

Dynamic cerebral autoregulation is impaired during sub-maximal handgrip in patients with heart failure

Caldas JR^{1,4,6}, Panerai RB^{2,3}, Salinet AM, Seng-Shu E⁴, Ferreira GSR¹, Camara L¹, Passos RH⁶; Galas FRBG¹Almeida JP, Nogueira, RC⁴, de Lima Oliveira M⁴, Robinson TG^{2,3}, Hajjar LA⁵.

¹ Department of Anesthesia, Heart Institute, University of Sao Paulo, Brazil; ² Department of Cardiovascular Sciences, University of Leicester, UK; ³ NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, UK; ⁴ Department of Neurosurgery, Hospital das Clinicas, University of São Paulo, Brazil. ⁵ Department of Cardiopneumology, Heart Institute, University of Sao Paulo, Brazil. ⁶Critical Care Unit Hospital São Rafael Salvador, Brazil.

Correspondence to: Dr Juliana Caldas

Surgical Intensive Care, Heart Institute, University of Sao Paulo.

Av. Dr. Enéas de Carvalho Aguiar, 44 – ZIP CODE 05403-000, São Paulo, Brazil –

Tel: +55 11 2661-5367; E mail: caldas.juliana@gmail.com

Keywords: cerebral blood flow, cerebral haemodynamics, transcranial Doppler ultrasound, exercise

Word count: 3321

ABSTRACT

Background: The incidence of neurological complications, including stroke and cognitive dysfunction is elevated in heart failure (HF) patients with reduced ejection fraction. We hypothesized that the cerebrovascular response to isometric handgrip (iHG) is altered in HF patients.

Methods: Adults with HF and healthy volunteers were included. Cerebral blood velocity (CBV, transcranial Doppler, middle cerebral artery) and arterial blood pressure (BP, Finometer) were continuously recorded supine for 6 minutes, corresponding to one min baseline, three min of static HG exercise, at 30% maximum voluntary contraction, followed by two min of recovery. Resistance-area product (RAP) was calculated from the instantaneous BP-CBV relationship. Dynamic cerebral autoregulation (dCA) was assessed with the time-varying autoregulation index (ARI_t) estimated from the CBV step response derived by an autoregressive moving-average time-domain model.

Results: Forty HF patients and 23 BP-matched healthy volunteers were studied. Median [IQR] LVEF was 38.5 [0.075] % in HF group. Compared with controls, HF patients exhibited lower ARI_t during HG indicating impaired dCA ($p < 0.025$). During HG there were steep rises in CBV, BP, and heart rate in controls, but with different temporal patterns in HF which, together with the temporal evolution of RAP, confirmed the disturbance in dCA in HF.

Conclusions: HF patients are more likely to have impaired dCA during HG in comparison with age-matched controls. Our results also suggest an impairment of myogenic, neurogenic and metabolic control mechanisms in HF. The relationship between impaired dCA and neurological complications in HF patients during exercise deserves further investigation.

New and Noteworthy

Our findings provide the first direct evidence that cerebral blood flow regulatory mechanisms can be affected in heart failure patients during isometric HG exercise. As a consequence, eventual BP modulations are buffered less efficiently and metabolic demands may not be met during common daily activities. These deficits in cerebral autoregulation are compounded by limitations of the systemic response to isometric exercise, suggesting that heart failure patients may be at greater risk for cerebral events during exercise.

INTRODUCTION

A complex interaction exists between the nervous and cardiovascular systems. Chronic heart failure (HF) is often associated with disturbances in cerebral hemodynamics that provoke neurological disorders, including stroke and cognitive dysfunction (4, 17, 57, 60).

Preservation of appropriate blood flow to the brain and heart is a critical task of the cardiovascular system. Contemporary data have shown that cerebral blood flow (CBF) is jeopardized in chronic HF conditions, which may be associated with central nervous system-related symptoms (18, 62). Disturbances in CBF regulation, caused by limitations in cardiac output or increased sympathetic stimulation, could contribute to neurological damage due to cerebral ischaemia or small vessel damage caused by hypo- or hyper-perfusion. Cerebral autoregulation (CA) represents the brain's ability to maintain a stable CBF despite changes in arterial blood pressure (BP). The classical view that CBF remains constant in the BP range from 60 to 150 mmHg (33) has been challenged by more recent studies (55, 61). Static CA refers to the steady-state relationship between BP and CBF. Dynamic cerebral autoregulation (dCA) reflects the transient response of CBF, often recorded as cerebral blood flow velocity (CBV) with transcranial Doppler ultrasound (TCD), to rapid changes in BP (53). Multiple studies have shown an association between impaired CA and cerebrovascular disorders (2, 14, 36, 47).

The isométrico handgrip manoeuvre (iHG) is a static exercise consisting of contraction of forearm muscles. In healthy subjects, iHG can lead to rapid and robust elevations in BP, heart rate (HR) and cardiac output (5, 33). It has been shown that isometric exercise induces variations in CBF, possibly due to bilateral activation of cortical brain areas implicated in muscle contraction and autonomic regulation (23). Isometric exercise presents a challenge to CA, not only due to elevations in BP, but also due to increases in sympathetic nerve activity (12). However, it is not known how HF influences the regulation of CBF during exercise.

99 This is important considering that the brain is closely related to the heart, and thus may play a
100 role in the progression of HF (4). Sympathetic activation and regulation of fluid homeostasis
101 through the brain is one of the most important causes of left ventricular remodelling and
102 symptom aggravation in HF (49). This complex syndrome is worsened by autonomic nervous
103 system dysfunction due to excess sympatho-excitation and/or vagal nerve withdrawal (22,
104 54).

105 Exercise in HF patients has been reported in several studies (19, 26). A recent review has
106 highlighted the need to improve our understanding of the role of the brain in exercise
107 intolerance in HF (4). Whilst we have recently reported that HF patients have depressed dCA
108 at rest when compared with healthy subjects (6), cerebrovascular responses to ~~HG~~ (iHG have
109 not been described for HF patients. Studying the effects of (iHG in these patients could lead
110 to better insights into the role of the autonomic nervous system in CBF control, as well as a
111 more sensitive test of patients at higher risk of neurological complications. For this reason,
112 we tested the hypothesis that dCA is impaired during sub-maximal (iHG) manoeuvre in HF
113 patients with reduced ejection fraction. This information could have considerable value for
114 tailoring treatment and/or monitoring of HF patients in response to rehabilitation and
115 activities of daily living involving isometric exercise.

