Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2018, Vol. 46(10) 4214–4225

DOI: 10.1177/0300060518791691
journals.sagepub.com/home/imr
SAGE

Cerebral blood flow changes during intermittent acute hypoxia in patients with heart failure

Antonio P. Mansur, Glaura Souza Alvarenga, Liliane Kopel, Marco Antonio Gutierrez, Fernanda Marciano Consolim-Colombo, Ludhmila Abrahão Hajjar and Silvia Gelas Lage

Abstract

Objective: Heart failure (HF) is associated with intermittent hypoxia, and the effects of this hypoxia on the cardiovascular system are not well understood. This study was performed to compare the effects of acute hypoxia (10% oxygen) between patients with and without HF.

Methods: Fourteen patients with chronic HF and 17 matched control subjects were enrolled. Carotid artery changes were examined during the first period of hypoxia, and brachial artery changes were examined during the second period of hypoxia. Data were collected at baseline and after 2 and 4 minutes of hypoxia. Norepinephrine, epinephrine, dopamine, and renin were measured at baseline and after 4 minutes hypoxia.

Results: The carotid blood flow, carotid systolic diameter, and carotid diastolic diameter increased and the carotid resistance decreased in patients with HF. Hypoxia did not change the carotid compliance, distensibility, brachial artery blood flow and diameter, or concentrations of sympathomimetic amines in patients with HF, but hypoxia increased the norepinephrine level in the control group. Hypoxia increased minute ventilation and decreased the oxygen saturation and end-tidal carbon dioxide concentration in both groups.

Conclusion: Hypoxia-induced changes in the carotid artery suggest an intensification of compensatory mechanisms for preservation of cerebral blood flow in patients with HF.

Heart Institute (InCor) - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil

Corresponding author:
Antonio P. Mansur, Heart Institute (InCor) - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Av. Dr. Enéas Carvalho de Aguiar, 44, São Paulo 05403-000, Brazil.
Email: apmansur@usp.br

Keywords
Heart failure, carotid artery, hypoxia, vascular reactivity, cerebral blood flow, cardiovascular system

Date received: 16 March 2018; accepted: 9 July 2018

Introduction

Heart failure (HF) is associated with intermittent periods of hypoxia. In healthy individuals, hypoxia increases the respiratory rate (RR) and sympathetic activity and changes peripheral vascular reactivity.[1] Acute hypoxia results in arterial vasodilation, but this vasodilation diminishes after prolonged periods of hypoxia. In patients with HF, the effects of intermittent hypoxia on the cardiovascular system are not well understood. Patients with HF have left ventricular dysfunction resulting in decreased cardiac output, which is offset by compensatory mechanisms to prioritize blood flow to the heart and brain.[2] The effects of hypoxia on cerebral and peripheral blood flow and the neurohumoral system are not fully understood. The cardiovascular effects of hypoxia result from complex interactions between the direct effects of hypoxia on the heart and peripheral vessels and chemoreceptor stimulation.[3] Chemoreceptors are located mainly in the aorta and carotid arteries and play a key role in detecting changes in the blood oxygen concentration. The responses to hypoxia that result in improved organ perfusion, increased cardiac output, and peripheral vasodilation in healthy individuals may not be the same in patients with HF.[4] Chemoreceptors are continuously stimulated in patients with HF, and transient periods of acute hypoxia may therefore not have an additional effect on the compensatory mechanisms, particularly in patients with New York Heart Association (NYHA) functional class II to IV HF. The present study was performed to evaluate the effects of acute hypoxia on the elastic properties of the carotid and brachial artery blood flow, ventilation, and the plasma levels of norepinephrine, epinephrine, dopamine, and renin.

Methods

Ethical approval

All patients provided written informed consent for inclusion in the study. The study protocol was approved by the institutional ethics committee. The study adhered to the principles of the latest revision of the Declaration of Helsinki.

Patients

We studied patients with HF (NYHA functional class II–IV) diagnosed by history, physical examination findings, and a resting left ventricular ejection fraction on echocardiography of ≤ 0.35 (mean, 0.31 ± 0.04; range, 0.25–0.35). The causes of HF were alcoholic cardiomyopathy, idiopathic cardiomyopathy, and peripartum cardiomyopathy, and medical treatments included digoxin, diuretics, and angiotensin-converting enzyme inhibitors. Angiotensin-converting enzyme inhibitors and diuretics were withheld for 24 hours before the study.

We also examined a control group of healthy subjects who were matched with the patient group for age, sex, and body mass index. All control group subjects all had an unremarkable medical history and

normal physical examination findings, and all were nonsmokers.

Two periods of hypoxia were studied. In the first period (P1), we examined responses in the carotid artery; in the second period (P2), we examined responses in the brachial artery. During each period, the studied parameters were recorded at baseline (B), after 2 minutes of hypoxia (H2), and after 4 minutes of hypoxia (H4). The study protocol is shown in Figure 1.

