

RESEARCH ARTICLE | *Cardiovascular and Renal Integration*

Cerebral blood flow autoregulation in ischemic heart failure

J. R. Caldas,^{1,4} R. B. Panerai,^{2,3} V. J. Haunton,^{2,3} J. P. Almeida,¹ G. S. R. Ferreira,¹ L. Camara,¹ R. C. Nogueira,^{4,5} E. Bor-Seng-Shu,⁴ M. L. Oliveira,⁴ R. R. V. Groehs,¹ L. Ferreira-Santos,¹ M. J. Teixeira,⁴ F. R. B. G. Galas,¹ T. G. Robinson,^{2,3} F. B. Jatene,⁶ and L. A. Hajjar⁶

¹Department of Anesthesia, Heart Institute, University of São Paulo, São Paulo, Brazil; ²Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom; ³Leicester National Institute for Health Research Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, United Kingdom; ⁴Department of Neurosurgery, Hospital das Clínicas, University of São Paulo, São Paulo, Brazil; ⁵Department of Neurology, Hospital das Clínicas, University of São Paulo, São Paulo, Brazil; and ⁶Department of Cardiopneumology, Heart Institute, University of São Paulo, São Paulo, Brazil

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Caldas JR, Panerai RB, Haunton VJ, Almeida JP, Ferreira GS, Camara L, Nogueira RC, Bor-Seng-Shu E, Oliveira ML, Groehs RR, Ferreira-Santos L, Teixeira MJ, Galas FR, Robinson TG, Jatene FB, Hajjar LA. Cerebral blood flow autoregulation in ischemic heart failure. *Am J Physiol Regul Integr Comp Physiol* 312: R108–R113, 2017. First published December 7, 2016; doi:10.1152/ajpregu.00361.2016.—Patients with ischemic heart failure (iHF) have a high risk of neurological complications such as cognitive impairment and stroke. We hypothesized that iHF patients have a higher incidence of impaired dynamic cerebral autoregulation (dCA). Adult patients with iHF and healthy volunteers were included. Cerebral blood flow velocity (CBFV, transcranial Doppler, middle cerebral artery), end-tidal CO₂ (capnography), and arterial blood pressure (Finometer) were continuously recorded supine for 5 min at rest. Autoregulation index (ARI) was estimated from the CBFV step response derived by transfer function analysis using standard template curves. Fifty-two iHF patients and 54 age-, gender-, and BP-matched healthy volunteers were studied. Echocardiogram ejection fraction was 40 (20–45) % in iHF group. iHF patients compared with control subjects had reduced end-tidal CO₂ (34.1 ± 3.7 vs. 38.3 ± 4.0 mmHg, $P < 0.001$) and lower ARI values (5.1 ± 1.6 vs. 5.9 ± 1.0 , $P = 0.012$). ARI < 4 , suggestive of impaired CA, was more common in iHF patients (28.8 vs. 7.4%, $P = 0.004$). These results confirm that iHF patients are more likely to have impaired dCA compared with age-matched controls. The relationship between impaired dCA and neurological complications in iHF patients deserves further investigation.

cerebral blood flow; dynamic cerebral autoregulation; transfer function analysis; transcranial Doppler; autoregulation index

ISCHEMIC HEART FAILURE (iHF) is the most common type of cardiomyopathy worldwide. It mainly affects middle-aged and elderly people, leading to high mortality rates, high health care costs, and worsening quality of life (8). There is a close link between the heart and the brain in ischemic and other forms of heart failure. Recent advances in the pathophysiology of heart failure in patients have shown the compromise of neural pathways (38), as well as cerebral structural abnormalities (39). Moreover, heart failure patients have increased rates of neuro-

logical complications, including stroke and cognitive dysfunction. Although the pathogenesis of neurological complications in these patients is not well known, they are probably due to low cardiac output and concomitant reduced flow to brain tissue, and/or embolism (6, 10).