MATERIALS AND METHODS

Research participants

This was an observational, single-centre study, performed at the Heart Institute of the University of São Paulo from May 2014 to July 2015. Patients were considered eligible to participate in the study if they fulfilled the following criteria (i) left ventricular ejection fraction (LVEF) $\leq 40\%$ on transthoracic echocardiography; (ii) clinically diagnosed ischaemic chronic HF with any functional class of the New York Heart Association (NYHA) classification (3); (iii) written informed consent. Age-, and BP-matched healthy controls were studied, free of neurological, cardiac disease, diabetes and carotid artery disease. Control subjects with treated mild hypertension were included as representatives of the matched older age group. The study was approved by the local research ethics committee and all participants provided written informed consent.

Procedure

Measurements and data analysis

The study was performed with participants lying in a supine position, with the head at 30°. Simultaneous TCD evaluation of both middle cerebral arteries (MCAs) was carried out using bilateral 2 MHz pulsed, range-gated probes (DWL, Dopplerbox, Germany), held in place with a head frame. Subjects with unilateral temporal acoustic window were excluded. Insonation depths varied from 50 to 55 mm, with slight anterior angulation (15– 30°) of the probe through the temporal window. BP was continuously measured non-invasively using finger arterial volume clamping (Finometer PRO; Finapres Medical Systems, Amsterdam, Netherlands) with the servo-adjust switched off after an acclimatization period of at least 5 min, when a stable waveform was achieved with the servo-adjust on. End-tidal CO₂ (EtCO₂) was continuously measured with an infrared capnograph (Dixtal, dx 1265 ETCO₂ Capnogard,

Manaus, Brazil) via a closely fitting mask and recorded at 1 min intervals. EtCO₂ was not monitored in controls. LVEF was derived by transthoracic echocardiography.

The ~~HG~~ (iHG) maneuver was performed with a dynamometer. For each subject, maximum contraction force was calculated as the average of three rounds of maximum effort values with at least ten seconds of recovery between each task. In the main experiment, subjects were instructed to perform (iHG) maneuver with the dominant arm at 30% of maximum contraction force for 3 minutes, and not to move any muscles other than those involved in the test. All the participants were informed when the 30% target was achieved and visual feedback was provided by the dynamometer scale to help participants to maintain the target contraction force.

After resting for at least five min, a continuous 6 min recording was obtained corresponding to one min of baseline, three min of (iHG) , followed by two min of recovery.

Signals were sampled at a rate of 100 Hz and stored on a dedicated personal computer for offline analysis. All recordings were visually inspected and the BP signal was calibrated using the systolic and diastolic values of radial sphygmomanometry. Narrow spikes (<100 ms) and artefacts were removed by linear interpolation. Subsequently, all signals were filtered in the forward and reverse direction using an eighth-order Butterworth low-pass filter with a cut-off frequency of 20 Hz. The beginning and the end of each cardiac cycle were detected in the BP signal, and mean values of BP, CBV and heart rate were obtained for each heart beat. Critical closing pressure (CrCP) and resistance area-product (RAP) were obtained using the first harmonic method for each cardiac cycle (35). Beat-to-beat parameters were interpolated with a third-order polynomial and resampled at 5 Hz to generate signals with a uniform time base.

To assess dCA during the (iHG) maneuver, the ARI index was estimated as a function of time (ARIt) using an autoregressive moving-average (ARMA) time-domain model, as

described previously (10, 38). The ARMA model was applied to a 60s window of data that was slid along the entire recording at 0.6s intervals. For this reason, the first and last 30 s of the recording cannot be used to generate values of ARI_t . At each 0.6s interval, the CBV step response was calculated from the ARMA model coefficients (10) and was compared with 10 template curves proposed by Tiecks et al. (53). The best fit curve then corresponds to ARI_t at that instant of time (41). Values of $ARI = 0$ indicate absence of CA, whilst $ARI = 9$ corresponds to the most efficient CA that can be observed (53). The ARI_t and all other cerebral haemodynamic parameters were averaged for time intervals of 30 s corresponding to T1: baseline before the maneuver, T2: beginning of (iHG), T3: last 30 s of the maneuver, and T4: last 30 s of the recovery period (48).

Statistical analysis

Following assessment of normality with the Shapiro-Wilk one-sample test, parametric (Student's t) or non-parametric (Mann-Whitney U) tests were used as appropriate. Fisher's exact test was used with categorical variables. Results are expressed as mean \pm SD or median with interquartile ranges [IQRs]. Inter-hemispherical differences in parameters were tested with the paired Student's t-test or Wilcoxon non-parametric test. In the absence of differences, values for the right and left MCAs were averaged. Changes in ARI and other parameters at T1, T2, T3 and T4 were assessed with repeated measures ANOVA or Friedman and Wilcoxon tests in the case of non-gaussian parameters. In the event of significant effects (either group or manoeuvre), inter-group differences were assessed with mixed-effects ANOVA or Mann-Whitney U test. Statistical analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL). A p -value < 0.05 was considered statistically significant.

RESULTS

Participants

Fifty-two patients were recruited; 12 excluded due to technical problems (5), absent temporal acoustic window bilaterally (5), or poor quality recording (2). Twenty-five healthy subjects were recruited; one excluded due to poor quality recordings and one due to absence of temporal acoustic windows bilaterally. The total number of recordings analysed was thus 40 HF patients and 23 healthy volunteers.

All subjects in HF group had clinically diagnosed ischaemic chronic heart failure, with median LVEF 38.5 [0.075] % on transthoracic echocardiography. Demographic and clinical characteristics of the population are described in Table 1. None of the bilateral cerebral haemodynamic parameters showed significant differences between the right and left MCAs, therefore values were averaged in further analyses (Table 1).

