Am J Physiol Heart Circ Physiol 315: H254–H261, 2018.
First published April 13, 2018; doi:10.1152/ajpheart.00727.2017.

RESEARCH ARTICLE | *Integrative Cardiovascular Physiology and Pathophysiology*

Dynamic cerebral autoregulation is impaired during submaximal isometric handgrip in patients with heart failure

J. R. Caldas,[1,4,6] R. B. Panerai,[2,3] A. M. Salinet, E. Seng-Shu,[4] G. S. R. Ferreira,[1] L. Camara,[1] R. H. Passos,[6] F. R. B. G. Galas,[1] J. P. Almeida, R. C. Nogueira,[4] M. de Lima Oliveira,[4] T. G. Robinson,[2,3] and L. A. Hajjar[5]

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

Submitted 18 December 2017; accepted in final form 4 April 2018

Caldas JR, Panerai RB, Salinet AM, Seng-Shu E, Ferreira GS, Camara L, Passos RH, Galas FR, Almeida JP, Nogueira RC, de Lima Oliveira M, Robinson TG, Hajjar LA. Dynamic cerebral autoregulation is impaired during submaximal isometric handgrip in patients with heart failure. *Am J Physiol Heart Circ Physiol* 315: H254–H261, 2018. First published April 13, 2018; doi:10.1152/ajpheart.00727.2017.—The incidence of neurological complications, including stroke and cognitive dysfunction, is elevated in patients with heart failure (HF) with reduced ejection fraction. We hypothesized that the cerebrovascular response to isometric handgrip (iHG) is altered in patients with HF. 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 min, corresponding to 1 min of baseline and 3 min of iHG exercise, at 30% maximum voluntary contraction, followed by 2 min of recovery. The resistance-area product was calculated from the instantaneous BP-CBV relationship. Dynamic cerebral autoregulation (dCA) was assessed with the time-varying autoregulation index estimated from the CBV step response derived by an autoregressive moving-average time-domain model. Forty patients with HF and 23 BP-matched healthy volunteers were studied. Median left ventricular ejection fraction was 38.5% (interquartile range: 0.075%) in the HF group. Compared with control subjects, patients with HF exhibited lower time-varying autoregulation index during iHG, indicating impaired dCA ($P < 0.025$). During iHG, there were steep rises in CBV, BP, and heart rate in control subjects but with different temporal patterns in HF, which, together with the temporal evolution of resistance-area product, confirmed the disturbance in dCA in HF. Patients with HF were more likely to have impaired dCA during iHG compared with age-matched control subjects. Our results also suggest an impairment of myogenic, neurogenic, and metabolic control mechanisms in HF. The relationship between impaired dCA and neurological complications in patients with HF during exercise deserves further investigation.

NEW & NOTEWORTHY Our findings provide the first direct evidence that cerebral blood flow regulatory mechanisms can be affected in patients with heart failure during isometric handgrip exercise. As a consequence, eventual blood pressure 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 patients with heart failure may be at greater risk for cerebral events during exercise.

cerebral blood flow; cerebral hemodynamics; exercise; transcranial Doppler ultrasound

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 (3, 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 resulting from cerebral ischemia or small vessel damage caused by hypo- or hyperperfusion. 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 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 (14, 36, 47, 56a).

The isometric handgrip (iHG) maneuver 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 (4, 33). It has been shown that isometric exercise induces variations in CBF, possibly because of bilateral activation of cortical brain areas implicated in muscle contraction and autonomic regulation (23). Isometric

Address for reprint requests and other correspondence: J. Caldas, Surgical Intensive Care, Heart Institute, University of Sao Paulo, Av. Dr. Enéas de Carvalho Aguiar, São Paulo 05403-000, Brazil (e-mail: caldas.juliana@gmail.com).

exercise presents a challenge to CA, not only because of elevations in BP but also because of 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 (3). Sympathetic activation and regulation of fluid homeostasis through the brain is one of the most important causes of left ventricular (LV) remodeling and symptom aggravation in HF (49). This complex syndrome is worsened by autonomic nervous system dysfunction resulting from excess sympathoexcitation and/or vagal nerve withdrawal (22, 54).