Cerebral autoregulation (CA) is the brain's ability to maintain a stable cerebral blood flow (CBF) despite changes in arterial blood pressure (BP) (24). More recently, the classical view that CBF remains constant in the BP range of 60–150 mmHg has been challenged (37). Assessments of CA are generally classified as being “static” or “dynamic” (1). Static CA refers to the steady-state relationship between BP and CBF (1, 32). Dynamic CA reflects the transient response of CBF, often recorded as CBF velocity (CBFV) with transcranial Doppler ultrasound (TCD), to rapid changes in BP (32). Impairment of CA can lead to brain ischemia or microvessel damage. Previous studies have shown an association of CA impairment with cerebrovascular disorders (18, 34).

Given the potential association between disturbances in CBF regulation and neurological complications, we tested the hypothesis that CA is impaired in patients with iHF.

MATERIALS AND METHODS

Research participants. This observational study was 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: heart failure due to ischemic, clinically diagnosed chronic heart failure; functional class II or III, according to the New York Heart Association classification (2); left ventricular ejection fraction (LVEF) $\leq 45\%$ on transthoracic echocardiography. Members of staff from the University of Leicester, Leicester, UK, and their relatives were used as the control group. Subjects were age-, sex- and BP-matched, free of neurological or cardiovascular disease, and were not prescribed any medications. Ethical approval for the study was obtained from the Northampton Research Ethics Committee (UK REC reference 11/EM/0369) and the Research Ethics Committee, Faculty of Medicine, University of São Paulo (Brazil, reference 835.731). All participants gave informed, written consent.

Measurements and data analysis. The study was performed with the participant lying in a supine position, with the head positioned 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 or Vyasis Companion III, Vya-

Address for reprint requests and other correspondence: R. B. Panerai, Dept. of Cardiovascular Sciences, Level 4 Robert Kilpatrick Clinical Sciences Bldg., Leicester Royal Infirmary, Leicester LE2 7LX, UK (e-mail: rp9@le.ac.uk).

sis, San Diego, CA), which were held in place using a head frame. If only one MCA could be insonated, then one side was used in the analysis. The 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 CO₂ (EtCO₂) was continuously measured with an infrared capnograph (Dixtal, dx 1265 EtCO₂ Capnogard, Manaus, Brazil, or with a Capnograph Plus, Smiths Medical) via a closely fitting mask and recorded at 1-min intervals. LVEF was derived by transthoracic echocardiography.

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 cut-off frequency of 20 Hz. The beginning and end of each cardiac cycle were detected in the BP signal, and mean values of BP, CBFV, and heart rate were obtained for each heartbeat. Beat-to-beat parameters were interpolated with a third-order polynomial and resampled at 5 Hz to generate signals with a uniform time base.

Dynamic CA was modeled using transfer function analysis (TFA), using spontaneous fluctuations of mean BP as input and corresponding changes in CBFV as output, as described previously (4, 12, 19, 21). The Welch method was adopted for smoothing spectral estimates obtained with the fast Fourier transform (102.4-s segments, 50% superposition), leading to frequency-dependent estimates of coherence, gain, and phase, which were then averaged for the very low- (VLF, 0.02–0.07 Hz), low- (Lf, 0.07–0.20 Hz), and high- (Hf, 0.20–0.50 Hz)-frequency ranges. Negative values of phase are indicative of the wrap-around phenomenon and were not included in the calculation of mean phase values in these frequency bands (4). Using the inverse fast Fourier transform, the CBFV response to a step change in BP was also derived (18, 23, 40). The CBFV step response was compared with 10 template curves proposed by Tiecks et al. (32), and the best fit curve corresponded to the ARI (23). An interpolation procedure was adopted to obtain real values of ARI (as opposed to only integer values) by fitting a second-order polynomial to the integer values of ARI neighboring the region of minimum error (23). Values of ARI = 0 indicate absence of CA, while ARI = 9 corresponds to the most efficient CA that can be observed (32). A new procedure was adopted using the normalized mean square error for fitting the Tiecks et al. model (32) to the CBFV step response and a minimum threshold for the Lf coherence function to accept or reject estimates of ARI (22).