Baseline conditions

Compared to controls, HR and ARI were significantly lower, and CrCP significantly higher in HF patients (Table 1). Otherwise no significant differences were seen between groups in peripheral or cerebral haemodynamic parameters (Table 1). EtCO₂ was 34.7 ± 3.8 mmHg in HF group.

Handgrip maneuver

With the exception of CrCP, all other parameters analysed showed significant changes in response to the HG (iHG) manoeuvre (Table 2). In control subjects, the onset of the HG (iHG) induced increases in BP, HR and CBV (Figs 1.A, B & C). RAP also showed a continuous rise, which tended to counteract the BP increase, whilst CrCP tended to remain constant (Figs 1.D & E). Different temporal patterns were observed in HF. BP rose much less steeply ($p=0.04$, Table 2, Fig. 1.A) and HR did not show a return to baseline at recovery

(Fig. 1.B). The rise in CBV was also considerably delayed in HF, again, not showing the same return to baseline as observed in controls (Fig. 1.C). Moreover, RAP had a dip at the beginning of (iHG) and did not increase as quickly nor returned to baseline during recovery, in contrast to controls (Fig. 1.D). Similarly, ARI_t showed a different pattern in HF patients compared to control subjects, with a significant drop over the first 30s in controls only. However, HF patients showed a continuous rise in ARI_t to reach values similar to control subjects by recovery (Fig. 1.F, Fig. 2). $EtCO_2$ did not show temporal changes during the manoeuvre in HF group ($p=0.38$).

DISCUSSION

Main findings

To our knowledge, this is the first study to report on alterations in cerebral haemodynamics in HF patients, including dCA, in response to isometric exercise. The major findings are twofold. First, patients with HF exhibited lower dCA during the (iHG) manoeuvre compared with age-matched healthy controls. Moreover, the temporal pattern of changes in dynamic dCA and other cerebrovascular parameters in HF patients was also different from controls. Secondly, in HF patients, most of the variables considered, including HR, CBV and BP, did not return to their baseline values after the manoeuvre. Taken together, these findings demonstrate that the alterations in dCA, previously shown in HF patients at rest, also affect their response to isometric exercise (6, 11).

Cerebrovascular response to handgrip

Human studies investigating the effects of HF on cerebral haemodynamics are limited. The heterogeneity in study design and methodology are major limitations to allow comparisons of our results with the wider literature, such as the use of patients with cardiac transplantation (16, 27, 51, 52), small sample sizes (16), and the use of drugs such as captopril or beta-blockers that can have a direct effect on CBF regulation (43). These studies reported CBV in HF patients, but did not include simultaneous BP measurements to allow assessment of dCA and other cerebral haemodynamic parameters, including CrCP and RAP.

Previous studies of the cerebrovascular response to (iHG) in healthy subjects have shown increases in CBV in the MCA, accompanying similar rises in BP and HR (20, 24, 30, 31). Whilst these temporal patterns were present in both control and HF groups in our study, there were significant differences. In HF, the rise in BP was much less pronounced (Fig. 1A), which may be explained by the well known limitations in cardiac output and baroreceptor

sensitivity in these patients, exacerbated by the use of beta-blockers in approximately 80% of the subjects (15, 28, 43). Despite the limited rise in BP, CBV in HF rose to similar values, around 50 s into the manoeuvre (Fig. 1.C), partly due to cerebral vasodilation as expressed by lower RAP values (Fig. 1.F). Noteworthy, CBV and RAP did not return to baseline in HF, in contrast to controls (Fig. 1.A/B/C/F). Since this pattern was also observed in BP and HR, it is likely to be caused by systemic alterations, rather than a disturbance in cerebral haemodynamics. The delayed recovery of BP to baseline levels in HF could be attributed to an exacerbated central command and mechanoreceptor reflex or an increased adrenaline ‘shunt’ (29, 50).

Dynamic cerebral autoregulation

Our estimates of ARI_t during the (iHG) manoeuvre are in good agreement with previous studies of dCA during exercise, showing that dCA parameters were similar during resting, exercise, and recovery conditions in healthy subjects (5, 13, 33). The results of Ogoh et al. indicate that the CBF response to exercise involves complex mechanisms, depending on exercise intensity (32). By contrast, a previous study of the cerebrovascular response to ~~HG~~ (iHG), based on a different population of healthy subjects, had a different temporal pattern of ARI_t , as will be discussed later (30).

Studies of cerebral haemodynamics have often calculated indices of cerebrovascular resistance (CVRi) or conductance (CVCi) to assess vasomotor activity, independently of separate changes in BP or CBV. The limitation of this approach though, is that detailed study of BP-CBV instantaneous relationships show that a two-parameter model (CrCP+RAP) is more accurate and responsive to reflect changes in arterial tone and the waterfall mechanism resulting from the influences of intracranial pressure and vasomotor tone (35, 39). In this study, CrCP did not show changes as the result of the maneuver, or between HF and CG. On

the other hand, RAP was valuable to explain and complement the ARI_t index. For dCA to be considered ‘active’, it is important that RAP changes in response to preceding changes in BP as indicated by Fig. 1F (40).