Exercise in patients with HF 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 (3). Although we have recently reported that patients with HF have depressed dCA at rest compared with healthy subjects (5), cerebrovascular responses to iHG have not been described for patients with HF. Studying the effects of iHG in these patients could lead to better insights into the role of the autonomic nervous system in CBF control and a more sensitive test of patients at higher risk of neurological complications. For this reason, we tested the hypothesis that dCA is impaired during submaximal iHG maneuver in patients with HF with reduced ejection fraction (EF). This information could have considerable value for tailoring treatment and/or monitoring of patients with HF in response to rehabilitation and activities of daily living involving isometric exercise.

MATERIALS AND METHODS

Research Participants

This was an observational single-center 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: *1*) LVEF $\leq$ 40% on transthoracic echocardiography; *2*) clinically diagnosed ischemic chronic HF with any functional class of the New York Heart Association classification (3); and *3*) written informed consent. Age- and BP-matched healthy control subjects 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.

Procedures

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) 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 noninvasively using finger arterial volume clamping (Finometer PRO, Finapres Medical Systems, Amsterdam, The 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 CO_2 was continuously measured with an infrared capnograph (Dixtal, dx 1265 $ETCO_2$, Capnogard, Manaus, Brazil) via a closely fitting mask and recorded at 1-min intervals. End-tidal CO_2 was not monitored in control subjects. LVEF was derived by transthoracic echocardiography.

The 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 10 s 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 min and not to move any muscles other than those involved in the test (46). All 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 5 min, a continuous 6-min recording was obtained corresponding to 1 min of baseline, 3 min of iHG, followed by 2 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 artifacts 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 cutoff 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 HR were obtained for each heart beat. Critical closing pressure (CrCP) and the 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 was estimated as a function of time (ARI_t) using an autoregressive moving-average time-domain model, as previously described (10, 38). The autoregressive moving-average model was applied to a 60-s window of data that was slided along the entire recording at 0.6-s intervals. For this reason, the first and last 30 s of the recording cannot be used to generate values of ARI_t. At each 0.6-s interval, the CBV step response was calculated from the autoregressive moving-average 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, whereas ARI = 9 corresponds to the most efficient CA that can be observed (53). ARI_t and all other cerebral hemodynamic parameters were averaged for time intervals of 30 s corresponding to baseline before the maneuver (T_1), beginning of iHG (T_2), last 30 s of the maneuver (T_3), and last 30 s of the recovery period (T_4) (48).

Statistical Analysis

After assessment of normality with the Shapiro-Wilk one-sample test, parametric (Student's *t*) or nonparametric (Mann-Whitney *U*) tests were used as appropriate. Fisher's exact text was used with categorical variables. Results are expressed as means $\pm$ SD or medians with interquartile ranges. Interhemispherical differences in parameters were tested with a paired Student's *t*-test or Wilcoxon nonparametric test. In the absence of differences, values for right and left MCAs were averaged. Changes in ARI_t and other parameters at T_1, T_2, T_3, and T_4 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 maneuver), intergroup differences were assessed with mixed-effects ANOVA or Mann-Whitney *U*-test. Statistical analyses were performed using SPSS version 24.0 (SPSS, Chicago, IL). *P* values of $<$0.05 were considered statistically significant.

