the lines additional lesions were made to electrically isolate the pulmonary veins. Attempts were made to isolate at the antrum, i.e. at the WACA circle, but a segmental approach was employed within the lines if needed.

RESULTS

Data were collected on eighty three consecutive cases. The demographics associated with these patients and procedure variables are reported in table 1. Complete follow-up with outcome is known in 79 patients (mean follow-up of 10 months (3-24). Recurrence was observed after the first procedure in 25 patients (31.6%). Atrial Fibrillation was present in 12 and atypical atrial flutter in 13 patients.

Table 1. Cohort demographics

Age	54.3±9.7
Gender	13 female
Procedure Time	344.7 (36.75)
Ablation Time	2684 (1004)
Fluoroscopy time	56.6 (15.8)
Left atrial Size	42.0±9.0
Duration Of Atrial Fibrillation	76.3±58.1

ATRIAL SUBSTRATE CHANGE

Of 79 subjects a WACA approach was employed in 28 and a Hybrid approach in 55. In all 55 patients the endpoint of bidirectional block into the pulmonary veins was achieved. The site where the final applications were made to achieve block, antral or ostial, were not recorded in the study log.

SAPW CHANGE IN COHORT

Signal averaged P wave variables recorded before and 24 hours after ablation demonstrated no overall change in filtered P wave duration for the group but a fall in P wave energy was observed.

NEURALLY MEDIATED SUBSTRATE CHANGE

The ECG data derived from the 10 minute high resolution recordings was employed in heart rate variability analysis reflecting neurally mediated change.

Variable	Pre [64]	Post [71]	P=
PWD	153.4 (2.2)	153.9 (2.3)	0.63
P30	21.3 (1.5)	15.2 (1.0)	<0.001
P60	2.8 (0.2)	2.0 (0.1)	<0.001
P80	1.3 (0.1)	0.8 (0.1)	<0.001
RMS30	3.7 (0.2)	3.1(0.2)	0.008

Table 2. Signal averaged P wave variables before and after WACA. SAPW data were missing in 19 initial pre-procedure recordings and 12 post procedure recordings. Mean (standard error of the mean) are presented. PWD : P wave duration in milliseconds; RMS: root mean square for the terminal 30 milliseconds in μV and for P wave energy in. P20: power between frequencies of 20 to 150Hz in KμV².s; P30: 30 to 150Hz etc.

Variable	Pre	Post	P=
Heart rate	63.2 (1.7)	72.7 (1.7)	<0.001
RMSSD	31.5 (3.2)	22.0 (2.6)	0.005
SD	49.1 (4.4)	24.0 (2.5)	<0.001
LF Ln(P)	5.6 (0.2)	3.4 (0.2)	<0.001
HF Ln(P)	4.8 (0.2)	3.5 (0.2)	<0.001
Ratio	3.7 (0.6)	2.2 (0.4)	0.006

Table 3. Heart rate variability before and after WACA. Mean (standard error of the mean) are presented for all patients with paired data n=52. HR: heart rate; SD: standard deviation of the RR intervals. LF Ln(P): Napierian Log of low frequency; HF Ln(P): Napierian Log of high frequency; LF/HF: ratio of low to high frequencies. Paired data is missing in 31 patients, analysis based on remaining 52.

RECURRENCE

When the data is grouped according to recurrence of atrial arrhythmia, including atrial flutter, differences between the groups can be observed (table 4). The group with recurrence demonstrated a trend toward older age 56.8±8 years vs. 53.5±10 (p=0.153); had a longer PWD post procedure (PWD-P) 166.8±6.3 vs. 147.5±2.5 (p

<0.001) and had a lower RMS30 post procedure 2.4±0.4 vs. 3.4±0.4 (p=0.03). A PWD-P of 157ms had a sensitivity and specificity of 65% and 77% respectively for arrhythmia recurrence (PPV and NPV 54% and 84% respectively).

	SUCCESS (36 of 54)			RECURRENCE (16 of 25)		
Gender	9/54 female			4/25 female		0.941
LA	40.7±9			44.8±9		0.212
Age	53.5±10			56.8±8		0.153
Hybrid	40/54			11/25		0.009
Procedure time (mins)	345.4±56.5			331.8±21.8		0.258
Ablation time (secs)	2593±1170			2732±813		0.572
Fluoroscopy time	54.5 ±17.0			58.6±16.1		0.338
	Pre	Post	P=	Pre	Post	P=
PWD	150.8(2.5)	147.5(2.5)	0.133	161.0±5.6	166.8(6.3)†	0.169
P30	20.6 (2.0)	14.5 (1.5)	<0.001	23.0±3.1	15.2±2.1	0.001
P60	2.7±0.3	2.1±0.2	0.003	2.3±0.7	1.6±0.3	0.003
P80	1.3±0.2	0.9±0.1	0.006	1.3±0.2†	0.8±0.1	0.024
RMS30	3.8±0.3	3.4±0.4	0.157	3.4±0.4	2.4 (0.4)‡	0.009
HR	64.7±2.3	73.9±2.2	<0.001	60.3±1.9	70.9±2.6	0.001
RMSSD	33.9±4.2	21.9±3.3	0.018	24.9±4.9	22.8±5.0	0.761
SD	49.1±5.1	22.3±2.7	<0.001	41.8±6.1	23.3±3.4	0.002
LF Ln (P)	5.8±0.2	3.4±0.2	<0.001	5.2±0.4	3.4±0.5	<0.001
HF Ln(P)	4.9±0.2	3.6±0.2	<0.001	4.3±0.4	3.7±0.4	0.175
Ratio	3.5±0.7	2.4±0.6	0.150	4.2±1.2	2.0±0.6	0.124

Table 4. Cohort by recurrence. Paired data was available in 36 of 54 patients demonstrating clinical success and 16 of 25 with clinical recurrence. Values and definitions as for tables 1 and 2. No significant difference in the pre ablation values between responders and non-responders. In the post ablation values there was no significant difference in the heart rate variability measures however the filtered P wave duration was significantly longer in the patients demonstrating recurrence. This was also reflected in the terminal portion of the P wave as assessed by root mean square of the terminal 30ms (RMS30). †indicates p<0.001 for comparison of post ablation values. ‡indicates p<0.05 for post ablation values.

REGRESSION ANALYSIS FOR RECURRENCE

Analysis of the data between successful patients and those with recurrence identified univariate variables associated with success. Candidate variables included were post procedure PWD, WACA with or without isolation (Hybrid) and RMS 30. Although patient age was not significantly different it was included in the model as a potentially clinically significant variable. The model had the four variables. Fifteen patients were missing data for at least one of these variables so they were dropped from the modelling process, leaving a sample size of 67 for analysis.

	Beta	S.E.	Wald	df	Sig.	OR
Age	.072	.042	2.990	1	.084	1.075
WACA 0 Hybrid 1	-1.767	.715	6.105	1	.013	.171
PWD post	.062	.025	6.336	1	.012	1.064
RMS30 post	-.225	.234	.925	1	.336	.798
Constant	-13.143	5.246	6.276	1	.012	.000

Table 5. Univariate predictors entered into a multivariate regression model. See text for details. Wald: Wald statistic; Sig: statistical significance ; OR: Odds Ratio. Other definitions as in table 2 other than PWD pre (pre procedure) and PWD post (post procedure). RMS 30 was not significant when controlled for PWD post.

The final model was adjusted by a factor of 10 to demonstrate a clinically meaningful outcome (table 6). Age falls short of significance but is probably worth retaining in the model since it is exploratory due to the small sample size (only 67 included in the analysis) and might be clinically meaningful.

							95.0% C.I. for OR	
	B	S.E.	Wald	df	Sig.	OR	Lower	Upper
Age 10years	.674	.415	2.637	1	.104	1.962	.870	4.425
WACA 0 Hybrid 1	-1.699	.700	5.893	1	.015	.183	.046	.721
PWD Post 10msec	.693	.242	8.187	1	.004	2.000	1.244	3.214
Constant	-14.634	5.122	8.164	1	.004	.000		

Table 6. Multivariate logistic model as in table 4 but adjusted by a factor of 10. CI: confidence intervals.

MULTIVARIATE ANALYSIS RESULTS

The data suggest that the odds of having a recurrence almost double (OR 1.96 (0.87-4.4) for every 10 years of advanced age, although this did not reach statistical significance. Wide area circumferential ablation without isolation of the pulmonary veins was associated with fivefold increase in risk of recurrence of atrial arrhythmia (OR 5.5 (1.4-21.7)). An increase in 10ms for the post procedure PWD is associated with a twofold increase in the risk of recurrence (OR2.0 (1.2-3.2)).

HYBRID VS. WACA APPROACH

The preliminary results suggested that a WACA approach without isolation of the pulmonary veins was associated with a prolonged post procedure filtered P wave duration and recurrence of atrial fibrillation. These data were grouped according to the procedure performed, Hybrid including pulmonary vein disconnection or WACA alone (table 7).

DISCUSSION

This study was primarily concerned with examining the change in SAPW as a potential predictor of recurrence of atrial fibrillation and assessment of atrial substrate with regard to presence or absence of electrical isolation. Data from the previous study[199] had indicated that a longer P wave after ablation might be associated with an adverse outcome and the effect of electrical isolation on the duration of the post procedure P wave was speculated upon. During the recruitment and analysis of the study reported in this chapter 6, a decision was made to adopt a *hybrid* approach of AF ablation incorporating a wide area approach but including electrical disconnection of the pulmonary veins, as determined by a multipole circular catheter, as the endpoint of the procedure. This allowed a comparison of two consecutive cohorts, without isolation (WACA) and with electrical isolation (Hybrid). Ablation and procedure times were similar and the cohorts were otherwise well matched. The results of this comparison (table 7) appear to support the hypothesis proposed in chapter 6 that change in P wave duration may reflect electrical isolation of the pulmonary veins. Representative examples of P waves from the WACA and hybrid cohort are shown in figure 1.

Mean P wave duration shortened significantly with isolation and increased significantly when attempts at isolation were not included in the procedure (table 7). When the group was examined as a whole both post procedure P wave duration and a WACA approach without attempts at isolation were independently associated with recurrence of atrial arrhythmia. It is interesting to speculate that incomplete ablation leaving small gaps in the WACA lines might result in activation with delay into the pulmonary veins causing prolongation of atrial activation time reflected in the P wave duration[200]. Such incomplete lines might represent a substrate for re-entry and there is some evidence to support this. A recent paper from Beijing comparing isolation of the WACA circles at the ablation line or within the line at the pulmonary vein orifice (WACA + PVI)

demonstrated an increased incidence of AF and flutter with incomplete circles (21 of 50 (42%)) compared to a very low recurrence in the cohort with isolation at the WACA lines after 3 months (9 of 50 (18%) p=0.01)[201]. Two recent studies examining the P wave in this context identified that shortening of the P wave duration occurred in successful procedures[200, 202]. The paper by Okumura *et al*[200] demonstrates a correlation between P wave duration and atrial conduction time, citing the delayed activation into the left pulmonary veins as a major contributor to P wave duration.