Cardiovascular measurements

Blood pressure was measured using an upper arm sphygmomanometer by an automated oscillometric method (Dinamap 1466; Critikon, Tampa, FL). Heart rate (HR) was monitored by electrocardiography. Forearm blood flow (FBF) was measured in the right arm by venous occlusion plethysmography (model EC-4; DE Hokanson, Bellevue, WA) with a mercury-filled strain gauge for approximately 10 seconds at 20-second intervals. Three readings were used to obtain each mean minute value. Forearm vascular resistance was calculated as the mean arterial pressure during a 1-minute recording divided by the mean minute FBF. Carotid and brachial artery images and the carotid artery blood flow velocity (CBF) and brachial artery blood flow velocity (BBF) were recorded as previously described[5,6] using an ultrasound scanner (Apogee-800 plus; ATL, Bothell, WA) equipped with a high-resolution transducer (7.5 MHz) and a pulsed Doppler system. Image analyses were performed using a dedicated image workstation to determine arterial diameters and flow velocity curves.[7]

Carotid artery elastic properties were examined by calculating distensibility and

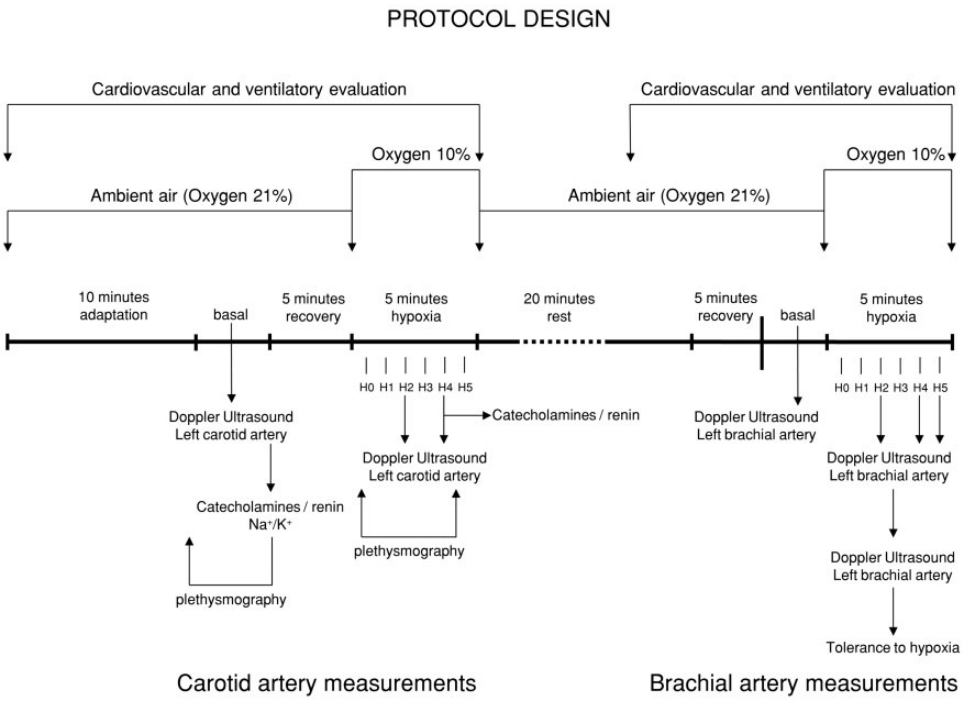

Figure 1. Design of the experimental protocol.

compliance according to the following equations[8]:

$$D = \frac{2(D_s - D_d)/D_d}{SBP - DBP}(10^{-6}.N^{-1}.m^2)$$

and

$$C = \frac{(D_s - D_d)/D_d}{2(SBP - DBP)}\pi D_d^2 \cdot (10^{-10}.N^{-1}.m^4)$$

where D is distensibility, C is compliance, D_s is the carotid artery diameter in systole, D_d is the carotid artery diameter in diastole, SBP is the systolic blood pressure, and DBP is the diastolic blood pressure.

Carotid artery blood flow (CBF) was calculated using CBFV and the carotid artery cross-sectional area (during systole) according to the following equation[4]:

$$CBF = \frac{CBFV.\pi D^2 s}{BSA.4}.0.06(L.min^{-1}.m^{-2})$$

where CBFV is expressed in m/s, BSA is the body surface area (m^2), and 0.06 is the unit conversion factor.

Brachial artery blood flow (BBF) was calculated similarly, using BBFV and the brachial artery cross-sectional area (during systole) according to the following equation:

$$BBF = \frac{BBFV.\pi D^2 s}{BSA.4}.0.06(L.min^{-1}.m^{-2})$$

Carotid artery resistance and brachial artery resistance were calculated as the mean arterial pressure divided by CBF and BBF, respectively ($mmHg/L \cdot min^{-1} \cdot m^{-2}$).

Respiratory measurements

The end-tidal carbon dioxide concentration ($EtCO_2$) was measured by capnography, and the oxygen saturation ($SatO_2$) was measured with a pulse oximeter (CO_2SMO model 7100 $EtCO_2/SpO_2$ Monitor; Novametrix Medical Systems Inc., Wallingford, CT). RR and minute ventilation (MV) were measured with a pneumotachograph (Heated Pneumotachometer; Hans Rudolph Inc., Shawnee, KS) and a differential pressure transducer (MP45-871; Validyne Engineering Corp., Northridge, CA) linked to a signal integrator amplifier (Gould Instrument Systems Inc., Valley View, OH). All signals were recorded simultaneously on a Gould strip-chart recorder (RS 3800; Gould Instrument Systems Inc.) and on a computer using customized CODAS software (Computer Operated Data Acquisition Software, AT-CODAS; DATAQ Instruments, Akron, OH).