Table 1. *Baseline characteristics including hemodynamic parameters in control subjects and patients with heart failure*

Variables	Control Group	Heart Failure Group	*P* Value
n	23	40	
Male/female, *n* (%)	5/18 (22/78)	31/9 (78/22)	<0.001
Age, yr	62.8 ± 8.6	62.9 ± 8.7	0.96
Left ventricular ejection fraction, %		40 (30–40)	
New York Heart Association			
Class I		11 (27.5)	
Class II		20 (50)	
Class III		8 (20)	
Class 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)	
Chronic obstructive pulmonary disease, *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 (body mass index >30 kg/m^2), *n* (%)		7 (17.5)	
Medication			
Acetylsalicylic acid, *n* (%)		33 (82.5)	
Vitamin K antagonist, *n* (%)		2 (5.0)	
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, *n* (%)	2 (8.7)	32 (80.0)	<0.001
β-Blocker, *n* (%)	1 (4.3)	32 (80.0)	<0.001
Heart rate, beats/min	72.1 ± 10.9	65.4 ± 13.3	0.004
Mean arterial pressure, mmHg	94.6 ± 13.4	93.5 ± 11.9	0.745
Cerebral blood velocity, cm/s	60.7 ± 12.3	59.7 ± 13.5	0.848
Critical closing pressure, mmHg	5.8 ± 8.1	14.8 ± 9.7	0.001
Resistance-area product, mmHg·s^{-1}·cm^{-1}	1.53 ± 0.36	1.4 ± 0.37	0.154

Values are population means ± SD; *n*, number of subjects. Units are medians (interquartile ranges) or *n* (%).

RESULTS

Participants

Fifty-two patients were recruited; 12 participants were excluded because of technical problems (4), absent temporal acoustic window bilaterally (4), or poor-quality recording (56a). Twenty-five healthy subjects were recruited; one subject was excluded because of poor-quality recordings and one subject because of absence of temporal acoustic windows bilaterally. The total number of recordings analyzed was thus 40 patients with HF and 23 healthy volunteers.

All subjects in the HF group had clinically diagnosed ischemic chronic HF, with a median LVEF of 38.5% (interquartile range: 0.075%) on transthoracic echocardiography. Demographic and clinical characteristics of the population are shown in Table 1. None of the bilateral cerebral hemodynamic parameters showed significant differences between the right and left MCAs; therefore, values were averaged in further analyses (Table 1).

Baseline Conditions

Compared with control subjects, HR was significantly lower and CrCP significantly higher in patients with HF (Table 1). Otherwise, no significant differences were seen between groups in peripheral or cerebral hemodynamic parameters (Table 1). End-tidal CO_2 was 34.7 ± 3.8 mmHg in the HF group.

Handgrip Maneuver

With the exception of CrCP, all other parameters analyzed showed significant changes in response to the iHG maneuver (Table 2). In control subjects, the onset of the iHG induced increases in BP, HR, and CBV (Fig. 1, *A–C*). RAP also showed a continuous rise that tended to counteract the BP increase, whereas CrCP tended to remain constant (Fig. 1, *D* and *E*). Different temporal patterns were observed in HF. BP rose much less steeply ($P = 0.04$; Table 2 and 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 control subjects (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 control subjects (Fig. 1*D*). Similarly, ARI_t showed a different pattern in patients with HF compared with control subjects, with a significant drop over the first 30 s in patients with HF only. However, patients with HF showed a continuous rise in ARI_t to reach values similar to control subjects by recovery (Figs. 1*F* and 2). End-tidal CO_2 did not show temporal changes during the maneuver in the HF group ($P = 0.38$).

DISCUSSION

Main Findings

To our knowledge, this is the first study to report on alterations in cerebral hemodynamics in patients with HF,

Table 2. *Peripheral and cerebral hemodynamic parameters during the handgrip maneuver*

Variables	Control Group				Heart Failure				*P* Value iHG Effect	*P* Value Group Effect
	T_1	T_2	T_3	T_4	T_1	T_2	T_3	T_4		
Mean arterial pressure, 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
Heart rate, beats/min	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
Cerebral blood velocity, cm/s	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
Critical closing pressure, 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
Resistance-area product, $mmHg \cdot s^{-1} \cdot cm^{-1}$	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
Autoregulation index	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 means ± SD. T_1, baseline (0–50 s); T_2, 50–100 s; T_3, 180–230 s; T_4, 250–300 s. *$P < 0.05$ vs. the control group; †$P < 0.05$ vs. time (repeated-measures ANOVA); ‡$P < 0.05$ vs. time (Friedman repeated-measures test).