Given the variability, and poor inter-method agreement, of CA metrics (56), quantification of CA should be based on multiple measures. In our case, this recommendation was met by observing that in the HF group, disturbances of CBF regulatory mechanisms were indicated by separate findings, namely: i) ARI_t dropped significantly at the beginning of (iHG), albeit gradually increasing towards the end of (iHG) and during recovery (Fig. 1.D); ii) the rise in RAP was interrupted and actually dropped half-way through the maneuver (Fig. 1.F); iii) despite the lower rate of BP rise CBV reached similar values as in controls (Fig. 1.C), indicating less efficient CA. CBF is known to be controlled by myogenic, metabolic and neurogenic mechanisms (1, 37). Our findings suggest that all three different mechanisms are likely to be impaired in HF. In our previous investigation (6), we found dCA to be depressed at rest, where the myogenic mechanism is thought to dominate the CBF response to fluctuations in BP (39). With sensorimotor stimulation, as is the case of (iHG), neurovascular coupling is activated, adding complexity to the CBF response (47). Moreover, the muscle metaboreflex also induces cerebral autonomic nervous system changes that have been suggested to be depressed in HF (45), although in our study $PaCO_2$ was not clamped. Finally, deficiencies in the metabolic, neurovascular coupling, component of the response in HF are suggested by the delayed increase in CBV (Fig. 1.C) The temporal pattern of the CBV response to (iHG) in HF (Fig. 1C) is markedly different from controls, as it suggests impairment of both the myogenic and metabolic mechanisms contributing to dCA. Considering the slow BP rise induced by (iHG) in HF (Fig. 1A), if one removes the velocity ‘surge’, starting at approximately 75 s (Fig. 1C), the underlying CBV rise follows that of BP, thus indicating absence of a myogenic response. On the other hand, when focusing on the

‘surge’, which would be ascribed to the increased metabolic demand induced by (iHG), there is a clear delay compared to controls, thus suggesting that the metabolic component, which could also be regarded as the neurovascular coupling contribution, is also impaired.

The relevance of these new findings, as compared to previous reports of a depressed dynamic dCA in HF at rest (5, 10), is that impairment of CBF regulation is not limited to the myogenic response to BP changes, but also applies to the metabolic and neurogenic control mechanisms as well, which may explain the increased risk of cognitive impairment in HF.

Clinical implications

The fact that CBF regulation is impaired in patients with HF during isometric exercise, has direct implications for the care and follow-up of these patients. Given the number of common daily activities that require an isometric muscle contraction (e.g. carrying foodstuffs, lifting light weights), our findings suggest that BP surges are buffered less efficiently, with more passive transmission of BP to the cerebral vasculature (36), whilst metabolic demands may not be met by the neurovascular coupling mechanism, thus leading to temporary ischaemia. Recent systematics reviews and meta-analyses (9, 19) reported that exercise training in HF does yield improvements in cardiorespiratory fitness, diastolic function, quality of life, and general health, but some studies only included patients with preserved ejection fraction (9) while others called attention to benefits dependence on the type of training performed (19). More work is needed to understand the role of exercise training in patients with low ejection fraction, as included in our study, ideally taking into account their cerebrovascular response to exercise. Of particular relevance, would be longitudinal assessments to test the hypothesis that exercise training might improve CBF regulatory mechanisms, thus reducing the risk of neurological complications. In the move towards more individualised medicine, it is

important to take into consideration the cerebrovascular response to exercise in HF patients. For this reason, incorporating techniques for assessment of CBF regulatory mechanisms during exercise into clinical practice should be seen as a priority (44). Moreover, further research into the role of phenotype in the response of HF patients, and other forms of exercise, will also contribute to better risk stratification of these patients.

Limitations of the study

TCD cannot provide absolute measurements of CBF, the use of CBV as a surrogate relies on the assumption that the MCA diameter remains approximately constant. This is likely to be the case during baseline measurements obtained at rest, but the effects of isometric exercise on MCA diameter have not been investigated. During rhythmic iHG, Verbree et al (58) assessed changes in MCA cross-sectional area (CSA) using MRI, detecting a 2% reduction in CSA, when young volunteers performed rhythmic handgrip at 60% maximum voluntary contraction. The small CSA changes they observed, resulting from much more intense exercise, would suggest nearly negligible MCA diameter changes in our case. Nevertheless, if MCA diameter was reduced during (iHG), CBV would overestimate corresponding changes in CBF, but estimates of ARI_t would not be affected as they only depend on the temporal pattern of the CBV step response. Differences in insonation angle, the chance of arteries other than the MCA being insonated, and inter-subject anatomical differences, including the acoustic permeability of temporal windows, are also factors that need to be considered as potential limitations.

Lack of information about the prevalence of carotid artery disease (CAD) in the HF group is also a limitation of the study. Several studies have shown that both the ARI and transfer function phase are depressed in patients with significant carotid artery stenosis (34). None of

the patients studied had symptoms of advanced CAD, but we cannot exclude the possibility that values of ARI_t could have been biased by the presence of asymptomatic CAD. For logistic reasons we have not been able to perform measurements of $EtCO_2$ in controls, but several studies have shown that $EtCO_2$ is not significantly altered during HG (iHG) (25, 30, 31, 59). This was confirmed in the patient group in the present study, although the values we found suggest these patients were mildly hypocapnic, given their mean $EtCO_2$ of 34.7 mmHg. If that was the case, then the differences in dCA that we found would be an underestimate given the expectation that dCA would be improved by hypocapnia (1). The higher values of CrCP observed in HF, compared to controls (Table 1, Fig. 1.E) also support the speculation that $PaCO_2$ was markedly reduced in HF in comparison with controls (35). In a previous study, Nogueira et al. (30) reported temporal changes in ARI_t during (iHG) in control subjects, differently from the relatively constant values observed in the present study (Fig. 1.D). The reasons for this difference are not clear, but these results might have been influenced by the relatively small sample size and it could be related to the wider age distribution of the former study which included subjects that were, on average, 23 years younger than in our CG. Another possibility is the occurrence of an alert reaction to the beginning of the maneuver in that study, which we tried to avoid in our protocol, by gradual warning of the moment to initiate hand contraction. The lack of matching for sex is also a limitation of the study, although its role in cerebral hemodynamics is still fairly controversial, with the majority of studies not detecting any effects (7, 21, 42). In older subjects (>70 years old), Deegan et al (8) reported better regulation in women compared to men. In our case though, there was one woman above 70 years of age in each group and for this reason it is unlikely that the lack of matching for sex would have influenced our results. Finally, we only investigated the cerebrovascular response to HG (iHG) that is a form of isometric exercise and this was limited to the MCA. Other forms of exercise, or other intra-

cerebral arteries, like the PCA or ACA, could lead to different results with pertinent implications for optimising rehabilitation programs for HF patients (3).