Norepinephrine, epinephrine, dopamine, and renin measurements

Venous blood samples were collected from an indwelling catheter in an antecubital vein to measure the plasma norepinephrine, epinephrine, and dopamine concentrations (pg/mL) and plasma renin activity (pg/mL/h). Samples were obtained at the B and H4 time points during P1. Plasma concentrations of norepinephrine were quantified by high-performance liquid chromatography, and plasma renin activity was determined by radioimmunoassay.[9,10]

Experimental protocol and procedures

We used an established experimental protocol described by Somers et al.[11] (Figure 1). All 31 subjects participated in both P1 (the carotid artery period) and P2 (the brachial artery period). The cardiovascular research laboratory was kept quiet, the temperature was controlled at 22°C to 25°C, and the lights were kept dimmed. All subjects rested in the supine position for $\geq$20 minutes

after an indwelling catheter was placed in an antecubital vein. All subjects were familiarized with the experimental protocol during the resting period. During P1, measurements were obtained for 5 minutes while the subjects breathed room air (baseline recording) and then for 5 minutes (analyzed in a minute-by-minute format) while breathing the gas mixture (described below) via a mouthpiece, with application of a nose clip to ensure exclusive mouth breathing (acute hypoxia recording). The gas mixture was composed of 10% oxygen in nitrogen, with carbon dioxide titrated to maintain isocapnia. The carotid artery diameter, CBFV, FBF, $SatO_2$, $EtCO_2$, RR, MV, mean arterial pressure, and HR were recorded at B, H2, and H4. At the end of each recording period (baseline and acute hypoxia), an 8-mL blood sample was collected to measure the plasma norepinephrine and renin levels. After a 20-minute resting period, P2 was started. During P2, the brachial artery diameter and BBFV were recorded using the same protocol as described for the carotid artery measurements during P1.

Statistical analyses

For continuous variables, the minimum and maximum values were recorded and the mean and standard deviation were calculated. Mean values were compared between the control and HF groups using Student's *t* test, and the paired Student's test was used for comparison between two time points (B *vs.* H2 and B *vs.* H4) of the control and HF groups. For categorical variables, the absolute and relative frequencies were calculated. Proportions were compared between the control and HF groups using Fisher's exact test. Values at different time points were compared within the control and HF groups using analysis of variance. Plasma levels of norepinephrine, epinephrine, dopamine, and renin were compared using the paired Student's *t* test. A value of $P < 0.05$ was considered significant. Statistical analyses were performed by an independent statistician using SAS Software version 9.0 (SAS Institute Inc., Cary, NC).

Results

The HF group comprised 14 patients (mean age, 44.4 ± 13.1 years; range, 25–65 years; 12 men, 2 women). HF was caused by alcoholic cardiomyopathy in eight patients, by idiopathic cardiomyopathy in five, and by peripartum cardiomyopathy in one. Nine patients had NYHA functional class II HF, 3 had class III, and 2 had class IV. Fourteen patients were taking digoxin, 12 were taking diuretics, and 13 were taking angiotensin-converting enzyme inhibitors. The control group comprised 17 healthy subjects (mean age, 38.5 ± 8.7 years; range, 25–53 years; 10 men, 7 women). The mean BSA in the control and HF groups was 1.84 ± 0.18 and 1.76 ± 0.17 m^2, respectively. Neither age nor BSA was significantly different between the two groups. The values of all parameters measured during P1 and P2 at B, H2, and H4 are shown in Table 1.

Results for P1

SBP, DBP, and mean blood pressure (MBP) were not significantly different among the three time points (B, H2, and H4) in either the control or HF group. SBP was significantly higher in the control group than in the HF group at all three time points (all $P < 0.01$), but DBP and MBP were not significantly different between the control and HF groups at any of the time points. In the control group, HR increased at H2 and H4 when compared with B (77.76 ± 10.84 *vs.* 94.77 ± 11.24 and 93.24 ± 10.27 beats/min, respectively; all $P < 0.001$). HR was higher in the HF than control group at all three time points (all

Table 1. Responses to acute hypoxia in control subjects and patients with heart failure