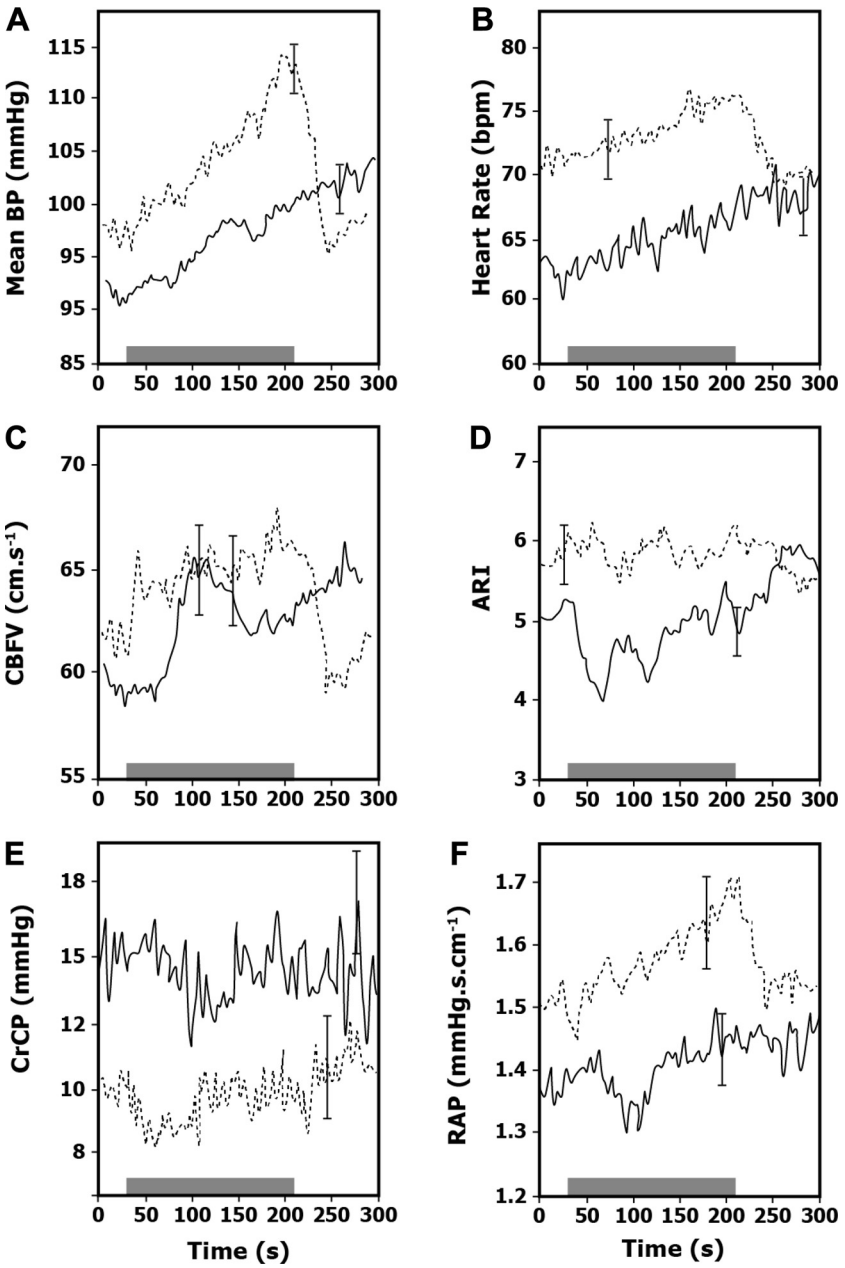

Fig. 1. Population averages of mean arterial blood pressure (MAP; *A*), heart rate [in beats/min (bpm); *B*], cerebral blood velocity (CBFV; *C*), autoregulation index (ARI; *D*), critical closing pressure (CrCP; *E*), and resistance-area product (RAP; *F*) for healthy control subjects (dashed lines) and patients with heart failure (solid lines). The horizontal gray bars represent the duration of the handgrip maneuver. Error bars correspond to the largest ±1 SE at the point of occurrence.