CONCLUSION

Dynamic dCA was impaired in response to ~~HG~~ (iHG) in HF patients with reduced LVEF. In contrast to healthy controls, BP, HR, CBV and RAP failed to return to their baseline levels with ~~HG~~ (iHG) cessation. Collectively, our results suggest that the cerebral vasculature of HF patients is at a greater risk to BP fluctuations, especially during activities encompassing isometric contractions, including rehabilitation. These findings are of particular importance given the number of common daily activities that require isometric muscle contraction. In addition, it could explain the higher rates of neurological complications such as stroke and cognitive dysfunction in HF patients. Further research is needed on the cerebrovascular response of HF patients to other forms of exercise, to allow a more comprehensive assessment and risk stratification in these patients.

419 REFERENCES

- 420 1. **Aaslid R, Lindegaard KF, Sorteberg W, Nornes H.** Cerebral autoregulation
421 dynamics in humans. *Stroke J Cereb Circ* 20: 45–52, 1989.
- 422 2. **Beek AH van, Claassen JA, Rikkert MG, Jansen RW.** Cerebral autoregulation: an
423 overview of current concepts and methodology with special focus on the elderly. *J*
424 *Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab* 28: 1071–1085, 2008.
- 425 3. **Bennett JA, Riegel B, Bittner V, Nichols J.** Validity and reliability of the NYHA
426 classes for measuring research outcomes in patients with cardiac disease. *Heart*
427 *Lung J Crit Care* 31: 262–270, 2002.
- 428 4. **Brassard P, Gustafsson F.** Exercise Intolerance in Heart Failure: Did We Forget
429 the Brain? *Can J Cardiol* 32: 475–484, 2016.
- 430 5. **Brys M, Brown CM, Marthol H, Franta R, Hilz MJ.** Dynamic cerebral
431 autoregulation remains stable during physical challenge in healthy persons. *Am J*
432 *Physiol Heart Circ Physiol* 285: H1048–1054, 2003.
- 433 6. **Caldas JR, Panerai RB, Haunton VJ, Almeida JP, Ferreira GSR, Camara L,**
434 **Nogueira RC, Bor-Seng-Shu E, Oliveira ML, Groehs RRV, Ferreira-Santos L,**
435 **Teixeira MJ, Galas FRBG, Robinson TG, Jatene FB, Hajjar LA.** Cerebral blood
436 flow autoregulation in ischemic heart failure. *Am J Physiol Regul Integr Comp*
437 *Physiol* 312: R108–R113, 2017.
- 438 7. **Deegan BM, Devine ER, Geraghty MC, Jones E, O'Laighin G, Serrador JM.** The
439 relationship between cardiac output and dynamic cerebral autoregulation in
440 humans. *J Appl Physiol Bethesda Md 1985* 109: 1424–1431, 2010.
- 441 8. **Deegan BM, Sorond FA, Galica A, Lipsitz LA, O'Laighin G, Serrador JM.** Elderly
442 women regulate brain blood flow better than men do. *Stroke* 42: 1988–1993, 2011.
- 443 9. **Dieberg G, Ismail H, Giallauria F, Smart NA.** Clinical outcomes and
444 cardiovascular responses to exercise training in heart failure patients with
445 preserved ejection fraction: a systematic review and meta-analysis. *J Appl Physiol*
446 *Bethesda Md 1985* 119: 726–733, 2015.
- 447 10. **Dineen NE, Brodie FG, Robinson TG, Panerai RB.** Continuous estimates of
448 dynamic cerebral autoregulation during transient hypocapnia and hypercapnia. *J*
449 *Appl Physiol Bethesda Md 1985* 108: 604–613, 2010.
- 450 11. **Erkelens CD, van der Wal HH, de Jong BM, Elting J-W, Renken R, Gerritsen M,**
451 **van Laar PJ, van Deursen VM, van der Meer P, van Veldhuisen DJ, Voors AA,**
452 **Luijckx G-J.** Dynamics of cerebral blood flow in patients with mild non-ischaemic
453 heart failure. *Eur J Heart Fail* 19: 261–268, 2017.
- 454 12. **Fadel PJ, Wang Z, Tuncel M, Watanabe H, Abbas A, Arbique D, Vongpatanasin**
455 **W, Haley RW, Victor RG, Thomas GD.** Reflex sympathetic activation during static
456 exercise is severely impaired in patients with myophosphorylase deficiency. *J*
457 *Physiol* 548: 983–993, 2003.

- 458 13. **Fisher JP, Ogoh S, Young CN, Raven PB, Fadel PJ.** Regulation of middle cerebral
459 artery blood velocity during dynamic exercise in humans: influence of aging. *J Appl*
460 *Physiol Bethesda Md* 1985 105: 266–273, 2008.
- 461 14. **Fontana J, Moratin J, Ehrlich G, Scharf J, Weiß C, Schmieder K, Barth M.**
462 **Dynamic Autoregulatory Response After Aneurysmal Subarachnoid Hemorrhage**
463 **and Its Relation to Angiographic Vasospasm and Clinical Outcome.** *Neurocrit Care*
464 **23: 355–363, 2015.**
- 465 15. **Fraser KS, Heckman GA, McKelvie RS, Harkness K, Middleton LE, Hughson RL.**
466 Cerebral hypoperfusion is exaggerated with an upright posture in heart failure:
467 impact of depressed cardiac output. *JACCHeart Fail* 3: 168–175, 2015.
- 468 16. **Gruhn N, Larsen FS, Boesgaard S, Knudsen GM, Mortensen SA, Thomsen G,**
469 **Aldershvile J.** Cerebral blood flow in patients with chronic heart failure before and
470 after heart transplantation. *Stroke* 32: 2530–2533, 2001.
- 471 17. **Haeusler KG, Laufs U, Endres M.** Chronic heart failure and ischemic stroke. *Stroke*
472 42: 2977–2982, 2011.
- 473 18. **Havakuk O, King KS, Grazette L, Yoon AJ, Fong M, Bregman N, Elkayam U,**
474 **Kloner RA.** Heart Failure-Induced Brain Injury. *J Am Coll Cardiol* 69: 1609–1616,
475 2017.
- 476 19. **Haykowsky MJ, Liang Y, Pechter D, Jones LW, McAlister FA, Clark AM.** A meta-
477 analysis of the effect of exercise training on left ventricular remodeling in heart
478 failure patients: the benefit depends on the type of training performed. *J Am Coll*
479 *Cardiol* 49: 2329–2336, 2007.
- 480 20. **Hellström G, Fischer-Colbrie W, Wahlgren NG, Jogestrand T.** Carotid artery
481 blood flow and middle cerebral artery blood flow velocity during physical exercise.
482 *J Appl Physiol Bethesda Md* 1985 81: 413–418, 1996.
- 483 21. **Katsogridakis E, Dineen NE, Brodie FG, Robinson TG, Panerai RB.** Signal-to-
484 noise ratio of bilateral nonimaging transcranial Doppler recordings of the middle
485 cerebral artery is not affected by age and sex. *Ultrasound Med Biol* 37: 530–538,
486 2011.
- 487 22. **Kim M-S, Kim J-J.** Heart and brain interconnection - clinical implications of
488 changes in brain function during heart failure. *Circ J Off J Jpn Circ Soc* 79: 942–947,
489 2015.
- 490 23. **Kim Y-S, Krogh-Madsen R, Rasmussen P, Plomgaard P, Ogoh S, Secher NH, van**
491 **Lieshout JJ.** Effects of hyperglycemia on the cerebrovascular response to rhythmic
492 handgrip exercise. *Am J Physiol-Heart Circ Physiol* 293: H467–H473, 2007.
- 493 24. **Krzemiński K, Cybulski G, Ziemba A, Nazar K.** Cardiovascular and hormonal
494 responses to static handgrip in young and older healthy men. *Eur J Appl Physiol*
495 112: 1315–1325, 2012.