	Time points							
	Baseline		H2		H4		*P*	
	Control	HF	Control	HF	Control	HF	Control	HF
Carotid Artery Period								
SBP (mmHg)	128.82 ± 14.32	114.38 ± 13.24	133.06 ± 14.24	118.46 ± 9.74	134.59 ± 15.97	115.62 ± 16.59	0.187	0.211
DBP (mmHg)	74.88 ± 11.92	75.46 ± 9.00	77.12 ± 13.08	76.92 ± 9.88	74.41 ± 12.30	74.15 ± 15.08	0.344	0.143
MBP (mmHg)	92.82 ± 12.05	88.46 ± 8.42	95.76 ± 12.39	90.85 ± 7.54	94.41 ± 12.05	88.15 ± 12.97	0.212	0.090
HR (bpm)	77.76 ± 10.84	94.77 ± 11.24	90.82 ± 11.83	98.38 ± 8.23	93.24 ± 10.27	98.85 ± 17.32	<0.001	0.155
CSD (mm)	6.53 ± 0.42	5.80 ± 1.03	6.64 ± 0.55	5.93 ± 1.00	6.60 ± 0.55	6.07 ± 0.99	0.480	0.045
CDD (mm)	6.07 ± 0.44	5.52 ± 1.01	6.25 ± 0.55	5.67 ± 0.98	6.15 ± 0.52	5.76 ± 0.96	0.208	0.041
C ($10^{-10} \cdot N^{-1} \cdot m^4$)	6.16 ± 2.35	4.66 ± 2.26	5.12 ± 1.37	4.54 ± 3.17	5.56 ± 1.97	6.30 ± 4.53	0.290	0.389
D ($10^{-6} \cdot N^{-1} \cdot m^2$)	21.68 ± 8.59	20.39 ± 12.90	16.88 ± 4.89	19.22 ± 14.37	19.10 ± 7.77	24.12 ± 14.16	0.129	0.383
CBF ($L \cdot min^{-1} \cdot m^{-2}$)	0.95 ± 0.13	0.58 ± 0.21	0.98 ± 0.15	0.61 ± 0.21	1.00 ± 0.16	0.67 ± 0.21	0.599	0.002
CR ($mmHg/L \cdot min^{-1} \cdot m^{-2}$)	99.17 ± 19.20	175.67 ± 76.58	100.83 ± 22.47	167.98 ± 67.75	97.78 ± 24.85	147.07 ± 59.02	0.796	0.005
FBF ($mL \cdot 100\ mL^{-1} \cdot min^{-1}$)	4.08 ± 1.60	2.73 ± 2.00	5.14 ± 2.59	2.50 ± 1.78	4.41 ± 1.66	3.11 ± 2.13	0.098	0.013
FVR (UR)	25.92 ± 9.86	47.11 ± 25.06	23.72 ± 12.49	55.87 ± 35.01	24.56 ± 9.85	40.60 ± 23.41	0.380	0.003
RR (breaths/min)	11.28 ± 4.39	18.95 ± 5.91	11.94 ± 5.04	20.54 ± 6.32	13.59 ± 6.02	21.23 ± 7.18	0.070	0.010
MV (L/min)	6.83 ± 1.71	7.43 ± 3.73	10.22 ± 3.66	10.17 ± 3.35	11.23 ± 3.91	10.16 ± 3.34	0.005	<0.001
$SatO_2$ (%)	97.06 ± 0.83	96.23 ± 1.42	87.41 ± 4.35	87.46 ± 3.99	83.65 ± 3.97	83.77 ± 5.17	<0.001	<0.001
$EtCO_2$ (mmHg)	38.65 ± 4.49	31.77 ± 5.53	36.88 ± 4.87	29.62 ± 5.01	36.29 ± 4.71	29.46 ± 5.59	0.013	0.003
Norepinephrine (pg/mL)	267.15 ± 108.20	728.25 ± 350.87	–	–	319.92 ± 162.56	723.42 ± 326.02	0.016	0.877
Epinephrine (pg/mL)	29.54 ± 28.66	86.00 ± 87.27	–	–	35.31 ± 28.06	91.83 ± 101.07	0.453	0.614
Dopamine (pg/mL)	32.54 ± 117.32	53.08 ± 82.64	–	–	29.15 ± 105.12	53.33 ± 78.28	0.337	0.936
Plasma renin activity (pg/mL/h)	1.78 ± 1.65	14.71 ± 17.34	–	–	1.53 ± 1.17	12.96 ± 14.01	0.641	0.420
Brachial Artery Period								
SBP (mmHg)	127.53 ± 13.56	114.79 ± 9.18	131.88 ± 12.93	118.36 ± 12.62	135.47 ± 13.68	118.21 ± 10.79	0.001	0.123
DBP (mmHg)	73.65 ± 10.97	73.50 ± 7.53	75.24 ± 11.16	75.29 ± 8.10	74.47 ± 14.15	75.79 ± 9.23	0.305	0.437
MBP (mmHg)	91.53 ± 10.57	87.29 ± 6.24	93.94 ± 11.03	89.64 ± 7.86	95.00 ± 13.23	89.93 ± 8.11	0.010	0.206
HR (bpm)	72.47 ± 8.54	89.64 ± 10.78	85.53 ± 8.79	95.07 ± 9.30	87.71 ± 8.67	98.50 ± 8.62	<0.001	0.003
BSD (mm)	3.63 ± 0.62	3.81 ± 0.70	3.68 ± 0.62	3.76 ± 0.67	3.68 ± 0.67	3.81 ± 0.77	0.445	0.670
BBF ($L \cdot min^{-1} \cdot m^{-2}$)	0.28 ± 0.10	0.21 ± 0.12	0.29 ± 0.11	0.20 ± 0.10	0.30 ± 0.11	0.22 ± 0.12	0.535	0.079
BR ($mmHg/L \cdot min^{-1} \cdot m^{-2}$)	358.05 ± 122.87	533.97 ± 228.82	365.98 ± 125.94	548.02 ± 225.59	344.21 ± 124.75	509.06 ± 229.21	0.414	0.466
$SatO_2$ (%)	96.88 ± 0.60	95.86 ± 1.70	87.53 ± 3.64	86.57 ± 3.30	84.00 ± 3.87	83.14 ± 3.39	<0.001	<0.001
$EtCO_2$ (mmHg)	39.47 ± 5.14	31.71 ± 5.93	37.87 ± 5.14	31.64 ± 5.33	36.93 ± 4.46	31.29 ± 5.84	<0.001	0.690