Baseline cerebral hemodynamic parameters are reported as the average over a 5-min recording at rest.

Statistical analysis. Continuous variables were compared using a Student's *t*-test or the Mann-Whitney *U*-test, and categorical variables were compared using Pearson χ^2 test or Fisher exact test as appropriate, following the Kolmogorov-Smirnov one-sample test. Results are expressed as means \pm SD or medians with interquartile ranges. Pearson's correlation coefficient was used to test for association between parameters. A *P* value <0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS version 22.0 (SPSS, Chicago, IL).

RESULTS

Participants. Seventy patients were recruited, but measurements could not be performed in the first six patients due to technical problems with equipment, and five patients were excluded due to the absence of temporal acoustic window

bilaterally. Fifty-nine healthy subjects were recruited with good-quality recordings. Application of the new procedure for acceptance of the ARI index estimated by TFA led to the rejection of seven patients and five control subjects. The total number of recordings was, thus, 52 iHF patients and 54 healthy volunteers.

All subjects in iHF group had clinically diagnosed ischemic chronic heart failure, functional class II or III, and a LVEF of 40% (20–45). Demographic and clinical characteristics of the population are described in Table 1. Patients and controls had similar ages and BP but significantly different values of EtCO₂ and CBFV.

Dynamic cerebral autoregulation. Population average transfer function results for each group are given in Fig. 1. The coherence function was significantly different in VLF and Lf frequency bands (Fig. 1A, Table 2). Differences in gain were only observed in the Hf band (Fig. 1B, Table 2) when expressed in absolute units (cm·mmHg⁻¹·s⁻¹), but were significantly different in all three frequency bands when calculated as %/mmHg. The phase frequency response was only significantly different in the LF band (Fig. 1C). The CBFV step response (Fig. 1D), reflecting the effect of a sudden change in BP, showed a much faster recovery toward its baseline value in controls than in patients, suggesting worse CA in patients.

There was no significant difference in ARI between the right and left hemispheres in both groups, so the mean value for the

Table 1. Subject characteristics and baseline parameters

Variables	Control	iHF	<i>P</i>
Number (<i>n</i> , male)	54 (35)	52 (42)	0.520
Age, yr	61.8 \pm 10.6	64.3 \pm 9.0	0.203
EtCO ₂ , mmHg	38.3 \pm 4.0	34.1 \pm 3.7	<0.001
Mean BP, mmHg	90.1 \pm 10.6	93.5 \pm 13.0	0.148
Systolic BP, mmHg	128.1 \pm 18.3	135.6 \pm 20.3	0.057
Diastolic BP, mmHg	71.7 \pm 8.3	70.4 \pm 10.3	0.463
HR, bpm	61.4 \pm 9.8	66.2 \pm 14.0	0.230
CBFV Right MCA, cm/s	51.9 \pm 14.2	58.4 \pm 14.5	0.007
CBFV Left MCA, cm/s	51.8 \pm 13.8	58.9 \pm 14.0	0.010
LVEF, %		40% (20–45)	
Risk factors, <i>n</i>			
Previous cardiac surgery			
Previous myocardial infarction		44	
Hypertension		37	
Peripheral vascular disease		5	
Chronic obstructive pulmonary disease		2	
Smoking		12	
Previous smoking		23	
Dyslipidemia		21	
Diabetes		24	
Atrial fibrillation		6	
Previous stroke		4	
Hepatic disease			
Obesity (BMI >30 kg/m ²)		6	
Medication, <i>n</i>			
Acetylsalicylic acid		40	
Vitamin K antagonist		2	
ACE inhibitor/ARB		38	
β -Blocker		41	

Values are population means \pm SD iHF, ischemic heart failure; EtCO₂, end-tidal CO₂; LVEF, left ventricular ejection fraction; BP, blood pressure; HR, heart rate; CBFV, cerebral blood flow velocity; BMI, body mass index; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MCA, middle cerebral artery.