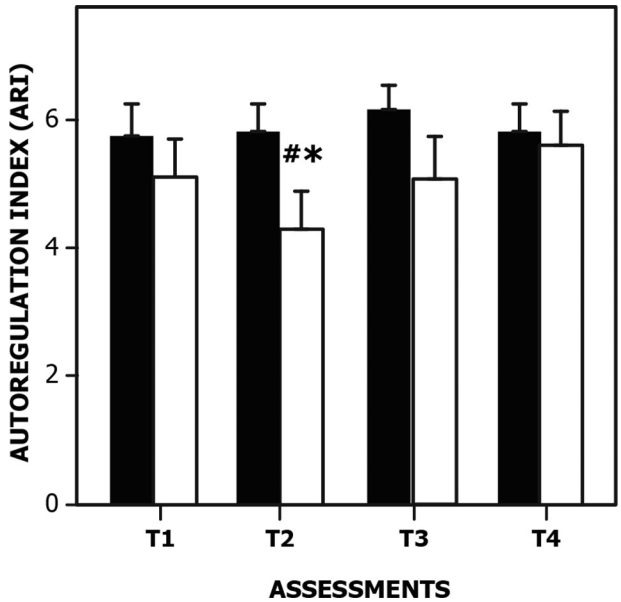

Fig. 2. Mean +1SE of cerebral autoregulation index (ARI) at baseline (T_1), beginning (T_2), last 30 s (T_3), and recovery (T_4) from handgrip in healthy control subjects (filled bars) and patients with heart failure (open bars). *$P <$ 0.05 vs. control subjects; #$P < 0.05$ vs. time.

including dCA, in response to isometric exercise. The major findings are twofold. First, patients with HF exhibited lower dCA during the iHG maneuver compared with age-matched healthy control subjects. Moreover, the temporal pattern of changes in dCA and other cerebrovascular parameters in patients with HF was also different from control subjects. Second, in patients with HF, most of the variables considered, including HR, CBV, and BP, did not return to their baseline values after the maneuver. Taken together, these findings demonstrate that the alterations in dCA, previously shown in patients with HF at rest, also affect their response to isometric exercise (5, 11).

Cerebrovascular Response to Handgrip

Human studies that have investigated the effects of HF on cerebral hemodynamics are limited. The heterogeneity in study design and methodology is a major limitation 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 β-blockers that can have a direct effect on CBF regulation (43). These studies reported CBV in patients with HF but did not include simultaneous BP measurements to allow assessment of dCA and other cerebral hemodynamic 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). Whereas 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. 1*A*), which may be explained by the well-known limitations in cardiac output and baroreceptor sensitivity in these patients, exacerbated by the use of β-blockers in ~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 maneuver (Fig. 1*C*), partly because of 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 control subjects (Fig. 1, *A*, *B*, *C*, and *F*). Because this pattern was also observed in BP and HR, it is likely to be caused by systemic alterations rather than a disturbance in cerebral hemodynamics. 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 maneuver 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 (4, 13, 33). The results of Ogoh et al. (32) indicate that the CBF response to exercise involves complex mechanisms, depending on exercise intensity. In contrast, a previous study of the cerebrovascular response to 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 hemodynamics have often calculated indexes of cerebrovascular resistance or conductance to assess vasomotor activity, independent of separate changes in BP or CBV. The limitation of this approach though is that detailed study of BP-CBV instantaneous relationships shows 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. 1*F* (40).