	Hybrid [55]			**WACA [28]**		P=
Gender	46 male			22 male		0.321
LA	42.3±5.4			41.4±13.5		0.814
Age	55.5±9.9			52.6±9.4		0.202
Procedure time (mins)	343.8±38.1			346.9±34.8		0.783
Ablation time (secs)	2757±1108			2521±718		0.310
Fluoroscopy time	56.2±16.8			57.6±13.1		0.723
Recurrence	11/51*			14/28		0.009
	Pre	Post	P=	Pre	Post	P=
PWD	155.3(3.4)	148.6(3.3)*	<0.001	152.2(3.7)	161.3(4.7)	0.007
P30	22.1(2.1)	14.5(1.6)	<0.001	20.6(2.6)	14.6(1.8)	<0.001
P60	2.9(0.3)	2.0(0.2)	0.001	2.5(0.3)	2.0(0.2)	0.035
P80	1.4(0.2)	0.9(0.1)	0.001	1.1(0.2)	0.8(0.1)	0.086
RMS30	3.6(0.3)	3.3(0.4)	0.206	4.0(0.3)	2.8(0.4)	0.004
HR	63.9(2.5)	71.7(2.5)	<0.001	62.0(2.0)	74.1(2.3)	<0.001
RMSSD	35.3(4.4)	25.1(3.9)	0.075	25.7(4.7)	17.7(2.8)	0.132
SD	54.4(6.5)	27.7(3.8)*	<0.001	41.6(4.8)	18.8(2.2)	<0.001
LF Ln (P)	5.7(0.2)	3.4(0.3)	<0.001	5.6(0.3)	3.4(0.4)	<0.001
HF Ln(P)	5.0(0.2)	3.7(0.3)	0.002	4.5(0.3)	3.3(0.3)	0.002
Ratio	3.4(0.8)	2.0(0.5)	0.079	4.3(0.9)	2.5(0.8)	0.164

*Table 7: Data grouped according to procedure performed, Hybrid with WACA and electrical isolation or WACA alone. Abbreviations defined in table 1 and 2. *p=0.008 for T-test between Hybrid post and WACA post; *p=0.012 for SD; * follow up missing on 4 patients.*

It is curious that the Hybrid approach and PWD proved independent predictors; perhaps because some isolation occurred inadvertently in the WACA cohort and it is possible that not all the hybrids were isolated the next day when recording occurred.

With insights gained from this study it is perhaps surprising that shortening of PWD was not seen in the PVI cohort from the study in Chapter 6. This could well be because the group was too small to identify a significant difference but it perhaps has more to do with the approach. This was ostial segmental isolation, performed most often at the entrance to the tubular portion of the vein. This approach has been abandoned by most operators in favour of a more antral isolation technique because of the incidence of pulmonary vein stenosis with the former. Minimal atrial tissue was isolated in this approach and therefore we are less likely to observe an impact upon P wave duration.

CLINICAL IMPLICATIONS

Current data are suggesting recurrence is due to incomplete lines and there is momentum toward a hybrid approach of WACA but with electrical isolation of the encircled veins as an endpoint[203]. The recent paper from Liu et al supports the notion that procedural success and reduction in iatrogenic flutters can be achieved through electrical isolation at the WACA lines[201]. The hypothesis that a strategy of lines without isolation is proarrhythmic is implicit in the findings of this study and the one reported here.

Should the above hypothesis be true a prolonged PWD and might represent a marker of slowed conduction through gaps in the WACA lines and this proarrhythmic substrate would explain the independent association with recurrence observed. As the ablation procedures for AF evolve the utility of the SAPW as a non-invasive marker of recovery of conduction into previously isolated areas resulting in delayed activation on the surface P wave and terminal low voltages represents an intriguing area of further research.

LIMITATIONS

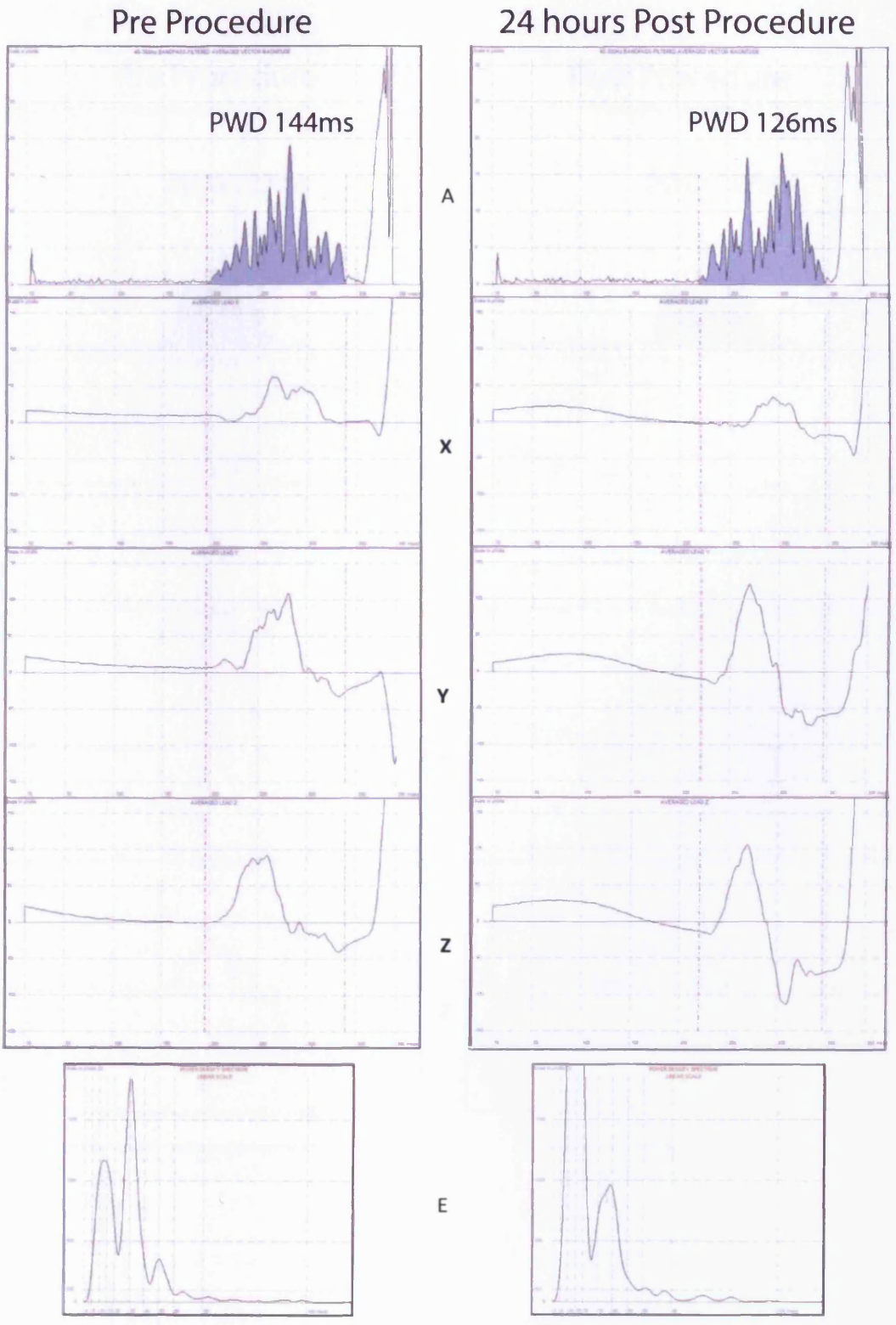
The study used a regression analysis on a 24 hour recording to identify significant associations with outcome. Later the speculative link is hypothesised between P wave duration and electrical isolation of the pulmonary veins. There are many assumptions in this argument: it is not clear if recurrence is entirely related to pulmonary vein isolation, the fact that many WACA patients remain free of AF strongly supports this. Also veins that were isolated at 24 hours may well have reconnected shortly after and thus the 24 hour recording cannot be assumed to always represent electrical disconnection of the pulmonary veins. Thus some patients may have presented an initial shortening of the PWD only to develop reconnection at a later possibly related to change in the PWD and clinical recurrence.

It is unlikely therefore that a single recording after catheter ablation will produce the necessary sensitivity or specificity to be clinically useful unless the technology for achieving permanent isolation at one sitting improves. The use of serial recordings may prove more insightful (see chapter 8).

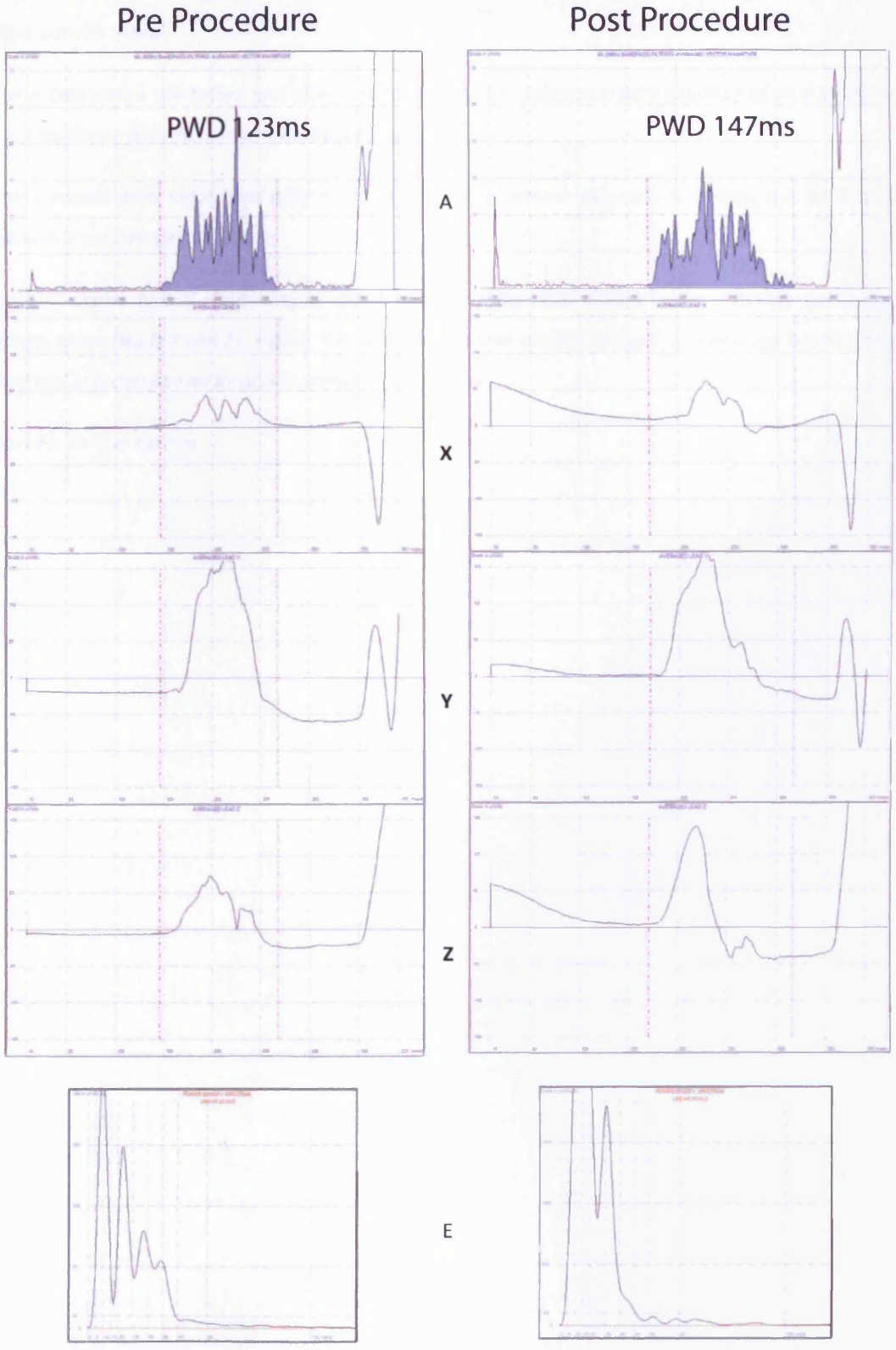
CONCLUSIONS

High resolution recordings after WACA show a marked change in both P wave and HRV parameters. Recurrence is associated prolongation of the filtered P wave duration and absence a WACA approach without additional attempts to isolate the veins. WACA without attempted isolation yields poorer outcomes and is associated with a longer post procedural PWD. SAPW might present a useful technique to determine PV isolation during follow-up.