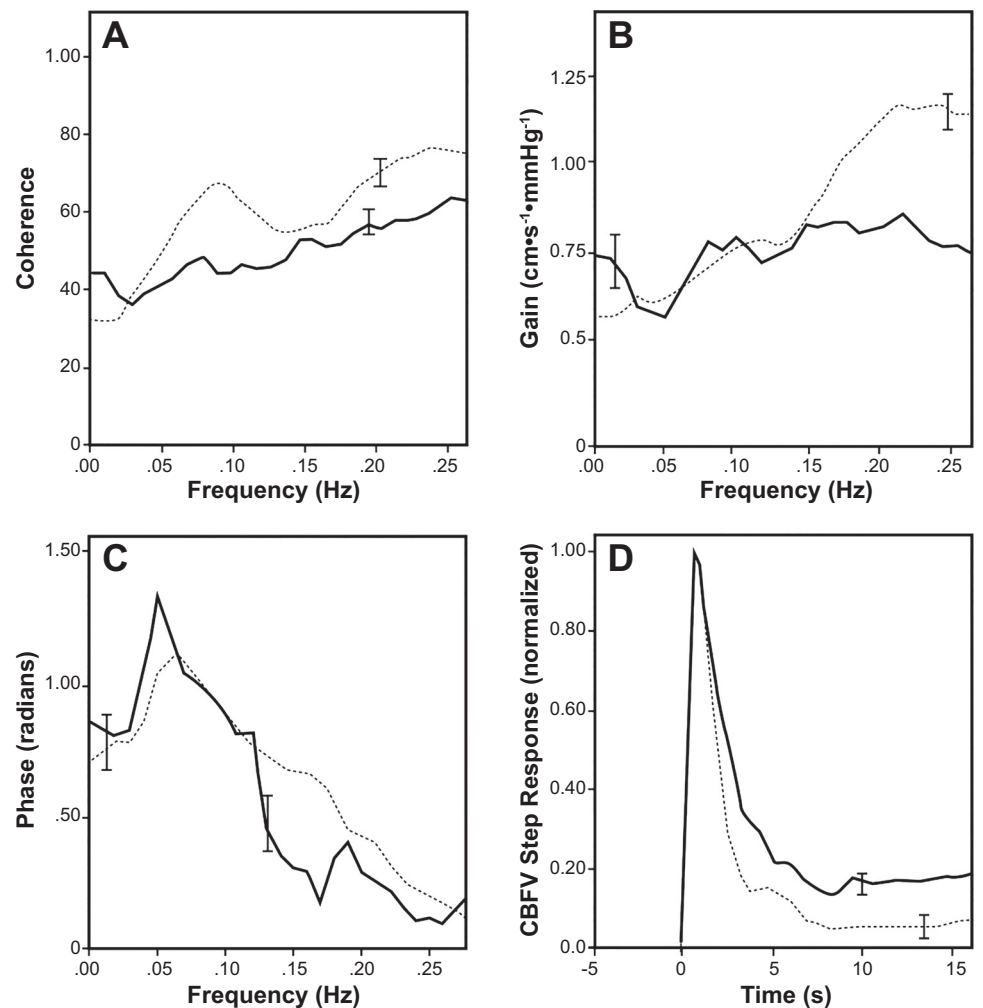


Fig. 1. Population average transfer function parameters. Coherence (A), gain (B), phase (C), and normalized cerebral blood flow velocity (CBFV) step response (D). Ischemic heart failure (continuous line) vs. controls (dashed line). Curves are averages for the right and left hemispheres. For clarity, only the largest \pm SE is represented at the point of occurrence.

two hemispheres was used in further comparisons. ARI was lower in the iHF (5.1 ± 1.8) compared with the control group (5.9 ± 1.3) ($P = 0.012$), thus, confirming the separation of CBFV step responses indicated in Fig. 1D. The correlation

coefficient between ARI and LVEF, or any of the other parameters in Table 1, was not statistically significant.