BBF, brachial artery blood flow; BR, brachial artery resistance; BSD, brachial artery systolic diameter; C, arterial compliance; CBF, carotid artery blood flow; CDD, carotid artery diastolic diameter; CR, carotid artery resistance; CSD, carotid artery systolic diameter; D, arterial distensibility; DBP, diastolic blood pressure; $EtCO_2$, end-tidal carbon dioxide; FBF, forearm blood flow; FVR, forearm vascular resistance; HR, heart rate; MBP, mean blood pressure; MV, minute ventilation; RR, respiratory rate; $SatO_2$, oxygen saturation; SBP, systolic blood pressure. Values at different time points (basal, H2, and H4) were compared within the control and HF groups using analysis of variance. Plasma levels (basal and H4) of norepinephrine, epinephrine, dopamine, and renin were compared using the paired Student's *t* test.

$P < 0.01$). The carotid artery systolic diameter (CSD) and carotid artery diastolic diameter (CDD) were not significantly different among the three time points in the control group. In the HF group, CSD increased significantly between B and H4 (5.80 ± 1.03 and 06.07 ± 0.99 mm, respectively; $P = 0.045$), as did CDD (5.52 ± 1.01 and 5.76 ± 0.96 mm, respectively; $P = 0.041$). CSD was significantly greater in the control than HF group at all three time points (all $P < 0.05$), whereas there were no significant differences in CDD between the two groups. Carotid compliance and distensibility were not significantly different between the control and HF groups or among the different time points within each group. CBF was not significantly different among the three time points in the control group, but they increased significantly between B and H4 in the HF group (0.58 ± 0.21 and 0.67 ± 0.21 L/min/m^2, respectively; $P = 0.002$). CBF was significantly higher in the control than HF group at all three time points (all $P < 0.001$). Carotid artery resistance was not significantly different among the three time points in the control group, but it decreased significantly between B and H4 in the HF group (175.67 ± 76.58 and 147.07 ± 59.02 mmHg/L $\cdot$ min^{-1} $\cdot$ m^{-2}, respectively; $P = 0.005$). Carotid artery resistance was significantly higher in the HF than control group at all three time points (all $P < 0.01$). FBF was not significantly different among the three time points in the control group, but it increased significantly between B and H4 in the HF group (2.73 ± 2.00 and 3.11 ± 2.13 mL/100 mL/min, respectively; $P = 0.015$). FBF was significantly higher in the control than HF group at all three time points (all $P < 0.05$). Forearm vascular resistance was not significantly different among the three time points in the control group, but it decreased significantly between B and H4 in the HF group (47.11 ± 25.06 and 40.60 ± 23.41 L/min/m^2, respectively; $P = 0.038$). RR was not significantly different among the three time points in the control group, but it increased significantly over the three time points in the HF group (18.95 ± 5.91, 20.54 ± 6.32, and 21.23 ± 7.18 breaths/min; all $P = 0.01$). RR was significantly higher in the HF than control group at all three time points (all $P < 0.05$). MV increased significantly over the three time points in both the control group (6.83 ± 1.71, 10.22 ± 3.66, and 11.23 ± 3.91 L/min; all $P = 0.005$) and the HF group (7.43 ± 3.73, 10.17 ± 3.35, and 10.16 ± 3.34 L/min; all $P < 0.001$). MV was not significantly different between the control and HF groups at any of the three time points. $SatO_2$ decreased significantly over the three time points in both the control group ($97.06\% \pm 0.83\%$, $87.41\% \pm 4.35\%$, and $83.65\% \pm 3.97\%$; all $P < 0.001$) and the HF group ($96.23\% \pm 1.42\%$, $87.46\% \pm 3.99\%$, and $83.77\% \pm 5.17\%$; all $P < 0.001$). $SatO_2$ was not significantly different between the control and HF groups at any of the three time points. $EtCO_2$ decreased significantly over the three time points in both the control group (38.65 ± 4.49, 36.88 ± 4.87, and 36.29 ± 4.71 mmHg; all $P = 0.013$) and the HF group (31.77 ± 5.53, 29.62 ± 5.01, and 29.46 ± 5.59 mmHg; all $P = 0.003$). $EtCO_2$ was significantly higher in the control than HF group at all three time points (all $P < 0.001$). The plasma levels of norepinephrine, epinephrine, dopamine, and renin were higher in the HF than control group. The plasma norepinephrine level increased significantly between B and H4 in the control group (267.15 ± 108.20 and 319.92 ± 162.56 pg/mL, respectively; $P = 0.016$) but did not change significantly in the HF group. The plasma levels of epinephrine, dopamine, and renin were not significantly different between B and H4 in either the control or HF group.

