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

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

Exercise in HF patients has been reported in several studies (19, 26). A recent review has highlighted the need to improve our understanding of the role of the brain in exercise intolerance in HF (4). Whilst we have recently reported that HF patients have depressed dCA at rest when compared with healthy subjects (6), cerebrovascular responses to ~~HG~~ (iHG have not been described for HF patients. Studying the effects of (iHG in these patients could lead to better insights into the role of the autonomic nervous system in CBF control, as well as a more sensitive test of patients at higher risk of neurological complications. For this reason, we tested the hypothesis that dCA is impaired during sub-maximal (iHG) manoeuvre in HF patients with reduced ejection fraction. This information could have considerable value for tailoring treatment and/or monitoring of HF patients in response to rehabilitation and 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) ≤ 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 slided 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 ARIt. 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 ARIt 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 ARIt 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 text was used with categorical variables. Results are expressed as mean ± 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, ARIt 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 ARIt to reach values similar to control subjects by recovery (Fig. 1.F, Fig. 2). EtCO2 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)(27,28), 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 ARIt 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 ARIt, 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 ARIt 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) ARIt 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 PaCO2 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 ARIt 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 ARIt could have been biased by the presence of asymptomatic CAD.

For logistic reasons we have not been able to perform measurements of EtCO2 in controls, but several studies have shown that EtCO2 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 EtCO2 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 PaCO2 was markedly reduced in HF in comparison with controls (35).

In a previous study, Nogueira et al. (30) reported temporal changes in ARIt 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.

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**TABLES**

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

|  |  |  |  |
| --- | --- | --- | --- |
| VARIABLES | CONTROL  (n=23) | HEART FAILURE  (n=40) | *P* |
| 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/m2) 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 |
|  |  |  |  |

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

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

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | CONTROLS |  |  |  | HEART FAILURE |  |  | p-value iHG  Effect | p-value Group  Effect |
| VARIABLES | 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.