- 496 25. **Low DA, Wingo JE, Keller DM, Davis SL, Cui J, Zhang R, Crandall CG.** Dynamic
497 cerebral autoregulation during passive heat stress in humans. *Am J Physiol Regul*
498 *Integr Comp Physiol* 296: R1598-1605, 2009.
- 499 26. **Mandic S, Tymchak W, Kim D, Daub B, Quinney HA, Taylor D, Al-Kurtass S,**
500 **Haykowsky MJ.** Effects of aerobic or aerobic and resistance training on
501 cardiorespiratory and skeletal muscle function in heart failure: a randomized
502 controlled pilot trial. *Clin Rehabil* 23: 207–216, 2009.
- 503 27. **Massaro AR, Dutra AP, Almeida DR, Diniz RV, Malheiros SM.** Transcranial
504 Doppler assessment of cerebral blood flow: effect of cardiac transplantation.
505 *Neurology* 66: 124–126, 2006.
- 506 28. **Meng L, Hou W, Chui J, Han R, Gelb AW.** Cardiac Output and Cerebral Blood Flow:
507 The Integrated Regulation of Brain Perfusion in Adult Humans. *Anesthesiology* 123:
508 1198–1208, 2015.
- 509 29. **Negrão CE, Rondon MU, Tinucci T, Alves MJ, Roveda F, Braga AM, Reis SF,**
510 **Nastari L, Barretto AC, Krieger EM, Middlekauff HR.** Abnormal neurovascular
511 control during exercise is linked to heart failure severity. *Am J Physiol Heart Circ*
512 *Physiol* 280: H1286-1292, 2001.
- 513 30. **Nogueira RC, Bor-Seng-Shu E, Santos MR, Negrão CE, Teixeira MJ, Panerai RB.**
514 Dynamic cerebral autoregulation changes during sub-maximal handgrip maneuver.
515 *PloS One* 8: e70821, 2013.
- 516 31. **Ogoh S, Ainslie PN.** Regulatory mechanisms of cerebral blood flow during
517 exercise: new concepts. *Exerc Sport Sci Rev* 37: 123–129, 2009.
- 518 32. **Ogoh S, Dalsgaard MK, Yoshiga CC, Dawson EA, Keller DM, Raven PB, Secher**
519 **NH.** Dynamic cerebral autoregulation during exhaustive exercise in humans. *Am J*
520 *Physiol Heart Circ Physiol* 288: H1461-1467, 2005.
- 521 33. **Ogoh S, Sato K, Akimoto T, Oue A, Hirasawa A, Sadamoto T.** Dynamic cerebral
522 autoregulation during and after handgrip exercise in humans. *J Appl Physiol*
523 *Bethesda Md* 1985 108: 1701–1705, 2010.
- 524 34. **Panerai RB.** Assessment of cerebral pressure autoregulation in humans--a review
525 of measurement methods. *Physiol Meas* 19: 305–338, 1998.
- 526 35. **Panerai RB.** The critical closing pressure of the cerebral circulation. *Med Eng Phys*
527 25: 621–632, 2003.
- 528 36. **Panerai RB.** Cerebral autoregulation: from models to clinical applications.
529 *Cardiovasc Eng Dordr Neth* 8: 42–59, 2008.
- 530 37. **Panerai RB.** Transcranial Doppler for evaluation of cerebral autoregulation. *Clin*
531 *Auton Res Off J Clin Auton Res Soc* 19: 197–211, 2009.