Figure 1


Pre Procedure
24 hours Post Procedure
PWD 144ms
PWD 126ms
A
X
Y
Z
E

(A)



(B)

Figure 1: Both (A) and (B) show 2 panels representing the P wave before and after catheter ablation. A: denotes the filtered P wave, a summation of the three averaged signals from the orthogonal leads shown below; X: represents averaged signal from lead X; Y: averaged signal from lead Y; Z: averaged signal from lead Z and E: represents the power density spectrum from which P wave energies are derived after fast Fourier transform of the time domain signal.

(A) These two panels are before and after a successful hybrid procedure with isolation of all 4 pulmonary veins and no recurrence documented at 6 months follow-up.

(B) These panels show before and after a WACA procedure without attempts to isolate, this patient developed symptomatic recurrence.

Figure 1(A) shows typical shortening of the P wave duration and change in morphology particularly in the horizontal plane (leads X and Z). Figure 1(B) also shows some subtle change in morphology but this appears less marked and is accompanied by prolongation of the P wave.

See text for further details.

CHAPTER EIGHT

SUMMARY AND DISCUSSION

INTRODUCTION

Previous studies using signal averaging of the surface P wave in a clinical setting have established a relationship between atrial fibrillation and change in the SAPW (chapter 1). Parameters derived from SAPW analysis appeared to demonstrate an association with AF in a variety of settings. These were reviewed in detail in chapter 1, namely:

- P wave energy higher in patients with documented AF compared with controls with similar atrial size.
- Prolonged P wave duration in patients at risk of developing AF after coronary bypass surgery.
- Increases in energy and prolongation of PWD predictive of AF after cardioversion.
- Prolonged filtered P wave associated with efficacy of propafenone and flecainide in PAF.
- Decrease in P wave energy with sotalol.

More specifically, the data derived following cardioversion appeared to show a reduction in P wave energy in the same time frame as one would expect reverse electrical remodelling to occur. Moreover, when examined directly negative correlation was observed between measured change in AERP and measured change in P wave energy. Sotalol was not associated with change in PWD but decrease in P wave energy was observed. Although not directly measured in this study, sotalol might be expected to prolong AERP with minimal effect on conduction velocity[204].

P wave duration is recognised as a marker of intra-atrial conduction delay however the changes observed in P wave energy content both after cardioversion and with sotalol use could not be readily explained by change in intra-atrial conduction delay. Thus the hypothesis was generated that change in the SAPW might represent a marker of change in electrophysiological substrate, specifically conduction which in turn may reflect local electrophysiologic conditions such as conduction velocity and atrial effective refractory period.

To develop this hypothesis I examined the methodology employed in high resolution acquisition using the SAPW technique and reproducibility of the measures before performing pilot studies where change in atrial substrate was anticipated.

METHODOLOGICAL REPRODUCIBILITY

Before the results are reviewed it is important to consider limitations in the methodology. Reproducibility of PWD is good, however in both the original and the Holter system reproducibility of P wave energy is poor (CR was 3.5% at 24 hours with PWD, 18.5% with P20 and 34.9% with P80). This represents both the variability of the biology and the acquisition of signals (change in skin impedance, local environment etc). In chapter 3 it was noted (and illustrated) how an averaged P wave from the same individual can maintain the same morphologic shape but increase in amplitude, thus PWD changes little but energy (a product of the area under the curve (power) and time) varies accordingly. It is not clear what the change represents, only that it occurs in otherwise healthy subjects and is assumed to represent non-pathologic manifestations of normal physiology. Thus some changes in the P wave can be expected due to normal variation, a disease would have to produce a large change in atrial substrate to manifest as an 'abnormal' change in energy values. This is not so for PWD which varied less and might be more sensitive to change.

Absolute change in values of 10KμV^2.sec and 1KμV^2.sec for P20 and P60, and 10ms for PWD were the order of magnitude that appeared clinically relevant in previous work using the same system[31, 55, 160]. Thus these values were chosen to represent a significant change from baseline. Sample sizes of greater than 17 provided 90% power to detect a change of this magnitude; however a larger sample (36) would be required to be confident of absence of significant change in P60.

THE SIGNAL AVERAGED P WAVE AS A MARKER OF SUBSTRATE CHANGE

EVIDENCE FROM DRUG STUDIES

The study in chapter 4 looked at change in SAPW parameters and intracardiac derived values after flecainide administration (a potent sodium channel blocker). Previous studies of class 1 c agents had demonstrated an association between prolonged PWD and sodium channel blockers. If we assume that there were no structural changes between baseline and flecainide administration to change distance travelled by a depolarising wave, then it is fair to say that conduction time should reflect conduction velocity (a more conventional electrophysiologic measure). Thus energy and PWD were associated with change in conduction times (equating to conduction velocity). A lower energy value and a longer PWD were associated with a longer conduction time.

Flecainide also induced a modest change in AERP at the lateral right atrium and this demonstrated an association with higher energies; however due to the known actions of Flecainide and the modest change observed the association may be erroneous due to small sample size and multiple comparisons (Type II error). Nevertheless this pattern of change is complimentary to that observed with sotalol. Sotalol has little effect on conduction velocity but lengthens AERP[204]. The changes seen in the SAPW with sotalol were mainly in P60 and

P80 with no change in PWD, whereas flecainide resulted in pronounced changes in lower energy bands and modest high frequency change with P wave prolongation. The two studies are compatible and suggest a differential effect of electrophysiologic change on P wave energy and time domain variables. We can speculate that ERP and conduction time might have been reflected in energy and possible reasons how this may occur are speculated on in the chapter (chapter 4, page 69 & 70), but further studies are required to support this hypothesis.

To explore the concept of non-invasive assessment of atrial electrophysiologic substrate from another perspective the SAPW was examined in the context of electrical cardioversion from AF. This has been studied before, invasively and non-invasively, and presents a predictable period of change in atrial electrophysiology that occurs in patients sustaining sinus rhythm.

Evidence for intracellular calcium overload as a factor in AF perpetuation encouraged interest in verapamil (an L-type calcium channel blocker) as a drug with the potential to reverse or ameliorate this phenomenon[174]. Although the literature on use of verapamil in this setting is controversial, randomised, controlled studies using an abbreviated regime appeared to show a benefit in terms of AF recurrence following cardioversion in those patients randomised to verapamil. The SAPW has shown change after cardioversion in a number of studies and thus the hypothesis that the impact of verapamil on atrial electrophysiologic substrate might be detected in SAPW variables measured over the week following cardioversion was investigated. I found that P wave variables from patients treated with verapamil approximated normal values more closely than a contemporaneous control group when measured immediately after cardioversion. Interestingly this was also associated with a significant reduction in recurrence of atrial fibrillation at 1 week.

Calcium unloading has been shown to restore conduction velocity to approximate normal values in laboratory animals[128, 129], we can speculate that verapamil exerts its benefit by restoring conduction velocity and reducing the proarrhythmic substrate. Support for this hypothesis is perhaps found in the shorter PWD associated with verapamil and relatively prolonged PWD in the control group possibly suggesting longer conduction times in controls given the similarity of LA size between groups. From this study we can conclude only that verapamil conferred clinical benefit and patients prescribed verapamil demonstrated higher P wave energy and shorter PWD. The observation of reduction in P wave duration after cardioversion in patients maintaining sinus rhythm has been made before[57] and was not restricted to verapamil. It has been postulated this reflects reverse remodelling after cardioversion; however this study merely documents the observation. Without additional data to comment on mechanism this hypothesis cannot be supported or refuted.

EVIDENCE FROM ATRIAL FIBRILLATION CATHETER ABLATION

Therapy for AF has evolved from cardioversion and drug control to catheter radiofrequency ablation of the left atrium. Ablation strategies differ with regard to procedural aim and chapter 6 studied the effect of a segmental isolation approach with minimal left atrial ablation (PVI) and a wide area ablation approach without electrical isolation on SAPW parameters (WACA). Anticipating an autonomic response from the procedures, heart rate variability was simultaneously measured by high resolution recordings according to standard ISHNE criteria[193]. The groups were compared and the study was adequately powered to show a statistical difference within patients and between groups if present. Both groups were well matched and both demonstrated a vagal withdrawal response to ablation; however only the WACA group demonstrated a change in P wave variables. The SAPW change was thus not likely related to change in vagal tone or heart rate. The SAPW appeared to reflect the substrate change conferred by the WACA technique. There is little data available on P wave energy after these differing techniques for AF ablation. This study is the first I am aware of examining the SAPW energy in this context.

Fractionated conduction in the atrium is thought to be part of the pathogenesis of AF and some investigators deliberately target fractionated electrograms for ablation[205]. Fractionated conduction has also been thought responsible for the increased high frequency energy in patients with paroxysmal AF[24, 160]. Indeed the methodology employed and developed by Stafford *et al*[46] purposefully incorporates the entire P wave to capture such signals from the left and right atrium. The pulmonary vein junctions are highly arrythmogenic areas and are largely responsible for the fractionated electrograms[205], thus a reduction in energy mirrors a reduction in the fractionated areas by inclusion in the ablation lines and to some extent may be related to one another.

In chapter 4 the increase in conduction time induced by flecainide was mirrored by a simultaneous reduction in P wave energy and increase in PWD. Change in conduction time appeared to be associated with change in P wave duration and energy. Atrial conduction times were not measured in either catheter ablation study so the relative contribution of electrical atrial 'debulking' and slowing of atrial conduction time cannot be determined, although the latter is well reflected in PWD.

SUMMARY

The results from these drug and catheter ablation studies imply that perturbation of atrial electrophysiologic substrate by catheter ablation or drugs produces a change in P wave measures supporting the general hypothesis that the SAPW is a non-invasive marker of atrial electrophysiologic change.

GENERAL LIMITATIONS

The objective of this thesis was to establish if a hypothesis linking change in P wave parameters to change in atrial electrophysiological substrate might be supported. The choice of flecainide and small numbers reduced the ability of this study to establish a correlation with SAPW parameters, the study merely demonstrated change in SAPW parameters and atrial electrophysiology occurred simultaneously but could not be causally linked. This study might yield a clearer picture if expanded to a larger population with homogeneous substrate. The link between refractory period change and high frequency change is tenuous because the change was observed solely at the right lateral wall and is not anticipated with flecainide, a drug more commonly expected to slow conduction velocity. Nevertheless the controlled setting and short duration of the study support the hypothesis that the SAPW change were related to electrophysiologic substrate change induced by flecainide.

Similarly the mechanism of benefit of verapamil is not known, it is not even clear if the mechanism is related to change in atrial electrophysiologic substrate compared with controls as this was not measured invasively. The SAPW reflected a change where expected but it is assumed to be related to be atrial substrate and the mechanism is speculated upon in the relevant chapter. A subset of patients cardioverted internally would have allowed invasive measures of conduction reducing speculation as to the mechanism of benefit. Additionally, 24 hour monitoring of rhythm would have been helpful in assessing burden of premature atrial beats.