In the iHF group, 15 patients (28.8%) had ARI <4.0 , suggestive of impaired CA, while in the control group, this was only observed in four subjects (7.2%) ($P = 0.004$). No significant difference in age, ejection fraction, EtCO₂, risk factors, or use of medication were observed when comparing iHF patients, with ARI <4 with those with ARI >4 .

Table 2. Dynamic CA parameters obtained from transfer function analysis

Variable	Control Group (n = 54)	iHF Group (n = 52)	P Value
ARI	5.9 ± 1.4	5.1 ± 1.8	0.012
ARI <4 , n	4	15	0.004
COH VLf	0.49 ± 0.16	0.42 ± 0.18	0.022
COH Lf	0.60 ± 0.14	0.47 ± 0.21	0.001
COH Hf	0.57 ± 0.14	0.52 ± 0.20	0.145
Gain VLf, cm·mmHg ⁻¹ ·s ⁻¹	0.64 ± 0.32	0.68 ± 0.31	0.212
Gain Lf, cm·mmHg ⁻¹ ·s ⁻¹	0.86 ± 0.31	0.78 ± 0.31	0.178
Gain Hf, cm·mmHg ⁻¹ ·s ⁻¹	1.06 ± 0.35	0.75 ± 0.33	0.001
Gain VLf, %/mmHg	0.94 ± 0.43	0.81 ± 0.41	0.101
Gain Lf, %/mmHg	1.28 ± 0.39	1.08 ± 0.55	0.001
Gain Hf, %/mmHg	1.58 ± 0.43	1.09 ± 0.68	<0.001
Phase VLf, radians	1.05 ± 0.31	1.02 ± 0.48	0.422
Phase Lf, radians	0.71 ± 0.20	0.64 ± 0.49	0.032
Phase Hf, radians	0.00 ± 0.11	0.08 ± 0.29	0.051

Values are population means \pm SD. ARI, autoregulation index; COH, coherence function; VLf, very low frequency; Lf, low frequency; Hf, high frequency (bands).

DISCUSSION

Main findings. This is the first study to investigate dynamic CA in human heart failure, reporting that dynamic CA was significantly reduced in iHF patients compared with age-matched controls. Moreover, the occurrence of impaired CA was much more frequent in the iHF group than in controls. The observation that patients had reduced EtCO₂, in comparison with controls, suggests that dynamic CA in iHF would be even more depressed if both groups were in normocapnia, given the well-known improvements in CA induced by reductions in PaCO₂ (1, 19, 28, 41).

Physiological perspectives. The interaction between the heart and the cerebral circulation have been the object of considerable debate in recent years (15). Of particular interest is whether physiological or pathological manifestations, link-

ing the heart to the brain, are the result of common underlying mechanisms, such as autonomic nervous system control, or due to cause-and-effect mechanisms. In patients with heart failure, the latter perspective could be ascribed to reductions in cardiac output leading to limitations in CBF and impairment of its regulatory mechanisms (15). However, this hypothesis was not supported in healthy subjects in which changes in cardiac output were not correlated to the ARI index (7).

Despite the ongoing controversy about the role of autonomic nervous system control of the human cerebral circulation (31), the well-known increase in sympathetic activity in iHF (15) could be a contributing factor in the reduced efficacy of cerebrovascular regulation in these patients. Future investigations of patient subgroups under different pharmacological regimens, such as the use of β -blockers, might shed light on the role of sympathetic overactivity on dynamic CA.