Given the variability, and poor intermethod 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: *1*) ARI_t dropped significantly at the beginning of iHG, albeit gradually increasing toward the end of iHG and during recovery (Fig. 1*D*); *2*) the rise in RAP was interrupted and actually dropped half-way through the maneuver (Fig. 1*F*); and *3*) despite the lower rate of BP rise, CBV reached similar values as in control subjects (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 (5), 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 arterial P_{CO_2} was not clamped. Finally, deficiencies in the metabolic, neu-

rovascular 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. 1*C*) is markedly different from control subjects, since it suggests impairment of both the myogenic and metabolic mechanisms contributing to dCA. Considering the slow BP rise induced by iHG in HF (Fig. 1*A*), if one removes the velocity "surge," starting at ~75 s (Fig. 1*C*), 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 with control subjects, 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, compared with previous reports of a depressed dCA in HF at rest (4, 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 followup of these patients. Given the number of common daily activities that require an isometric muscle contraction (e.g., carrying foodstuffs and lifting light weights), our findings suggest that BP surges are buffered less efficiently, with more passive transmission of BP to the cerebral vasculature (36), whereas metabolic demands may not be met by the neurovascular coupling mechanism, thus leading to temporary ischemia. Recent systematics reviews and meta-analyses (9, 19) have 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 EF (9), whereas 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 EF, 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 toward more individualized medicine, it is important to take into consideration the cerebrovascular response to exercise in patients with HF. 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 patients with HF, 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 handgrip, Verbree et al. (58) assessed changes in MCA cross-sectional area using MRI, detecting a 2% reduction in cross-sectional area, when young volunteers performed rhythmic handgrip at 60% maximum voluntary contraction. The small cross-sectional area 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, since 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 intersubject anatomic 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 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 carotid artery disease, but we cannot exclude the possibility that values of ARI_t could have been biased by the presence of asymptomatic carotid artery disease.

For logistic reasons, we were not able to perform measurements of end-tidal CO_2 in control subjects, but several studies have shown that end-tidal CO_2 is not significantly altered during 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 end-tidal CO_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 patients with HF compared with control subjects (Table 1 and Fig. 1*E*) also support the speculation that arterial P_{CO_2} was markedly reduced in patients with HF compared with control subjects (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 yr younger than in our control group. 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 yr old), Deegan et al. (8) reported better regulation in women compared with men. In our case though, there was one woman of >70 yr 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 iHG that is a form of isometric exercise, and this was limited

to the MCA. Other forms of exercise, or other intracerebral arteries, like the posterior cerebral *artery* or anterior cerebral *artery*, could lead to different results with pertinent implications for optimizing rehabilitation programs for patients with HF (2).

Conclusions

dCA was impaired in response to iHG in patients with HF with reduced LVEF. In contrast to healthy control subjects, BP, HR, CBV, and RAP failed to return to their baseline levels with iHG cessation. Collectively, our results suggest that the cerebral vasculature of patients with HF 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 patients with HF. Further research is needed on the cerebrovascular response of patients with HF to other forms of exercise, to allow a more comprehensive assessment and risk stratification in these patients.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.R.C., E.B.-SS., F.R.B.G.G., G.S.R.F., L.C., J.P.A., R.C.N., M.d.L.O.M., and L.A.H. conceived and designed research; J.R.C., A.S.S., L.C., R.C.N., and M.d.L.O.M. performed experiments; J.R.C. and R.B.P. analyzed data; J.R.C. and R.B.P. interpreted results of experiments; J.R.C. prepared figures; J.R.C. and R.B.P. drafted manuscript; J.R.C., R.B.P., E.B.-SS., R.H.P., T.G.R., and L.A.H. edited and revised manuscript; J.R.C., R.B.P., A.S.S., E.B.-SS., F.R.B.G.G., G.S.R.F., L.C., R.H.P., J.P.A., R.C.N., M.d.L.O.M., T.G.R., and L.A.H. approved final version of manuscript.

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