The effect of extensive left atrial ablation was evident in the SAPW but again no invasive measures were made to attempt to correlate SAPW variables with electrophysiologic findings such as delayed conduction into the ablated areas of the left atrium followed by isolation and repeat measure. Although results discussed in chapter 7 do lend support to this hypothesis, a longer period of follow-up and repeated measures correlating with outcome would improve the ability to resolve these issues.

Thus no individual study presented provides compelling evidence to confirm or refute a hypothesis that SAPW variables might provide a reliable and predictable marker of specific atrial electrophysiologic change. However when the data is examined together and in the context of previous work, the notion that changes in atrial substrate might be reflected in the P wave can be supported.

To explore this further requires an understanding of the questions asked. For example it is unlikely that the P wave changes after ablation in chapter 6 are reflecting cellular changes induced by flecainide in chapter 4 despite similar changes in SAPW derived parameters. Future experiments must be cognisant of this fact and interpret the results in the setting in which they are made. In addition, these pilot studies examined all the parameters delivered by the P wave analysis system, it is likely that many of these would be clinically irrelevant and should be chosen for investigation based upon temporal and expectation outcomes.

FUTURE DIRECTIONS

Despite the limitations outlined above and in each chapter the SAPW appears to reflect atrial interventions and this warrants further investigation. The advent of ablation for atrial fibrillation and observations made in chapter 6 and 7 suggest a possible role for P wave analysis in the care of post ablation patients. Our ability to monitor the effectiveness of an intervention is crucial to the development and refinement of technique. Reproducibility of PWD is good compared with P wave energy and compares favourably with HRV measures.

To date current strategies rely on patients reporting symptoms combined with periodic Holter monitoring to estimate response to intervention[206]. A non-invasive measure of atrial substrate change might allow assessment of the risk of recurrence in an otherwise asymptomatic subject during sinus rhythm. Such a test may be desirable to help determine which patient requires long term anticoagulation or antiarrhythmic drugs and subsequently monitor them.

Some of these concepts might be examined prospectively. In order to test the hypothesis that incomplete WACA may result in delayed conduction into the pulmonary veins and thus prolong P wave duration.

P WAVE DURATION AFTER CATHETER ABLATION FOR ATRIAL FIBRILLATION IS DIRECTLY RELATED TO ANTRAL ISOLATION

This study centres on examination of the SAPW during ablation for atrial fibrillation using a WACA methodology with isolation at the WACA circles (a hybrid approach, see chapter 7). High resolution recordings made during ablation and examined as separate files according to stage of the procedure. Initial pre-procedure recording; after initial WACA circles inscribed but before attempts to close gaps; after attempts to close gaps. A multipole circular catheter would be employed to map for gaps and determine isolation.

The objective of this study would be to identify at what point PWD increases and whether the PWD then shortens when isolation is completed thus supporting the hypothesis outlined in the discussion of chapter 7.

Figure 1 provides the best example to date of intra-operative recordings observed during catheter ablation of atrial fibrillation. To obtain the recording post WACA it was necessary to disconnect the electroanatomic mapping system from the patient highlighting the difficulties involved in obtaining this research (see figure 2). The level of noise is to some degree related to the electroanatomic system but there are many sources of interference in a clinical laboratory.

The recording in figure 1 is remarkable in that the noise level was low enough to allow a reasonable attempt at SAPW analysis. In other attempts the noise has resulted in an inability to determine PWD at critical time points during the procedure. The recording above was taken without the NavX (Endocardial Solutions Inc (ESI), St

Paul, Minnesota) electroanatomic system connected to the patient by disconnection at the break out box (BOB). Recording with and without connection are illustrated in Figure 2.

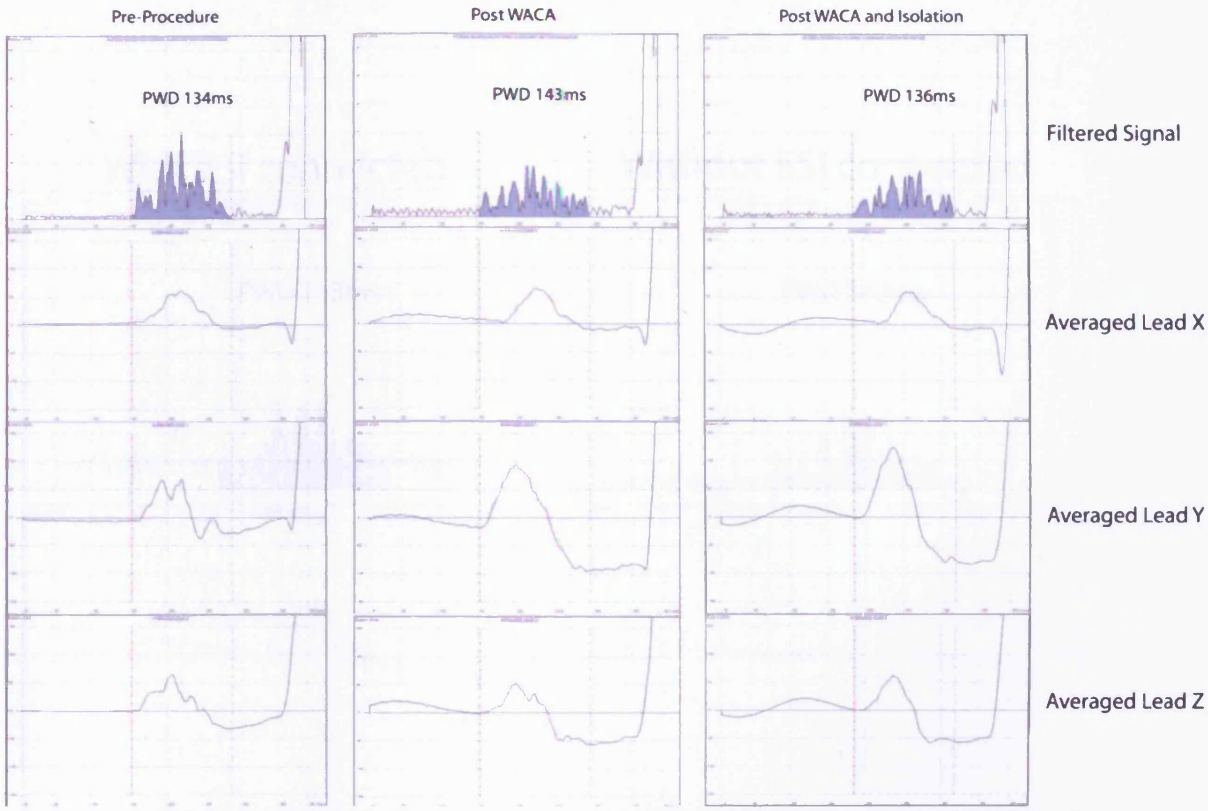


Figure 1: Recordings from a 54 year old female patient with a history of paroxysmal atrial fibrillation without change in lead position during a 'hybrid' ablation procedure. The filtered signal represents single vector magnitude display from which the P wave limits are defined. The filtered averaged signal from each orthogonal vector is shown below: X, Y and Z respectively. The initial P wave duration is not prolonged by any great degree however after WACA without isolation the P wave appears to lengthen (to 143ms) and subsequently shorten again to 136ms.

This line of research will very much depend upon a rigorous and systematic eradication of sources of noise during the procedure. The areas to investigate will be the effect of additional linear lesions such as roof lines and mitral lines on the P wave duration.

USE OF P WAVE DURATION AS A MARKER OF RECURRENCE OF ATRIAL FIBRILLATION OR FLUTTER DURING FOLLOW-UP.

SAPW recordings are performed serially after a Hybrid WACA procedure to identify if a subsequent change in P wave duration might predict recurrence before symptomatic recurrence or provide insight into asymptomatic recurrence. The hypothesis tested is based on the assumption that a reversal of shortening after catheter

ablation is related to reconnection of previously isolated areas and this 'delay' is linked with arrhythmia recurrence. The figure below illustrates an example of the filtered P wave duration for a patient developing recurrence and a patient maintaining sinus rhythm without evidence of symptomatic or asymptomatic recurrence.

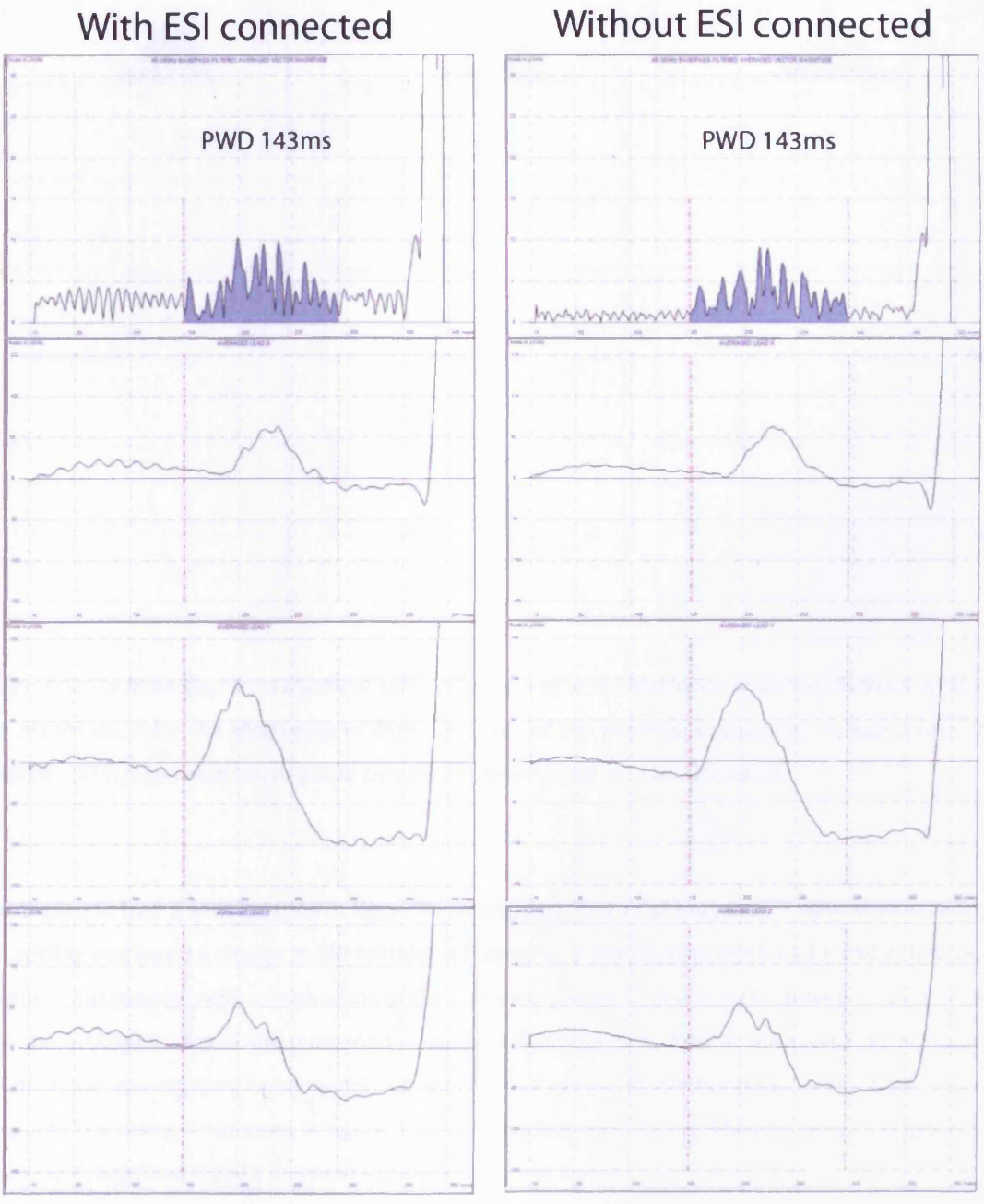


Figure 2: Immediately consecutive recordings with the BOB disconnected (see text for details). Figure presented as in figure 1 above.