- 532 38. **Panerai RB, Dineen NE, Brodie FG, Robinson TG.** Spontaneous fluctuations in
533 cerebral blood flow regulation: contribution of PaCO₂. *J Appl Physiol Bethesda Md*
534 *1985* 109: 1860–1868, 2010.
- 535 39. **Panerai RB, Eyre M, Potter JF.** Multivariate modeling of cognitive-motor
536 stimulation on neurovascular coupling: transcranial Doppler used to characterize
537 myogenic and metabolic influences. *Am J Physiol Regul Integr Comp Physiol* 303:
538 R395-407, 2012.
- 539 40. **Panerai RB, Moody M, Eames PJ, Potter JF.** Cerebral blood flow velocity during
540 mental activation: interpretation with different models of the passive pressure-
541 velocity relationship. *J Appl Physiol Bethesda Md 1985* 99: 2352–2362, 2005.
- 542 41. **Panerai RB, White RP, Markus HS, Evans DH.** Grading of cerebral dynamic
543 autoregulation from spontaneous fluctuations in arterial blood pressure. *Stroke J*
544 *Cereb Circ* 29: 2341–2346, 1998.
- 545 42. **Patel N, Panerai RB, Haunton V, Katsogridakis E, Saeed NP, Salinet A, Brodie F,**
546 **Syed N, D'Sa S, Robinson TG.** The Leicester cerebral haemodynamics database:
547 normative values and the influence of age and sex. *Physiol Meas* 37: 1485–1498,
548 2016.
- 549 43. **Paulson OB, Jarden JO, Vorstrup S, Holm S, Godtfredsen J.** Effect of captopril on
550 the cerebral circulation in chronic heart failure. *Eur J Clin Invest* 16: 124–132, 1986.
- 551 44. **Poole DC, Richardson RS, Haykowsky MJ, Hirai DM, Musch TI.** Exercise
552 Limitations in Heart Failure with Reduced and Preserved Ejection Fraction. *J. Appl.*
553 *Physiol. Bethesda Md 1985* (October 19, 2017). doi:
554 10.1152/jappphysiol.00747.2017.
- 555 45. **Prodel E, Balanos GM, Braz ID, Nobrega ACL, Vianna LC, Fisher JP.** Muscle
556 metaboreflex and cerebral blood flow regulation in humans: implications for
557 exercise with blood flow restriction. *Am J Physiol Heart Circ Physiol* 310: H1201-
558 1209, 2016.
- 559 46. **Ravits JM.** AAEM minimonograph #48: autonomic nervous system testing. *Muscle*
560 *Nerve* 20: 919–937, 1997.
- 561 47. **Salinet AS, Robinson TG, Panerai RB.** Effects of cerebral ischemia on human
562 neurovascular coupling, CO₂ reactivity, and dynamic cerebral autoregulation. *J*
563 *Appl Physiol Bethesda Md 1985* 118: 170–177, 2015.
- 564 48. **Salinet ASM, Robinson TG, Panerai RB.** Reproducibility of cerebral and
565 peripheral haemodynamic responses to active, passive and motor imagery
566 paradigms in older healthy volunteers: a fTCD study. *J Neurosci Methods* 206: 143–
567 150, 2012.
- 568 49. **Schrier RW, Abraham WT.** Hormones and hemodynamics in heart failure. *N Engl J*
569 *Med* 341: 577–585, 1999.

- 570 50. **Silber DH, Sutliff G, Yang QX, Smith MB, Sinoway LI, Leuenberger UA.** Altered
571 mechanisms of sympathetic activation during rhythmic forearm exercise in heart
572 failure. *J Appl Physiol Bethesda Md* 1985 84: 1551–1559, 1998.
- 573 51. **Smirl JD, Haykowsky MJ, Nelson MD, Altamirano-Diaz LA, Ainslie PN.** Resting
574 and exercise cerebral blood flow in long-term heart transplant recipients. *J Heart*
575 *Lung Transplant Off Publ Int Soc Heart Transplant* 31: 906–908, 2012.
- 576 52. **Smirl JD, Haykowsky MJ, Nelson MD, Tzeng Y-C, Marsden KR, Jones H, Ainslie**
577 **PN.** Relationship between cerebral blood flow and blood pressure in long-term
578 heart transplant recipients. *Hypertens Dallas Tex* 1979 64: 1314–1320, 2014.
- 579 53. **Tiecks FP, Lam AM, Aaslid R, Newell DW.** Comparison of static and dynamic
580 cerebral autoregulation measurements. *Stroke J Cereb Circ* 26: 1014–1019, 1995.
- 581 54. **Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J.**
582 The sympathetic nervous system in heart failure physiology, pathophysiology, and
583 clinical implications. *J Am Coll Cardiol* 54: 1747–1762, 2009.
- 584 55. **Tzeng Y-C, Ainslie PN.** Blood pressure regulation IX: cerebral autoregulation
585 under blood pressure challenges. *Eur J Appl Physiol* 114: 545–559, 2014.
- 586 56. **Tzeng YC, Ainslie PN, Cooke WH, Peebles KC, Willie CK, MacRae BA, Smirl JD,**
587 **Horsman HM, Rickards CA.** Assessment of cerebral autoregulation: the quandary
588 of quantification. *Am J Physiol Circ Physiol* 303: 658, 2012.
- 589 57. **van der Velpen IF, Yancy CW, Sorond FA, Sabayan B.** Impaired Cardiac Function
590 and Cognitive Brain Aging. *Can J Cardiol* 33: 1587–1596, 2017.
- 591 58. **Verbree J, Bronzwaer A, van Buchem MA, Daemen M, van Lieshout JJ, van Osch**
592 **M.** Middle cerebral artery diameter changes during rhythmic handgrip exercise in
593 humans. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab* 37: 2921–
594 2927, 2017.
- 595 59. **Vianna LC, Deo SH, Jensen AK, Holwerda SW, Zimmerman MC, Fadel PJ.**
596 Impaired dynamic cerebral autoregulation at rest and during isometric exercise in
597 type 2 diabetes patients. *Am J Physiol Heart Circ Physiol* 308: H681–687, 2015.
- 598 60. **Vogels RLC, Scheltens P, Schroeder-Tanka JM, Weinstein HC.** Cognitive
599 impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail* 9:
600 440–449, 2007.
- 601 61. **Willie CK, Tzeng YC, Fisher JA, Ainslie PN.** Integrative regulation of human brain
602 blood flow. *J Physiol* 592: 841–859, 2014.
- 603 62. **WRITING COMMITTEE MEMBERS, Yancy CW, Jessup M, Bozkurt B, Butler J,**
604 **Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson**
605 **MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJV, Mitchell JE,**
606 **Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WHW, Tsai EJ, Wilkoff BL,**
607 **American College of Cardiology Foundation/American Heart Association**
608 **Task Force on Practice Guidelines.** 2013 ACCF/AHA guideline for the

609 management of heart failure: a report of the American College of Cardiology
610 Foundation/American Heart Association Task Force on practice guidelines.
611 *Circulation* 128: e240-327, 2013.