Results for P2

SBP increased significantly between B and H4 in the control group (127.53 ± 13.56 and 135.47 ± 13.68 mmHg, respectively; $P = 0.001$) but did not change significantly among the three time points in the HF group. SBP was higher in the control than HF group at all three time points (all $P < 0.01$). DBP did not change significantly among the three time points in either the control or HF group. MBP increased significantly between B and H4 in the control group (91.53 ± 10.57 and 95.00 ± 13.23 mmHg, respectively; $P = 0.010$) but did not change significantly among the three time points in the HF group. DBP and MBP were not significantly different between the control and HF groups. HR increased significantly over the three time points in both the control group (72.47 ± 8.54, 85.53 ± 8.79, and 87.71 ± 8.67 beats/min; $P < 0.001$) and the HF group (89.64 ± 10.78, 95.07 ± 9.30, and 98.50 ± 8.62 beats/min; $P = 0.003$). HR was higher in the HF than control group at all three time points (all $P < 0.01$). The brachial systolic artery diameter and BBF were not significantly different among the three time points in either the control or HF group. BBF was significantly higher in the control than HF group at all three time points (all $P < 0.05$). HR did not change significantly among the three time points in either the control or HF group. HR was significantly higher in the HF than control group at all three time points (all $P < 0.05$). $SatO_2$ decreased significantly over the three time points in both the control group ($96.88\% \pm 0.60\%$, $87.53\% \pm 3.64\%$, and $84.00\% \pm 3.87\%$; $P < 0.001$) and HF group ($95.86\% \pm 1.70\%$, $86.57\% \pm 3.30\%$, and $83.14\% \pm 3.39\%$, $P < 0.001$). $SatO_2$ was not significantly different between the control and HF groups at any of the three time points. $EtCO_2$ decreased significantly over the three time points in the control group (39.47 ± 5.14, 37.87 ± 5.14, and 36.93 ± 4.46 mmHg; $P < 0.001$), but it was not significantly different among the three time points in the HF group.

Discussion

The main findings of this study are that CSD, CDD, and cerebral blood flow increased during acute hypoxia in patients with HF, but not in control subjects. A previous study of healthy subjects showed that acute hypoxia was associated with carotid artery vasodilation.[12] However, this was not observed in the control subjects in our study. Previous *in vivo* and *in vitro* studies revealed that norepinephrine caused vasoconstriction of the carotid artery.[13,14] In the *in vivo* condition, several compensating mechanisms might interfere in carotid flow regulation. During the P1 phase of the present study, we found no variation in the arterial pressure or HR in the control group. Notably, this group showed an increase in the plasma norepinephrine level, which could partially explain the absence of vasodilation. Marked hypoxia is needed to induce significant carotid artery vasodilation.[15] Tamisier et al.[16] reported that in healthy subjects, marked and prolonged hypoxia caused initial increases in blood pressure and regional blood flow, but intermittent hypoxia did not cause these changes. In addition, Willie et al.[17] reported that in normal subjects, severe hypoxia (35 mmHg) for approximately 15 minutes increased the vertebral artery diameter and flow by 50% more than the increases in internal carotid artery diameter and flow, with the internal carotid artery being more reactive to hypocapnia. These findings indicate differences in blood flow regulation to the brain stem and cortex according to differences in arterial blood gas parameters. In patients with HF, however, the carotid artery diameter