Figure 3 contrasts with figure 4 in the pre-procedure and follow up recording; a significant prolongation of P wave duration was recorded during follow up at 3 months. The patient reported symptomatic recurrence and

provided ECG evidence of atrial fibrillation and atrial flutter. Figure 4 however is a more typical example of follow up recordings with progressive shortening over time.

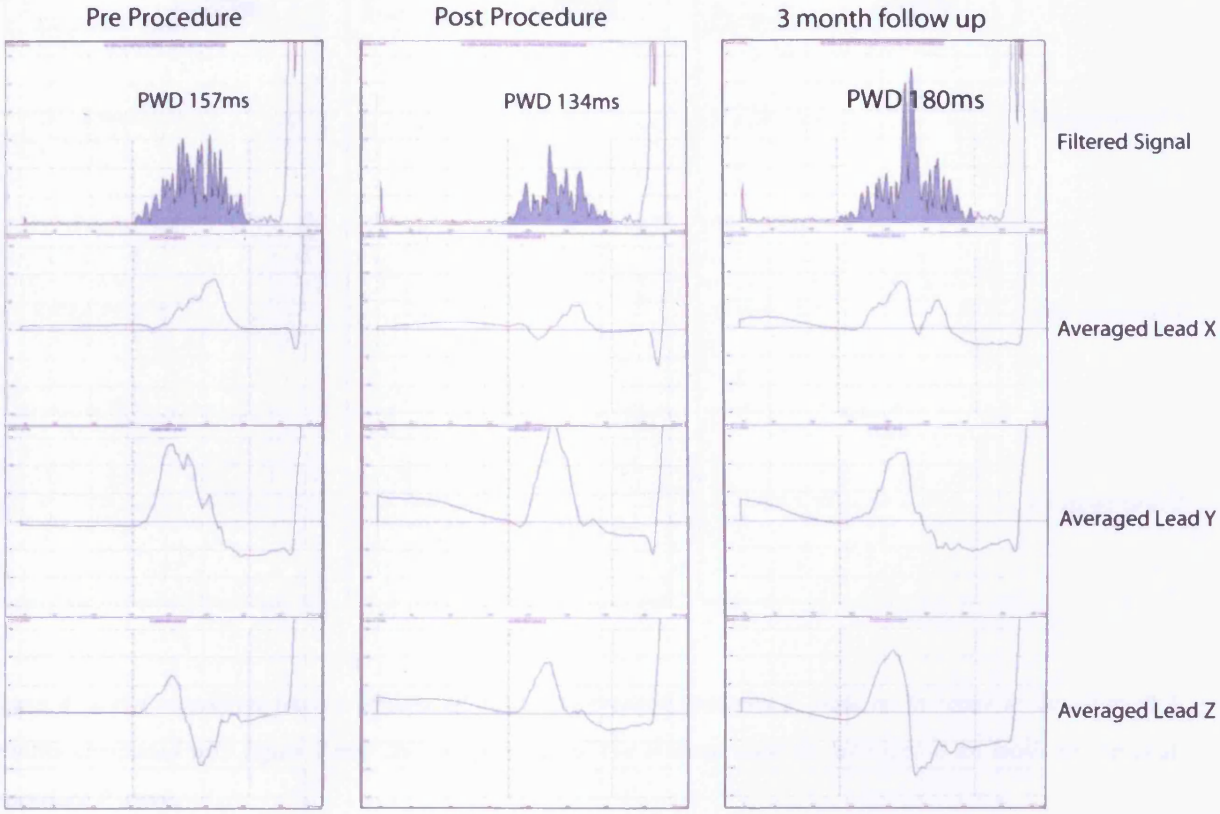


Figure 3: Serial recordings from a patient with recurrence of atrial fibrillation and atrial flutter 6 weeks following the procedure. Note the shortening of PWD and loss of the negative component in lead Z after successful isolation. With recurrence this negative component returns and the PWD increases.

The change in lead Z with isolation in figure 3 is intriguing. Date *et al* examined P wave vectorcardiography in this setting and found a change in the horizontal P wave loop (corresponding to lead X and Z) before and after isolation that reversed with reconnection of the pulmonary veins[207]. The authors studied 21 patients and found that the activation time of the pulmonary veins contributed 40% to 84% of the total P wave duration. With isolation the investigators found a shift of the P wave vector in the horizontal plane both anteriorly and leftward. The changes observed in figure 3 are compatible with this observation with changes in the forces observed in both lead X and Z (horizontal plane orthogonal leads).

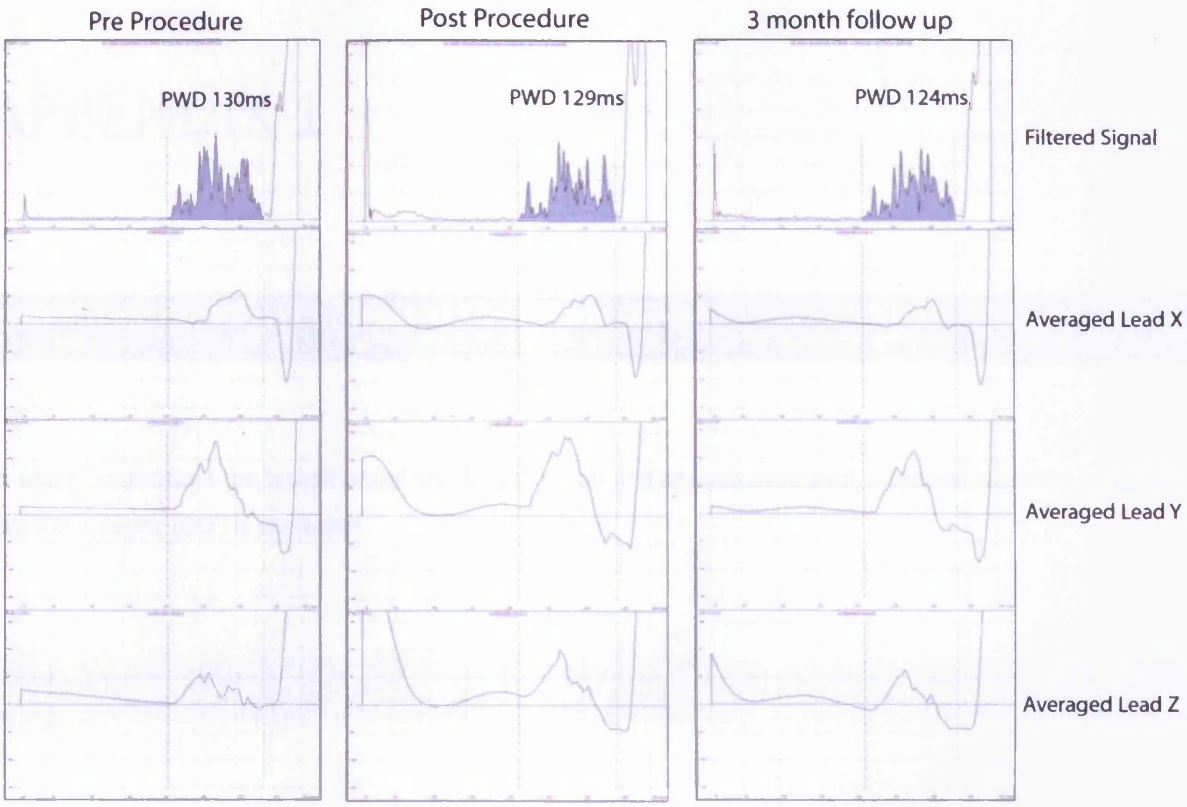


Figure 4: Serial recordings from a patient without documented recurrence. Note no increase in duration at 3 months compared with figure 3 and the morphology of the P wave appears identical in all leads to the post procedure P wave.

CONCLUSION

Despite limitations the data presented within this thesis is consistent with the SAPW presenting a marker of short term change in atrial electrophysiologic substrate.

Assessment of the SAPW is easy, low cost and safe; however to date a lack of a standardised methods of analysis and interpretation across investigators and only modest specificity and sensitivity in the clinical scenarios investigated have limited the clinical usefulness. Nevertheless, atrial fibrillation is a very common condition associated with significant morbidity and intervention is increasing. The possibility remains that observations of change in atrial electrophysiologic substrate may be monitored non-invasively and the observed change in SAPW make a compelling argument for further investigation as a clinical tool.

APPENDIX 1

GENERAL CONCEPTS OF DIGITAL SIGNAL PROCESSING

To better understand the techniques of SAPW acquisition and analysis described, a general overview of digital signal processing (DSP) is presented.

DATA ACQUISITION

ANALOGUE TO DIGITAL CONVERSION

SAMPLING AND ALIASING

The waveform depicted in Fig1a is an analogue waveform, i.e. a continuous stream of data; conversion of this into a digital signal requires periodic sampling of the signal with each sample assigned a value. The number of samples taken needs to be adequate to describe the original analogue signal; too few samples may provide an erroneous digital counterpart. The analogue signal in Fig 1a is sampled at three points; when these points are used to recreate the signal digitally, the original signal is not reproduced (figure 1b). A higher sampling rate reproduces the analogue signal faithfully in Fig 1d.

High frequencies found in the analogue signal that are inadequately sampled will cause low frequency contamination of the subsequent digital signal as illustrated in Fig 1b. The appropriate sampling rate for a signal of given frequency is given by Shannon's *Sampling Theorem* which states:

"An analogue signal containing components up to some maximum frequency f_1 Hz may be completely represented by regular-spaced samples, providing the sampling rate is at least $2f_1$ samples per second."

Thus a waveform of 300Hz should be sampled at least 600 times per second. Fig 1c illustrates a correct sampling interval that is adequate without being excessive.