Interpretation of our findings should also take into consideration previous observations of arterial baroreflex sensitivity blunting in heart failure patients (26, 27). As suggested by Ogoh et al. (17), cardiac baroreflex dysfunction could attenuate dynamic CBF regulation. Similar consideration applies to the role of PaCO_2 and its well-known effects on CBF. Georgiadis et al. reported impaired cerebrovascular reactivity to CO_2 in heart failure patients (9), but CO_2 reactivity and dynamic CA are different regulatory mechanisms (19, 23, 24, 34). However, it is possible that under conditions of limited cardiac output, both mechanisms might reflect exhaustion of CBF reserve. Further studies are needed to assess CBF reserve in iHF, for example, with assessment of neurovascular coupling, similar to that reported in patients with stroke (29).

Clinical implications. There has been increasing clinical interest in the role that CA impairment might play in the causation, progression, and risk of debilitating disorders. Our results confirm that iHF patients are more likely to have impaired dynamic cerebral autoregulation (dCA) in comparison with age-matched controls; there was an increased prevalence of impaired CA in the iHF group, as reflected by the larger number of individuals with $\text{ARI} < 4$ when compared with controls. The choice of $\text{ARI} < 4$ as a threshold for abnormal CA was arbitrary. Further studies are needed to assess its generalizability to other studies. Nevertheless, most studies of dynamic CA in healthy subjects (MCA, supine) have found population average values of ARI ranging from 4.9 to 6.7 (7, 18, 22, 23, 30, 32, 35), and several clinical studies reported mean values of $\text{ARI} \sim 4$ in different cerebrovascular conditions (18), thus justifying the choice of $\text{ARI} < 4$ as a useful threshold. In the patient group, there was no significant difference in risk factors between those with ARI above and below 4. However, there was a trend toward a higher prevalence of dyslipidemia ($P = 0.064$) in the patient group with $\text{ARI} < 4$. Dynamic CA has been shown to be impaired in several conditions, such as stroke, carotid artery disease, severe head injury, diabetes, sepsis, and intracerebral hemorrhage (3, 13, 18, 34), but there is a dearth of information in the literature about the potential influence of human dyslipidemia as a significant cofactor for poor dCA. In mice, hypercholesterolemia was associated with oxidative stress and endothelial dysfunction in cerebral arterioles (11). In human subjects, dyslipidemia was reported in those with spinal cord injury who had CA impairment (25). The confirmation that dynamic CA is

impaired in iHF patients, with the potential involvement of dyslipidemia, should stimulate new avenues of research on optimal management of patients at risk of neurological complications such as stroke or cognitive impairment. In particular, decision-making on arterial blood pressure management and drug therapy should take into account their effects on the cerebral circulation of iHF patients. For this purpose, incorporating techniques for assessment of cerebral blood flow regulatory mechanisms into clinical practice should be seen as a priority.

Limitations of the study. TCD cannot provide absolute measurements of CBF, and the use of CBFV as a surrogate relies on the assumption that the MCA diameter remains approximately constant. This is likely to be the case during 5-min baseline measurements obtained at rest, without large fluctuations in PaCO_2 , as was the case of our study (5). Nevertheless, differences in insonation angle, the chance of arteries other than the MCA being insonated, and intersubject anatomical differences, including the acoustic permeability of temporal windows, are factors that need to be considered as potential limitations.

Multimodal recordings in critically ill patients represent a considerable challenge when compared with similar measurements in healthy controls. As a consequence, patient data are often of poorer quality, and this is reflected by the lower coherence obtained for the patient group compared with controls. Despite these differences though, visual inspection of all coherence function estimates confirmed satisfactory values of coherence for all BP-CBFV relationships quantified by TFA, and the temporal pattern of the CBFV step response was also considered as part of the new acceptance criteria, based on the statistical properties of the step response estimation process (22).