612

613

614

615

616

617

618

619

620

621

622

623

624

625

626

627

628

629

630

631

632

633

634

635

636

637

638

639

640

641

642

643

644

645

646

647

648

649

650

651

652

653

654

655 **TABLES**

656 **Table 1** Baseline characteristics including haemodynamic parameters in control subjects and
657 heart failure patients

VARIABLES	CONTROL (n=23)	HEART FAILURE (n=40)	<i>P</i>
Male n (%)	5 (22%)	31 (78%)	< 0.001
Age (years)	62.8 ± 8.6	62.9 ± 8.7	0.96
LVEF %	-	40 [30 - 40]	
NYHA			
I	-	11 (27.5%)	
II	-	20 (50%)	
III	-	8 (20%)	
IV	-	1 (2.5%)	
Risk Factors			
Previous cardiac surgery n (%)	-	-	
Previous myocardial infarction n (%)	-	27 (68%)	
Hypertension n (%)	2 (8.6%)	34 (85%)	< 0.001
Peripheral vascular disease n (%)	-	5 (13%)	
COPD n (%)	-	2 (5.0%)	
Smoking n (%)	-	15 (37.5%)	
Previous smoking n (%)	4 (17.4%)	14 (35.0%)	0.06
Diabetes n (%)	-	17 (42.5%)	
Atrial fibrillation n (%)	-	4 (10%)	
Previous stroke n (%)	-	3 (7.5%)	
Obesity (BMI >30 kg/m ²) n (%)	-	7 (17.5%)	
Medication			
Acetylsalicylic acid n (%)	-	33 (82.5%)	
Vitamin K-antagonist n (%)	-	2 (5.0%)	
ACE inhibitor/ ARB n (%)	2 (8.7%)	32 (80.0%)	< 0.001
Beta blocker n (%)	1 (4.3%)	32 (80.0%)	< 0.001
HR (bpm)	72.1 ± 10.9	65.4 ± 13.3	0.004
MAP (mmHg)	94.6 ± 13.4	93.5 ± 11.9	0.745
CBV (cm/s)	60.7 ± 12.3	59.7 ± 13.5	0.848
CrCP (mmHg)	5.8 ± 8.1	14.8 ± 9.7	0.001
RAP (mmHg.s/cm)	1.53 ± 0.36	1.4 ± 0.37	0.154

658 Values are population mean ± SD, median (interquartile range), or n (%). LVEF, left
659 ventricular ejection fraction; BMI, body mass index; COPD, chronic obstructive pulmonary
660 disease; ACE, Angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker.
661 MAP, mean arterial pressure; HR, Heart rate; CBV, cerebral blood velocity; CrCP, critical
662 closing pressure; RAP, resistance area-product; ARI, autoregulation index.

Table 2. Peripheral and cerebral hemodynamic parameters during the handgrip manoeuvre

VARIABLES	CONTROLS				HEART FAILURE				p-value iHG Effect	p-value Group Effect
	T1	T2	T3	T4	T1	T2	T3	T4		
MAP (mmHg)	97.2 ± 12.1	99.8 ± 12.4*	112.7 ± 13.5* [#]	98.9 ± 11.4	91.5 ± 11.3	92.5 ± 11.8	99.2 ± 15.2* [#]	102.8 ± 15.2*	0.001	0.04
HR (bpm)	71.1 ± 10.9 [#]	72.0 ± 9.8 [#]	75.4 ± 9.3* [#]	73.0 ± 8.3	63.5 ± 13.7 [#]	64.0 ± 14.4 [#]	67.5 ± 14.4* [#]	69.5 ± 14.6*	0.001	0.001
CBV (cm.s-1)	61.5 ± 12.6	64.3 ± 13.5*	66.3 ± 14.5*	61.5 ± 13.4	59.1 ± 14.8	59.2 ± 15.7*	62.3 ± 15.8*	63.9 ± 16.0*	0.001	0.197
CrCP (mmHg)	10.0 ± 8.6	8.5 ± 7.5	9.9 ± 9.4	10.8 ± 9.8	14.1 ± 11.8	14.4 ± 12.1	14.1 ± 12.6	12.9 ± 12.1	0.757	0.231
RAP (mmHg.s/cm)	1.50 ± 0.44	1.53 ± 0.47	1.67 ± 0.57*	1.53 ± 0.48	1.52 ± 0.60	1.40 ± 0.44*	1.45 ± 0.45*	1.48 ± 0.44*	0.001	0.202
ARI	5.8 ± 1.5	5.9 ± 1.1	6.2 ± 1.0	5.9 ± 1.2	5.1 ± 2.8	4.3 ± 2.5 ^{\$&}	5.1 ± 2.7	5.6 ± 2.7*	0.025	0.021

Values are population mean ± SD.

MAP, mean arterial pressure; HR, heart rate; CBV, cerebral blood velocity; CrCP, critical closing pressure; RAP, resistance area-product; ARI: autoregulation index.

T1, baseline 0-50 s; T2, 50-100 s, T3, 180-230 s, T4, 250-300s.

[#]P < 0.05 vs. controls; *P < 0.05 vs. time (repeated measures ANOVA).

^{\$}P < 0.05 vs. controls; [&]P < 0.05 vs. time (Friedman repeated measures test).

FIGURE LEGENDS

Figure 1. Population averages of (A) mean arterial blood pressure, (B) heart rate, (C) cerebral blood velocity, (D) autoregulation index, (E) critical closing pressure, and (F) resistance area product for healthy control subjects (dashed line) and heart failure patients (continuous line). Gray bar represents duration of handgrip maneuver. Error bars correspond to the largest ± 1 SE at the point of occurrence.

Figure 2. Mean $+1$ SE of cerebral autoregulation index (ARI) at baseline (T1), beginning (T2), last 30 s (T3) and recovery (T4) from handgrip in healthy controls (black bar) and heart failure patients (white bar). * $p < 0.05$ vs. controls; # $p < 0.05$ vs. time.