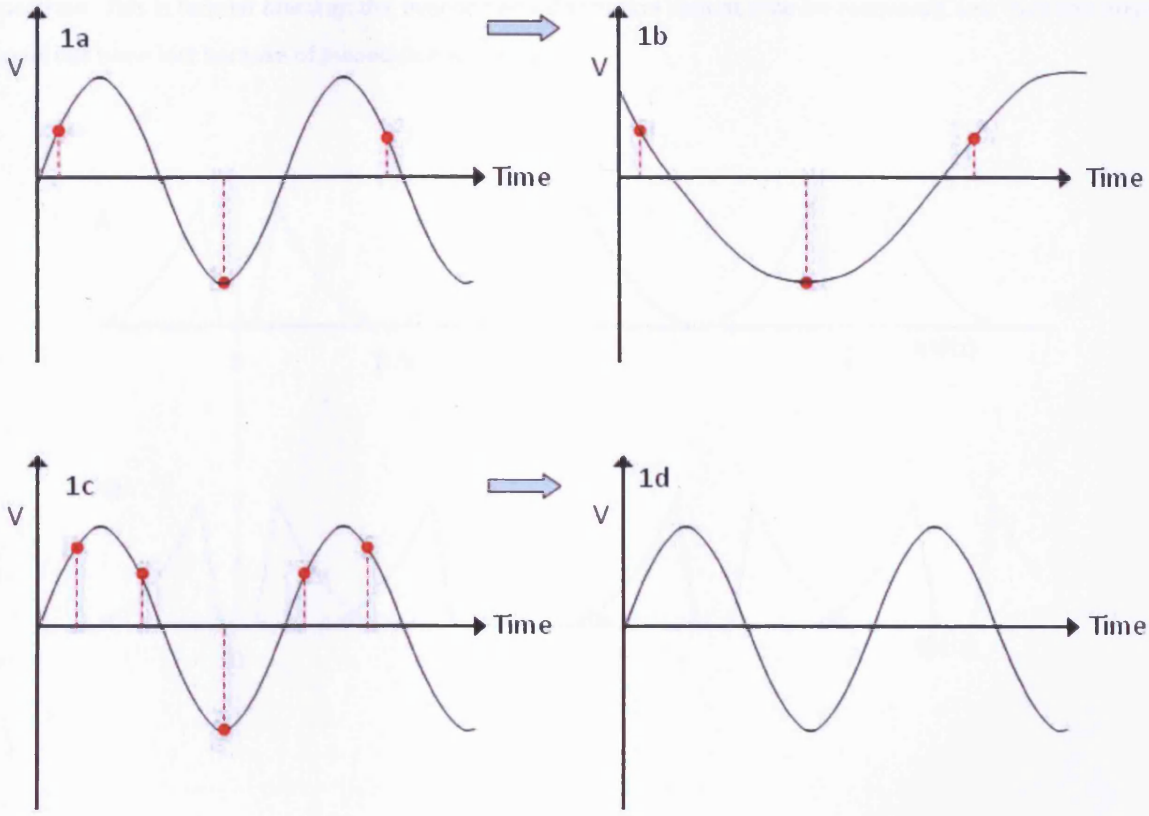


Figure 1: An analogue waveform is represented with an amplitude V over time. The signals in (a) and (c) are sampled at different sampling rates; the reconstructed signals are represented in (b) and (d). Under sampling of the analogue signal in (a) fails to reproduce the signal accurately.

A mathematical consequence of representing a smooth analogue waveform by a set of narrow samples is the repetition of the original spectrum around multiples of the sampling frequency e.g. for a sampling frequency of 1000 samples per second, the original spectrum will repeat around 1kHz, 2kHz, and so on. These spectral repetitions extend to infinitely high frequencies. Figure 2 (over) is a widely used representation of spectral repetition. An original spectrum is represented as an *even* function, extending to negative frequencies. Two repetitions are shown at 1kHz and 2kHz.

To recover the original analogue signal the spectral repetitions need to be rejected. This function can be performed by employing a 'low-pass' filter (reconstituting filter) set at a point prior to the first spectral repetition. Thus in figure 2, 0.5 kHz would comfortably allow elimination of spectral repetitions without contamination of the original spectrum in Fig 2a.

If the maximum frequency f_1 has been underestimated the sampling frequency will be reduced and the spectral repetitions will overlap, as illustrated in Fig 2 b, and the original spectrum will become contaminated. A reconstituting filter cannot now eliminate the spectral repetitions without contamination of the original

spectrum. This is termed ***aliasing***: the overlapped information cannot now be recovered and thus the original signal has been lost because of inadequate sampling.

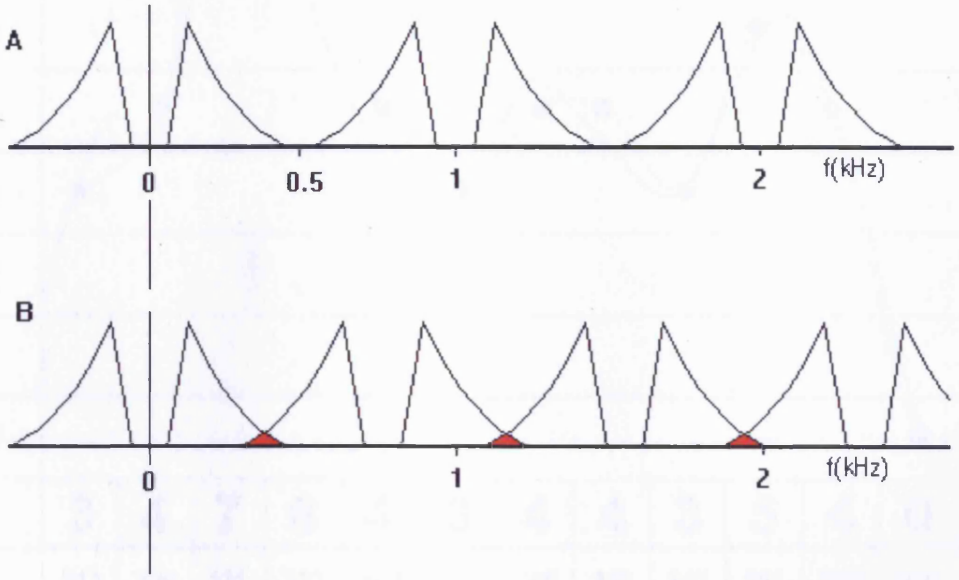


Figure 2: (A): Spectral repetitions separate and recoverable; (B): Reduced sampling frequency results in overlap and corruption of the signal.

The *Sampling Theorem* defines the minimum sampling rate to avoid spectral overlap i.e. aliasing. It is therefore good practice to sample at a higher rate than the sampling theorem suggests, introducing a *guard band* between adjacent spectral repetitions, this allows a safety margin for the reconstituting filter. In addition an *anti-aliasing* filter is applied to all analogue signals to ensure the maximum frequency f_1 is not exceeded. The anti-aliasing filter is a low-pass analogue filter that will ensure the system in question will not receive analogue signals at a frequency higher than can be accommodated by the minimum sampling rate of the system.

BINARY CODES

Sampling is performed by an analogue to digital converter (ADC) that transforms the samples into binary code. A binary code *N* bits long allows 2^N separate signal values to be represented; a 3-bit code may represent 8 separate values (2^3=8). These values are called *quantization slots* and represent the total amplitude. Each *quantization slot* is allotted a binary code and thus the signal may be represented in binary form and processed digitally.

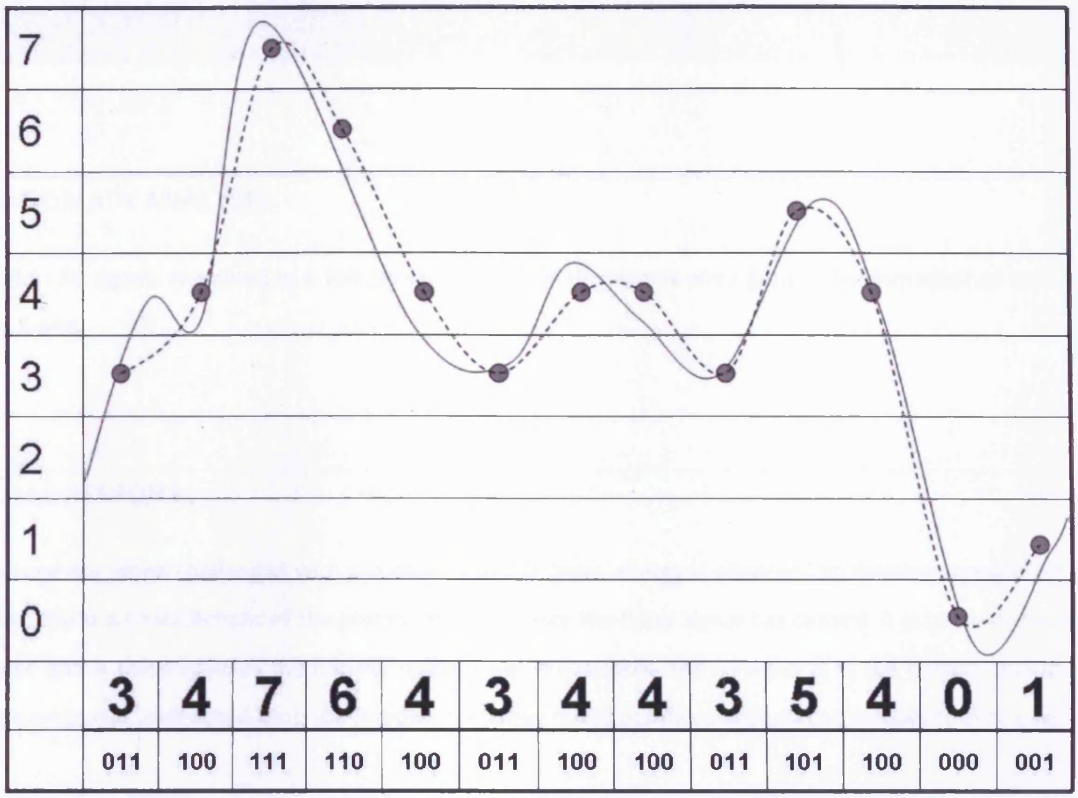


Figure 3: Sampling of an analogue signal. Each sample is allotted a value based on the amplitude of the signal. The length of binary code dictates the number of values available. In this instance a 3 bit code allows 8 slots. The three digit binary code is displayed beneath the allotted value. See text for detailed explanation.

This is illustrated in figure 3; the 3-bit code allows the amplitude to be described by 8 separate quantization slots (0-7). Sampling of an analogue waveform (solid line) is pictured with the amplitude at the point sampled providing a value for the sample (this is depicted under each sample with reference in the left hand column). The binary code (a series of ones and zeros) is constructed from each quantization slot and is shown below. The error inherent in this method is plus or minus half a *quantization level* introduced into each sample value (dotted line). In this example it is ±1/16 of the total available amplitude range.

The error remains in the coding process and is termed *quantization noise.* Analogue to digital conversion will always degrade the signal a little; however with a sufficiently large number of bits in the binary code *quantization noise* is small and need not result in significant degradation.

To ensure the signal of interest takes full advantage of the number of bits available from the ADC it is usual for the signal to be pre-amplified.

DATA ANALYSIS

TIME-DOMAIN ANALYSIS

This refers to signals examined as a function of time i.e. if the signals were graphically represented time would be the X-axis.

IMPULSE RESPONSE

Each processor when challenged with a sudden burst of finite energy is observed to develop a response to the impulse; this is a characteristic of the processor itself, since the input signal has ceased. It is termed the *impulse response* and is referred to as the *natural response* of the system. For an input $\delta[n]$ the output, including the impulse response, is denoted $h[n]$; the impulse response is frequently oscillatory and decays to zero over time.

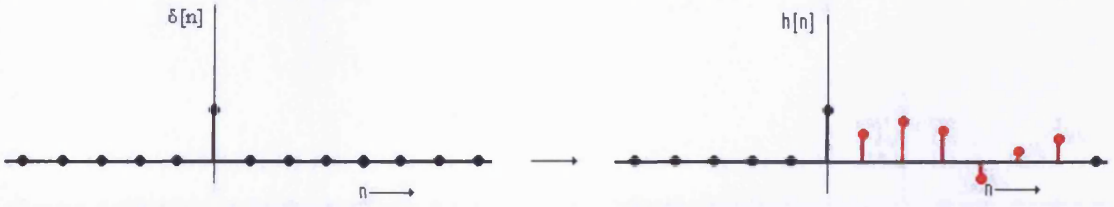


Figure 4: The impulse δ[n] produces an impulse response h[n].

STEP RESPONSE

The step response of a linear processor is a running sum of the impulse response $h[n]$ and is termed $s[n]$. The step response is an alternative way of describing the impulse response and is used to assess a system's response to an abrupt disturbance.

The effect of a signal on a system can be implemented by using these principles in *convolution*.

DIGITAL CONVOLUTION

This technique is one of a number that may be employed to implement a DSP system such as a filter on a given signal. Digital convolution generates the response of a DSP system to an input signal by expressing output as a sum of the impulse responses of the DSP system to a complex input signal decomposed into its simpler components.