increased during acute hypoxia, which was probably caused by increased regional blood flow. One variable that causes increased regional blood flow is increased blood pressure. The arterial pressure did not change during the P1 phase of the study; however, the HR increased. We know that the compensatory mechanism of regional flow in patients with HF is limited. The arterial pressure was probably not supported by a lower cardiac stroke volume. The HR is likely to have been the only compensatory mechanism to provide for the increase in the patients' brain blood flow. Previous studies have revealed contradictory findings regarding blood pressure responses to acute and intermittent hypoxia. In patients with obstructive sleep apnea, an association was reported between intermittent hypoxia and increased blood pressure.[18,19] In other studies, acute hypoxia was found to be associated with increased SBP, although SBP normalized with intermittent hypoxia.[2,20] Another study showed no significant associations between acute hypoxia and blood pressure.[21] Narkiewicz et al.[22] observed no significant associations between hypoxia and mean arterial pressure in either healthy subjects or patients with HF. In patients with HF, regional blood flow decreases in proportion to decreased cardiac output.[23] The reduced blood flow promotes a reduction in the arterial diameter in patients with HF, and in these patients the neurohumoral activation system provides the main compensatory mechanism for maintaining adequate cerebral and coronary blood flow. Ding et al.[24] recently reported that chronically reduced blood flow to the carotid body resulted in augmentation of peripheral chemoreflex sensitivity and consequent activation of the sympathetic nervous system in patients with HF. Therefore, patients with HF had significantly increased neurohumoral activity at baseline, masking the usual increases in serum levels of sympathomimetic amines in response to hypoxia and their potential effects of increasing regional blood flow. There were also no changes in the carotid artery diameter secondary to changes in compliance or distensibility of the artery. Moreover, we observed that patients with HF had significantly increased neurohumoral activity at baseline and that carotid artery compliance and distensibility did not change in response to acute hypoxia. Previous studies have shown contradictory findings regarding changes in compliance and distensibility of the carotid artery in response to hypoxia.[25,26] Khder et al.[27] found no significant difference in radial artery compliance (measured noninvasively) between healthy subjects and patients with HF. They observed that the diastolic diameter of the radial artery was not significantly different between healthy subjects and patients with HF. A compliant isobaric radial artery, which is not influenced by blood pressure and which reflect the viscoelastic behavior of the arterial wall, is not different between healthy subjects and patients with HF, suggesting that changes in compliance must be attributable to changes in blood pressure. We found that FBF did not change in response to acute hypoxia as analyzed by two methods: venous occlusion plethysmography during P1 and vascular ultrasonography with a high-resolution transducer during P2. However, FBF was higher in healthy individuals than in patients with HF, similar to the differences in CBF observed between these two groups. The absence of brachial artery vasodilation in response to acute hypoxia may be explained by sympathetic hyperstimulation in healthy subjects and by impairment in endothelial vasodilator function in patients with HF.[28] However, the observed vascular dysfunction in patients with HF is probably not caused by impaired endothelium-mediated vasodilation.[29] During P1, the RR increased in patients with HF, and $SatO_2$ and $EtCO_2$

decreased in both the control and HF groups; however, MV remained unchanged in both groups. The results of our study are similar to those of other studies of short-term hypoxia,[22,30] which reported similar contributions by peripheral chemoreceptors to the respiratory effects of healthy subjects and patients with HF. However, the hemodynamic changes resulting from greater chemoreceptor stimulation by hypoxia were different in healthy subjects than in patients with HF, resulting in increased CBF but not increased FBF in patients with HF. The changes in CBF and BBF indicate that the vascular resistance in these arteries was higher in patients with HF than in control subjects and that hypoxia resulted in a decrease in carotid artery resistance only in patients with HF. The mechanisms underlying preferential carotid artery vasodilation during hypoxia in patients with HF are currently not well understood.

This study has three main limitations. First, we analyzed the hemodynamic and adrenergic changes in the cerebral flow in response to intermittent acute hypoxia. This analysis did not allow assessment of the influence of the chemoreflex in the cerebral flow, which is known to be complex and to involve several pathophysiological mechanisms that were not contemplated in the study. Second, the measurements of flow and diameter of the carotid and brachial arteries were performed by the same operator to obtain ultrasonographic images. In this way, a small time interval between the measurements of the carotid and brachial arteries occurred. However, because this interval was so short, it probably did not significantly interfere with the values obtained. Finally, the inclusion of patients with NYHA functional class II, III, and IV HF could have influenced the response to hypoxia due to different degrees of cardiac muscle damage. However, all patients were clinically and hemodynamically stable at the time of the study.

In conclusion, acute hypoxia was associated with increased CSD, CDD, and CBF in patients with HF but did not change the brachial artery diameter or BBF. These results suggest intensification of the compensatory mechanisms for preserving cerebral blood flow in patients with HF.

Author contributions

Antonio P. Mansur: data analysis and interpretation; manuscript writing.
Glaura Souza Alvarenga: study conception and design; data analysis and interpretation.
Liliane Kopel: study design; data analysis and interpretation.
Marco Antonio Gutierrez: data analysis and interpretation.
Fernanda Marciano Consolim-Colombo: data analysis and interpretation.
Ludhmila Abrahão Hajjar: data analysis and interpretation.
Silvia Gelas Lage: study conception and design; data analysis and interpretation.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Antonio P. Mansur http://orcid.org/0000-0003-3051-1090

References

1. Marshall JM. Peripheral chemoreceptors and cardiovascular regulation. *Physiol Rev* 1994; 74: 543–594.
2. Zelis R, Sinoway LI, Leuenberger U, et al. Time-constant adaptations in heart failure. *Eur Heart J* 1991; 12(Suppl C): 2–7.

