ESC HEART FAILURE
ESC Heart Failure 2017; **4**: 341–350
Published online 30 March 2017 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12142

ORIGINAL RESEARCH ARTICLE

Cardiac and peripheral autonomic control in restrictive cardiomyopathy

Ana Luiza C. Sayegh[1], Marcelo R. dos Santos[2], Adriana O. Sarmento[2], Francis R. de Souza[2], Vera M.C. Salemi[3], Viviane T. Hotta[1], Akothirene Cristhina D.B. Marques[2], Heidrum H. Krämer[4], Ivani C. Trombetta[2], Charles Mady[1] and Maria Janieire de Nazaré Nunes Alves[2]*

[1]*Clinical Unit of Cardiomyopathy, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil;* [2]*Cardiovascular Rehabilitation and Exercise Physiology Unit, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil;* [3]*Clinical Unit of Heart Failure, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil;* [4]*Departmente of Neurology, Justus-Liebig-University, Giessen, Germany*

Abstract

Aims Autonomic dysfunction determines the advance of dilated cardiomyopathy (DCM) and is related to poor outcomes. However, this autonomic imbalance is unknown in patients with restrictive cardiomyopathy (RCM) even though they have similar symptoms and poor quality of life as DCM patients have. The aim of this study was to evaluate if autonomic and neurovascular controls were altered in RCM patients.

Methods and results Fifteen RCM patients, 10 DCM patients, and 10 healthy subjects were evaluated. Heart rate and blood pressure (BP) were recorded. Peripheral sympathetic activity [muscle sympathetic nerve activity (MSNA)] by microneurography and cardiac sympathetic activity by power spectrum analysis of heart rate variability. Spontaneous baroreflex sensitivity (BRS) was evaluated by the sequence method and forearm blood flow by venous occlusion plethysmography. Both cardiomyopathy groups had higher MSNA frequency ($P < 0.001$) and MSNA incidence ($P < 0.001$), higher cardiac sympathovagal balance ($P < 0.02$), reduced BRS for increase ($P = 0.002$) and for decrease in BP ($P = 0.002$), and lower forearm blood flow ($P < 0.001$) compared with healthy subjects. We found an inverse correlation between BRS for increase and decrease in BP and peripheral sympathetic activity ($r = -0.609$, $P = 0.001$ and $r = -0.648$, $P < 0.001$, respectively) and between BRS for increase and decrease in BP and cardiac sympathetic activity ($r = -0.503$, $P = 0.03$ and $r = -0.487$, $P = 0.04$, respectively).

Conclusions The RCM patients had cardiac and peripheral autonomic dysfunctions associated with peripheral vasoconstriction. Nonetheless, the presence of normal ejection fraction underestimates the evolution of the disease and makes clinical treatment difficult. These alterations could lead to a similar cardiovascular risk as that observed in DCM patients.

Keywords Sympathetic activity; Neurovascular control; Baroreflex control; Restrictive cardiomyopathy; Dilated cardiomyopathy; Heart failure

Received: 30 November 2016; Revised: 19 January 2017; Accepted: 3 February 2017
**Correspondence to: Maria Janieire de Nazaré Nunes Alves, Unidade de Reabilitação Cardiovascular e Fisiologia do Exercício from Heart Institute (InCor), University of São Paulo Medical School, Av. Dr. Enéas de Carvalho Aguiar, 44—Cerqueira César—São Paulo—SP, 05403-000 São Paulo, Brazil. Tel: (5511) 2661-5099; Fax: (5511) 2661-5043. Email: janieire.alves@incor.usp.br*

Introduction

Restrictive cardiomyopathy (RCM) is characterized by decreased diastolic volume in one or both ventricles, leading to diastolic dysfunction with high filling pressures and preserved ventricular systolic function.[1–3] The RCM is a cardiomyopathy that affects up to 5% of the population worldwide[1,4] and is associated with low functional capacity and high mortality.[4,5] Interestingly, unlike patients with dilated cardiomyopathy (DCM), left ventricular systolic function is normal or only slightly depressed in RCM patients.[6,7]

Autonomic imbalance triggered by sympathetic hyperactivity causes the advancement of diseases in patients with DCM and is related to poor outcome.[8] In fact, muscle sympathetic nerve activity (MSNA) is an independent marker of mortality in DCM patients.[9] Some studies,[10,11] but not all,[12] suggest that impairment of arterial baroreflex regulation is one of the main mechanisms involved in sympathetic

hyperactivation in DCM patients, especially in the early stage of the disease.[13,14] On the other hand, in RCM, the autonomic control is completely unknown, even though RCM patients experience similar symptoms and poor quality of life as seen in DCM patients.

In the present study, we aimed to evaluate the peripheral autonomic control, cardiac sympathovagal balance, and spontaneous baroreflex sensitivity (BRS) in patients with RCM. In addition, we evaluated muscle forearm blood flow (FBF) functional capacity.