In figure 5a an input signal X[n] is represented - opposite is the impulse response of the DSP (5b). The illustration below X[n] (5c) is the input signal decomposed to a set of individual signals and then opposite is the weighted, time shifted, impulse response of the system to the individual signal.

The sum (superposition) of the individual impulse responses provides the output Y[n]. Thus the input signal and the impulse response of the DSP have been combined (convoluted) to produce the output.

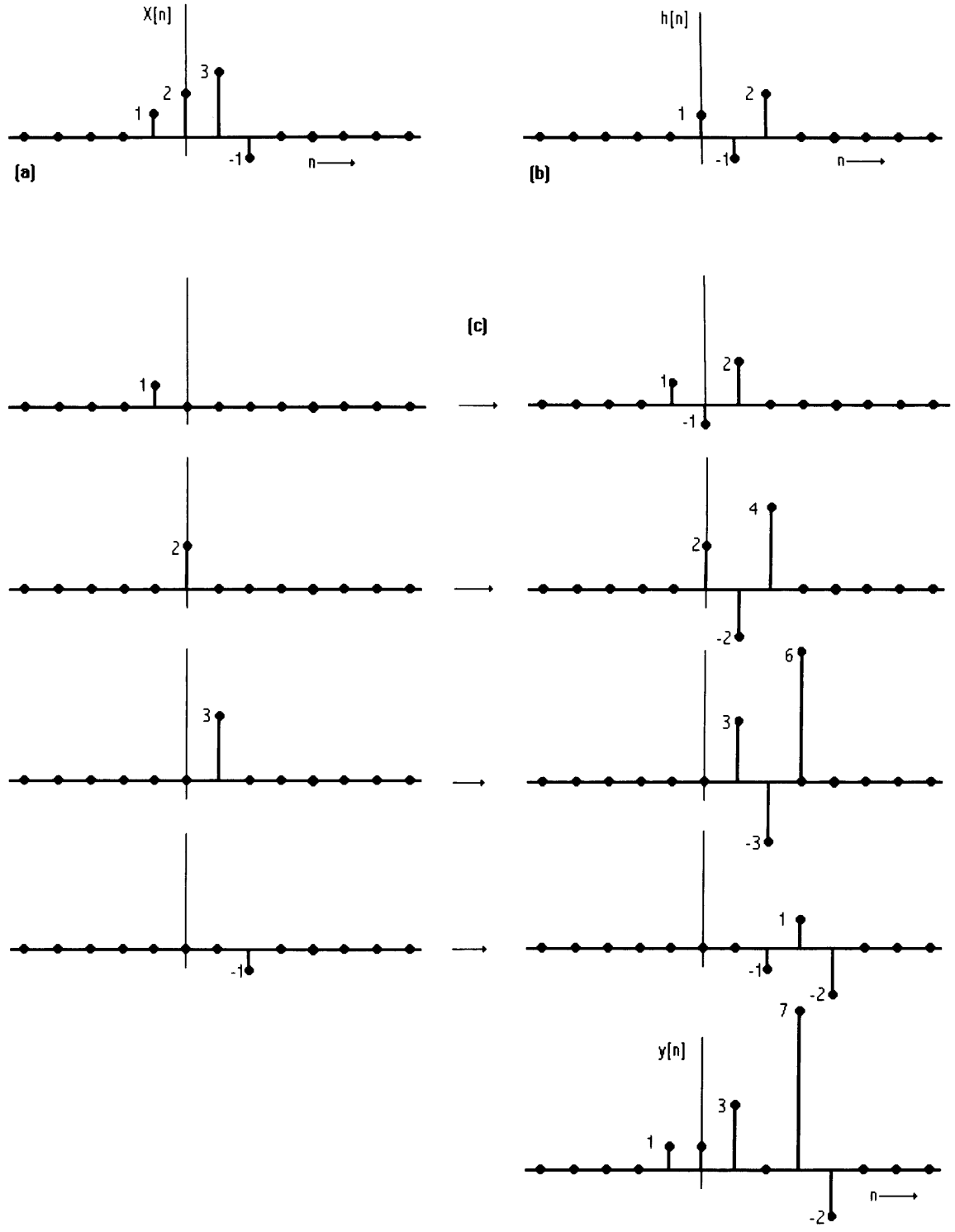


Figure 5: a: input signal; b: impulse response of the digital signal processor; c: Impulse signal X[n] in (a) is decomposed to generate individual impulse responses. Y[n] is the superposition, or summation, of these responses.

FREQUENCY DOMAIN ANALYSIS

A given signal represented in the time domain will have a frequency calculated by how many periods there are per time unit (figure 6). This may alternatively be expressed using a graph with frequency on the X-axis. Thus the same signal may be expressed in either the time domain or frequency domain. A series of mathematical equations can be used to describe a periodic (repetitive) signal as a frequency. In terms of linear processors the time-domain may be converted to frequency domain using the trigonometric Fourier series.

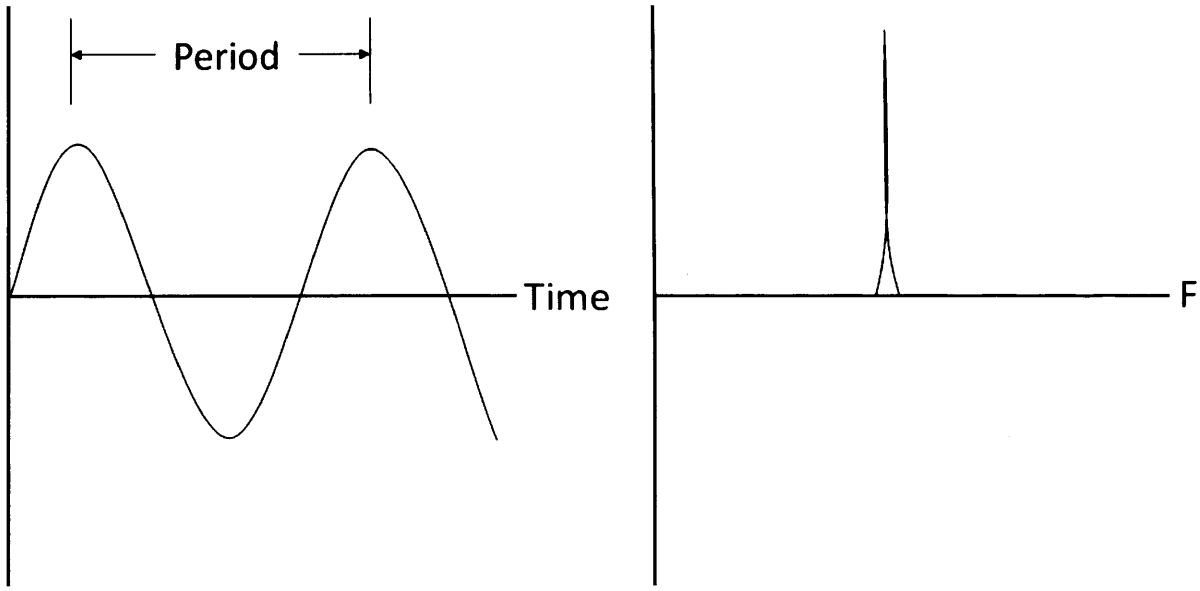


Figure 6: The frequency of an analogue signal in the left graph is represented in the frequency domain on the right graph. F: frequency in Hertz; Time in seconds.

FOURIER TRANSFORM

Fourier was a French mathematician who, in the early nineteenth century, developed a series of complex formulae to describe analogue signals in the time domain. The Fourier series deals with *periodic* i.e., repetitive signal that are continuous; it describes the signal as a frequency spectrum: a number of distinct frequency components, drawn as vertical lines, which produce a *spectrum*. As the frequency of a given signal gets longer (i.e. the time between peaks) the vertical lines, also known as *harmonics*, bunch together and the magnitude of each harmonic is reduced whilst maintaining the same spectrum. As the time between peaks increases toward infinity the whole spectrum will disappear. Thus, to apply the Fourier series to non-repetitive, aperiodic signals, the Fourier coefficients are redefined.

Jean Baptiste Joseph Fourier

The Fourier transforms deal with aperiodic signals, such as the majority of signals found in nature, and describes them as frequency spectra. Spectral energy density may be calculated using Parseval's theorem: "the power or energy in a signal may be found either in terms of its time domain waveform, or in terms of its frequency spectrum." The equation can be altered to calculate the energy of time limited aperiodic signals.

A Discrete Fourier transform (DFT) describes a sampled digital aperiodic signal of finite length; for computational purposes, the signal is assumed to be periodic. Highly efficient fast Fourier transform (FFT) algorithms are often used to implement the DFT.

From the complex Fourier spectrum we may calculate the phase, amplitude and power spectra; F(k), A(k) and P(k) respectively. The units of power are power per Hertz and the actual power over any frequency band is found by rectangular integration of the area under P(k); this is more properly termed *power density spectrum (PDS).*

SPECTRAL ANALYSIS -WINDOWING

Aperiodic signals in the time domain have sharp discontinuities at their edges, this disruption, and the assumption of periodic signals by the DFT, produces pronounced '*sidelobes*' (increased amplitude of the tails of the peaks) that is known as *spectral leakage,* (see Fig 7). This is spreading of the spectral peaks results in contamination of the neighbouring frequencies and difficulty in interpretation. To reduce this effect, tapering of the signal in the time domain prior to DFT by 'windowing' attenuates discontinuities at the edges. Inevitably this process results in some loss of information but side lobe amplitude is reduced.

The ideal window would produce a narrow main lobe without side lobes. In practice this cannot be achieved, the sharper the cut-off in the time-domain the greater the spread in the frequency domain; thus, there is a trade off with broadening of the main lobe and reduction of the side lobes. This is illustrated in figure 7. Transformation of a signal without a window is like applying a rectangular window (i.e. a very sharp transition), producing the narrowest possible main lobe but resulting in large side lobes i.e. spectral leakage. 'Tapered widowing' of the original signal broadens the main lobe but significantly reduces spectral leakage (Right hand pane of Fig 7).

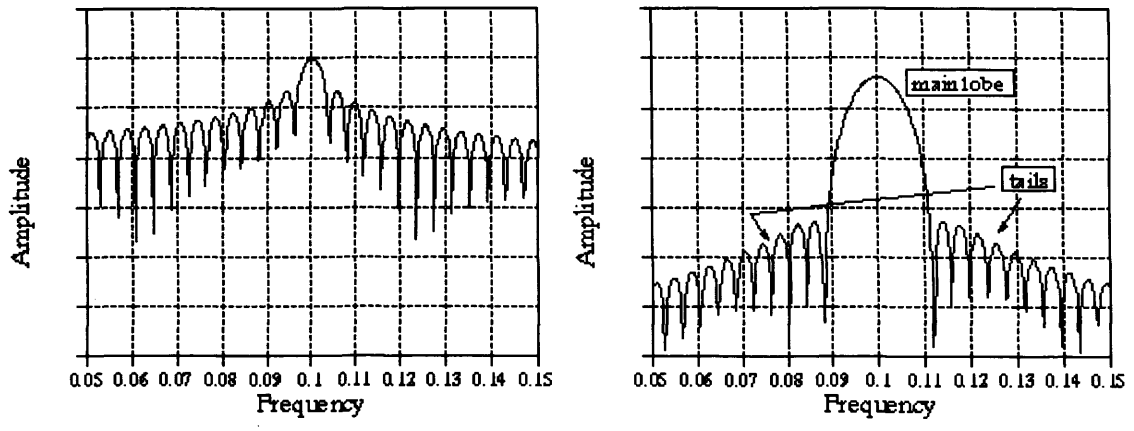


Figure 7: Spectral Leakage. A narrow main lobe with large sidelobes is observed without windowing. A Blackman window reduces sidelobes (tails) but with broadening of the main lobe.