3. Calbet JA and Joyner MJ. Disparity in regional and systemic circulatory capacities: do they affect the regulation of the circulation? *Acta Physiol (Oxf)* 2010; 199: 393–406.
4. Casey DP and Joyner MJ. Local control of skeletal muscle blood flow during exercise: influence of available oxygen. *J Appl Physiol* 2011; 111: 1527–1538.
5. Lage SG, Kopel L, Medeiros CC, et al. Angiotensin II contributes to arterial compliance in congestive heart failure. *Am J Physiol Heart Circ Physiol* 2002; 283; H1424–H1429.
6. Lagudis S, Yamada AT, Vieira ML, et al. The effect of dobutamine without and with L-arginine on arterial compliance in heart failure patients. *Echocardiography* 2009; 26: 934–942.
7. Gutierrez MA, Pilon PE, Lage SG, et al. Automatic measurement of carotid diameter and wall thickness in ultrasound images. *Computers in Cardiology* 2002; 29: 359–362.
8. Van Merode T, Hick PJ, Hoeks AP, et al. Carotid artery wall properties in normotensive and borderline hypertensive subjects of various ages. *Ultrasound Med Biol* 1988; 14: 563–569.
9. Bouloux P, Perrett D and Besser GM. Methodological considerations in the determination of plasma catecholamines by high-performance liquid chromatography with electrochemical detection. *Ann Clin Biochem* 1985; 22(Pt 2): 194–203.
10. Emanuel RL, Cain JP and Williams GH. Double antibody radioimmunoassay of renin activity and angiotensin II in human peripheral plasma. *J Lab Clin Med* 1973; 81: 632–640.
11. Somers VK, Mark AL, Zavala DC, et al. Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans. *J Appl Physiol* 1989; 67: 2101–2106.
12. Ainslie PN and Poulin MJ. Ventilatory, cerebrovascular, and cardiovascular interactions in acute hypoxia: regulation by carbon dioxide. *J Appl Physiol* 2004; 97: 149–159.
13. Bolton TB. Mechanisms of action of transmitters and other substances on smooth muscle. *Physiol Rev* 1979; 59: 606–718.
14. Vanhoutte PM, Verbeuren TJ and Webb RC. Local modulation of adrenergic neuroeffector interaction in the blood vessel wall. *Physiol Rev* 1981; 61: 151–247.
15. Heistad DD, Abboud FM, Mark AL, et al. Effect of hypoxemia on responses to norepinephrine and angiotensin in coronary and muscular vessels. *J Pharmacol Exp Ther* 1975; 193: 941–950.
16. Tamisier R, Anand A, Nieto LM, et al. Arterial pressure and muscle sympathetic nerve activity are increased after two hours of sustained but not cyclic hypoxia in healthy humans. *J Appl Physiol* 2005; 98: 343–349.
17. Willie CK, Macleod DB, Shaw AD, et al. Regional brain blood flow in man during acute changes in arterial blood gases. *J Physiol* 2012; 590(Pt 14): 3261–3275.
18. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American heart association/American college of cardiology foundation scientific statement from the American heart association council for high blood pressure research professional education committee, council on clinical cardiology, stroke council, and council on cardiovascular nursing. In collaboration with the national heart, lung, and blood institute national center on sleep disorders research (national institutes of health). *Circulation* 2008; 118: 1080–1111.
19. Sahlin C, Sandberg O, Gustafson Y, et al. Obstructive sleep apnea is a risk factor for death in patients with stroke: a 10-year follow-up. *Arch Intern Med* 2008; 168: 297–301.
20. Foster GE, Brugniaux JV, Pialoux V, et al. Cardiovascular and cerebrovascular responses to acute hypoxia following exposure to intermittent hypoxia in healthy humans. *J Physiol* 2009; 587(Pt 13): 3287–3299.
21. Ainslie PN, Barach A, Murrell C, et al. Alterations in cerebral autoregulation and cerebral blood flow velocity during acute hypoxia: rest and exercise. *Am J Physiol Heart Circ Physiol* 2007; 292: H976–H983.
22. Narkiewicz K, Pesek CA, van de Borne PJ, et al. Enhanced sympathetic and ventilatory responses to central chemoreflex activation

in heart failure. *Circulation* 1999; 100: 262–267.
23. Leithe ME, Margorien RD, Hermiller JB, et al. Relationship between central hemodynamics and regional blood flow in normal subjects and in patients with congestive heart failure. *Circulation* 1984; 69: 57–64.
24. Ding Y, Li YL and Schultz HD. Role of blood flow in carotid body chemoreflex function in heart failure. *J Physiol* 1997; 589(Pt 1): 245–258.
25. Lage SG, Kopel L, Monachini MC, et al. Carotid arterial compliance in patients with congestive heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol* 1994; 74: 691–695.
26. Ramsey MW, Goodfellow J, Jones CJ, et al. Endothelial control of arterial distensibility is impaired in chronic heart failure. *Circulation* 1995; 92: 3212–3219.
27. Khder Y, el Ghawi R, Boscs LB, et al. Investigations of the peripheral vascular mechanisms implicated in congestive heart failure by the non-invasive evaluation of radial artery compliance and reactivity. *Int J Cardiol* 1996; 56: 149–158.
28. Katz SD, Biasucci L, Sabba C, et al. Impaired endothelium-mediated vasodilation in the peripheral vasculature of patients with congestive heart failure. *J Am Coll Cardiol* 1992; 19: 918–925.
29. Negrão CE, Hamilton MA, Fonarow GC, et al. Impaired endothelium-mediated vasodilation is not the principal cause of vasoconstriction in heart failure. *Am J Physiol Heart Circ Physiol* 2000; 278, H168–H174.
30. Chua TP, Ponikowski P, Webb-Peploe K, et al. Clinical characteristics of chronic heart failure patients with an augmented peripheral chemoreflex. *Eur Heart J* 1997; 18: 480–486.