In comparison with most studies of cerebral hemodynamics in the literature, the relatively high number of patients that provided good-quality data ($n = 52$) is an important feature of our study. To obtain a similar age-matched control group though, we resorted to a high-quality set of recordings obtained in the Cardiovascular Sciences Department at the University of Leicester, UK. All data analyses were performed by the first author, and data collection in both centers followed the same procedure for acquiring the CBFV signals in the MCA. The use of different TCD equipment and operators could be the reason for the differences observed between mean values of CBFV. However, parameters like the ARI, coherence, and TFA phase are independent of CBFV amplitude. On the other hand, the gain or amplitude frequency response is amplitude-dependent, and it showed discrepancy in relation to ARI and phase estimates, mainly when expressed in $\%/mmHg$, when it was greater in controls compared with the iHF group for the Lf band. The white paper from the International Cerebral Autoregulation Research Network (4) recommends that gain is reported in both relative and absolute units. Our results add to several others in the literature (18, 33), in which gain did not show agreement with phase and/or ARI. For this reason, we based our conclusions on the differences in ARI and phase (in the Lf region) to suggest that dynamic CA is impaired in iHF patients.

A wider study of the literature also indicates that dCA parameters of our control group are in excellent agreement

with values reported for healthy adults in a number of international studies. In their original proposal of the ARI index, Tiecks et al. (32) suggested that, on average, healthy subjects are expected to have values of $ARI = 5$. Other studies have confirmed this expectation (7, 30), but it is important to note that these values apply to estimates of ARI derived from thigh cuff maneuvers (7, 30, 32) and that estimates obtained from spontaneous baseline fluctuations in BP and CBFV tend to be higher, in agreement with the values given in Table 2 (18, 20, 28, 35). Of particular interest, is the observation that patients with iHF in this study showed a reduction in ARI, compared with controls that was more accentuated than that reported for patients with mild stroke (28). The gain, phase, and coherence parameters of our control group (Table 2) are also in good agreement with the synthesis of 55 studies involving 958 healthy subjects (14). Contrary to our expectations though, the mean values of phase for the VLF range did not reflect impairment of dynamic CA similarly to the ARI and phase in the LF band. Similar limitations, involving intermethod agreement have been previously addressed (4, 14, 18, 33, 34).

Lack of information about the prevalence of carotid artery disease (CAD) in the iHF 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 (16, 23). None of the patients studied had symptoms of advanced CAD, but we cannot exclude the possibility that values of ARI could have been biased by the presence of asymptomatic CAD.

We only studied autoregulation within the context of spontaneous fluctuations in BP at rest. Potentially, techniques to increase BP variability, such as the thigh cuff maneuver (1, 7, 30) or the sit-stand test could lead to more robust results (34). We wanted to adopt a protocol with minimum physiological disruption to patients' physiology, to avoid adding to the sympathetic nervous system overactivity that occurs with iHF. Moreover, the use of spontaneous fluctuations has been favored by most centers, and its standardization and large literature available should allow for greater comparability between studies (4, 12–14, 18, 23, 25, 28, 30, 33–35, 40).

Measurements of $EtCO_2$ in the patient group were only recorded at 1-min intervals, and this limited the possibility of exploring more advanced multivariate modeling techniques using breath-by-breath values of $EtCO_2$ to explore the influence of hypocapnia in the patient group.

Our study was limited to the analysis of dynamic CA in iHF patients. Dynamic CA involves myogenic, metabolic and, possibly, neurogenic mechanisms as well (31, 33, 34, 36). By investigating other aspects of CBF regulation in the same group of patients, such as neurovascular coupling and CO_2 reactivity (9), there is the possibility of gaining additional information about which mechanisms are more affected in iHF.

Perspectives and Significance

The elevated prevalence of impaired dynamic CA, which we found in subjects with iHF, adds to the growing interest on the heart-brain interaction, with potential involvement of the autonomic nervous system. This finding could explain the higher rates of neurological complications, such as stroke and cognitive dysfunction, in iHF patients. Further investigations are needed to establish causal relationships to explain the effects of

iHF on the cerebral circulation and assess the prognostic value of dynamic CA parameters for the medium- and long-term outcomes of iHF patients, including the neuropsychological deficits encountered in this population.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

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

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