SAMPLING AND RESOLUTION

The sampling rate of the signal determines the frequency range of the Fourier transform, a 1000Hz sampling rate will give a frequency range of 0 – 500. The resolution depends on the number of points of the FFT (frequency resolution is the frequency range divided by the number of sample points). If the peaks of the signal are close together the sampling spacing must be smaller than the distance between the two peaks. To achieve this, the sampling frequency is often over sampled, to enable a greater sampling frequency. This does not add any information to the original signal but does increase frequency resolution. This can be accomplished by using zero padding of the time-domain waveform. The added zeros do not change the shape of the spectrum but do increase the number of samples in the frequency domain providing a smoother waveform and better spectral resolution

The figure below shows how a 512 point DFT can distinguish between two closely related peaks that a 128 point DFT cannot. In practice a longer signal produces a longer frequency transformation and better frequency resolution.

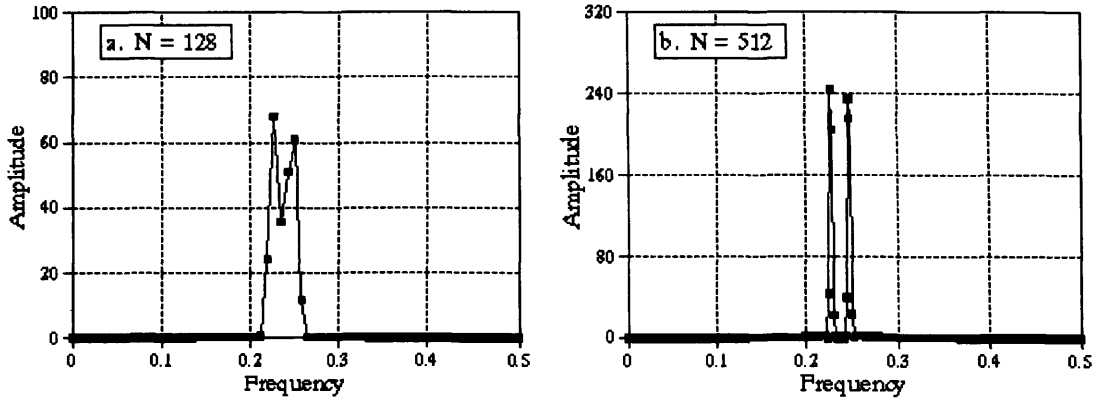


Figure 8: Frequency Spectrum resolution. The longer the DFT the greater the ability to separate closely spaced features. Below a 512 DFT resolves two peaks a 128 DFT cannot.

FILTERING

This is used to transmit or reject well-defined frequency ranges. When examining a signal any part of the signal that is not of direct interest is noise. Filters are employed to remove unwanted parts of the signal. This is most often accomplished in the frequency domain. In effect any circuitry or program that alters an input signal to produce an output signal may be termed a filter.

Section 1.4 reviewed the impulse response of a system; generally filters can be divided into how they employ this response. Non-Recursive filters calculate the response from the current and previous input values; this is also termed 'finite impulse response' (FIR) because the impulse response of the system is of finite duration. Recursive filters employ previously calculated output values back into the calculation of the latest output. This is also known as an 'infinite impulse response filter' (IIR) as the impulse response (theoretically) continues for ever, because the recursive (previous output) terms feedback energy into the filter input and keeps it going.

'Bandstop' or 'Notch' filter are very common filters in DSP and are often used to eliminate noise contamination; such as from the DC mains supply (50Hz). The difference between high pass, low pass and band pass filters is illustrated in figure 9. A low pass filter allows undisturbed that portion of the input signal that lies below a specified frequency and suppresses the signals with a higher frequency. A high pass filter allows frequencies higher than a specified frequency to pass whilst suppressing those with frequencies below it. A band pass filter is the result of using both high pass and low pass filters so that only the portion that remains between the two filters is allowed to pass.

Unlike the idealised diagram in Fig. 9, the transition from pass band to stop band is variable so the transition is never sharp, the main lobe is never rectangular and there are substantial sidelobes, the sharper the transition the greater the sidelobes (section 1.8; figure 7). The selection of filter influences the transition.

The digitally implemented recursive Butterworth filter is often used because of its relatively sharp transitions. However there are two main problems with using recursive filters and they are *'ringing'* and *'phase shifting'*. Ringing (Gibb's phenomena) occurs in IIR recursive filters when the input is a steep step (as is common in ECG signals). Small unpredictable oscillations can occur in the output and as these are fed back into the filter (to make it more computationally efficient) the filter may become unstable unless the coefficients are very carefully chosen.

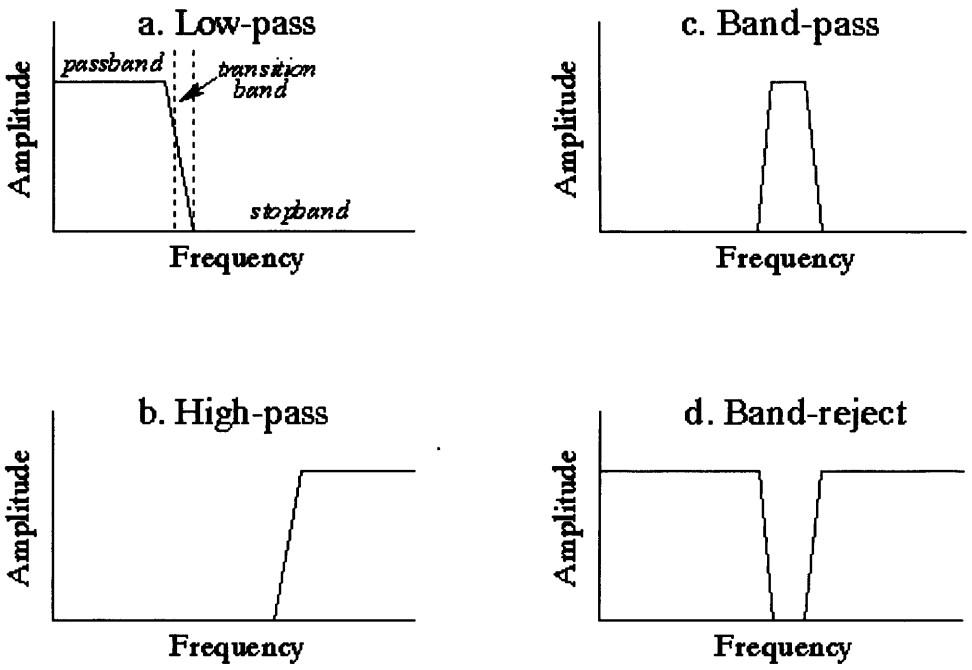


Figure 9: High pass, Low pass and Band pass filter. See text below for details.

The second problem is that recursive designs assume an infinite impulse response; this means that it cannot follow linear phase response. Alteration of phase distorts the signal in the time domain.

Although non-recursive *'finite impulse response filters'* do not exhibit ringing to the same extent or display time distortion; they are computationally inefficient repeating the same calculations many times, and they do not produce sharp transitions from the pass band to the stop band. However FIR filters may be implemented by convolution (section 1.6) using FFTs and are stable.

NOISE ATTENUATION

The principles of noise reduction are central to understanding signal averaging. Signal averaging itself is a tool used to reduce unwanted 'random' noise. Noise is evident from three main sources: the equipment, the patient and the analogue to digital conversion. High-resolution electrocardiography involves amplifying the wanted signal but also the unwanted noise.

Power frequency noise is reduced prior to signal analysis by design of the differential preamplifier; a high level of impedance and rejection of signal common to all the leads. A notch filter may be employed to remove 50Hz DC mains contamination.

Electrode noise is present due to high impedance between the electrode and the skin. The ionic medium present in the electrode enables ionic conduction in the tissues to be converted into electrical conduction and thus an analogue recording. However in the presence of high skin impedance the ionic/ metal interface in the electrode creates a voltage resulting in large potentials that vary with the electrodes stability. In order to reduce this noise, prior preparation of the skin with abrasives and alcohol lowers impedance with the additional use of high quality silver/ silver chloride electrodes.

A great deal of noise is generated by skeletal muscle and is termed electromyographic noise. Any contraction of the skeletal muscle, which the electrode overlies, will produce signals similar in frequency to the cardiac signal of interest. This type of signal is therefore quite difficult to remove with a filter; a relaxed, warm, supine patient is the best way to reduce the contraction of skeletal muscle and thus electromyographic noise.

Quantization noise has been described earlier in this chapter (section 1.2/ figure 3).

SIGNAL AVERAGING

Cranefield and Hoffman originally discussed the concept of 'high resolution' electrocardiography in a lead article during 1968 for the Journal of Electrocardiology[208]. They commented that the standard surface electrocardiogram provides relatively little information about electrical activity of the heart, and speculated that high resolution techniques might allow observation of 'crucial events'.

Signal averaging was described by Berbari as a: "signal processing technique, usually done digitally, whereby repeated or periodic waveforms which are contaminated by noise can be enhanced. That is, the signal-to-noise ratio can be improved. By summating successive noisy wave forms the non-random components, i.e., the desired signal, will be unchanged"[209]. Signal averaging was first used to extract EEG signals from noise (the

fiducial event being the light flashed into the eyes). The technique was subsequently applied to enhancement of P-wave analysis by Brody et al in 1967[210].

The high-resolution surface ECG is contaminated by unwanted signals from the patient and equipment used. However the cardiac signal is a repetitive waveform that is assumed to change little in the recording time. In contrast noise contaminating the signal is of a random nature. Thus aligning successive waveforms enhances the true signal and reduces random noise. Ideally the signal to noise ratio improves by the square root of the number of P waves averaged.

To successfully average a signal a fiducial point (a fixed repeated point that may be used to align successive signals) must be provided to the system to allow signals to be superimposed correctly. There are several methods used to accomplish this but each has its flaws. Commonly used algorithms employed are: voltage triggered, the rate of change of voltage (dv/dt) and template matching where a template of the signal of interest is constructed and subsequent candidate signals compared then accepted or rejected based on a predefined error limit. The algorithms employed in template matching are described below.

JITTER

Error may be incurred when aligning each successive signal to the given template. Malalignment of the signal is termed jitter and reduction of jitter is associated with increased accuracy. To accomplish this two software algorithms are employed to align the signals with minimum error and thus allow accurate rejection and inclusion and in addition enhance the frequency response of the system.

CROSS CORRELATION

To optimise the alignment between the sampled signal and the reference this technique minimises the temporal disparities between selected points on the sampled signals. The accuracy depends on the sampling rate and the underlying cardiac variability; in addition, the technique is insensitive to amplitude variations in waves and relatively insensitive to variations in morphology.

MODULUS DIFFERENCE

This software algorithm is an alternative to cross correlation. The error between signals is calculated by estimation of the total absolute difference between data from the reference template signal and the sampled signal at each time shift. Accurate alignment is achieved with more sensitivity to morphology and is thus more

beneficial in situations where the morphology of the presented signals may vary, as is the case with electrocardiography.

CONCLUSIONS

DSP of the cardiac signal assumes many elements of the signal during calculations that compromise the end result to some degree. The signal averaging methodology used in these studies is described in chapter 3; reference is made to the concepts explained above. Further information regarding DSP is available from the reference texts listed below.

Reference texts:

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