Our hypotheses were that (i) there was an increase in MSNA and cardiac sympathovagal balance in RCM and DCM compared with that in healthy individuals; (ii) spontaneous baroreflex control would be reduced in patients with RCM compared with healthy individuals, and this could explain sympathetic hyperactivity in RCM; (iii) RCM would show a reduction in FBF levels compared with healthy subjects (HS); and (iv) there is an association between central and peripheral autonomic controls.

Methods

Study population

In this prospective study, we evaluated 35 patients: 15 patients with RCM and 10 patients with DCM. In addition, 10 age-matched HS were included. All measures were blinded for the investigators.

The inclusion criteria for patients with RCM were (i) endomyocardial fibrosis (EMF) aetiology; (ii) endocardial resection surgery >6 months (with or without atrioventricular valve replacement without altering systolic function); (iii) left ventricular ejection fraction (LVEF) >50%; (iv) New York Heart Association (NYHA) functional class II or III; and (v) being compensated with optimal medication.

The inclusion criteria for the patients with DCM were (i) dilated heart failure diagnosis >6 months; (ii) NYHA functional class II or III; (iii) LVEF <40%; (iv) ischemic and nonischemic etiologies; and (v) compensated heart failure with optimal medication.

In the HS, the inclusion criteria were (i) a normal history and physical examinations and (ii) no metabolic, cardiovascular, kidney, and liver diseases.

Exclusion criteria for all patients were (i) regular exercise training; (ii) history of coronary revascularization or myocardial infarction <6 months before the study; (iii) diabetes; (iv) bi-ventricular pacemakers with or without implantable cardioverter defibrillator; (v) obesity (body mass index >30 kg/m^2); and (vi) alcohol intake.

Written informed consent was obtained for this study, which were approved by the Local Ethics Committee (CAPPesq—number 0130/09) and by the Scientific Research Committee of the Heart Institute (InCor) (SDC-3151/08/067). All study participants provided written informed consent and were selected from a database of studies performed in the Cardiovascular Rehabilitation and Exercise Physiology Unit of the Heart Institute (InCor), Medical School, University of São Paulo.

This study followed the recomendations of the STROBE statement.[15]

Measures and procedures

Echocardiography

Echocardiography was performed on all participants for cardiac functional evaluation according to the American Society of Echocardiography recommendations[16] with a Sequoia 512 ultrasound machine (Acuson, Mountain View, CA, USA) and a 2.5 MHz harmonic imaging transducer.[17]

Assessment of endomyocardial fibrosis (EMF) was performed through the presence of obliteration in the apex in one or both ventricles, with or without atrioventricular regurgitation.[18] Ejection fraction was calculated by using the Simpson method determined by two-dimensional echocardiography.

Cardiopulmonary exercise test

All patients underwent maximal cardiopulmonary exercise testing (CPET) as previously described,[19] assessed during a maximal progressive exercise test on a cycle ergometer (Ergoline, Spirit 150, Bitz, Germany), using a ramp protocol with work rate increments of 5–10 W every minute until exhaustion. The patients were instructed to pedal at 60 rpm. The CPET was considered maximal when (i) maximal respiratory exchange ratio was higher than 1.10; (ii) peak HR was higher than 95% of age predicted; and (iii) despite verbal encouragement, the subject could no longer maintain the exercise intensity.[20] Heart rate (HR) was continuously recorded at rest and during the graded exercise testing using a 12-lead digital electrocardiogram (ERGO PC 13, MICROMED Biotechnology Ltda., Brasília—DF—Brazil). Peak oxygen consumption (peak VO_2) was determined by means of gas exchange on a breath-by-breath basis in a computerized system (model Vmax 229, Sensor Medics, Buena Vista, CA). Peak VO_2 was defined as the maximum attained VO_2 at the end of the exercise period. Its value averaged from the last 30 s of the CPET.

Heart rate, blood pressure, and respiratory rate evaluations

Heart rate was monitored through lead II of the ECG. At the same time, noninvasive, beat-to-beat blood pressure (BP; SBP, systolic blood pressure; DBP, diastolic blood pressure; and MBP, mean blood pressure) was monitored using a Finometer® (Finapres Medical Systems—FMS) as previously described.[19] Respiratory rate was monitored with a

piezoelectric thoracic belt (Pneumotrace II, model 1132, Respiration Transducer, UFI, USA) placed around the upper abdomen.

Muscle sympathetic nerve activity

The MSNA was measured at rest using the microneurography technique. The MSNA of the peroneal nerve, as previously described, is a safe, precise, direct technique to record sympathetic nerve activity directed to muscle.[21] In summary, a tungsten microelectrode was used to record the postganglionic vasoconstrictor activity. Signals were amplified by a factor of 50 000 to 100 000 and bandpassed filtered (700 to 2000 Hz). Nerve activity was rectified and integrated (time constant 0.1 s) to obtain a mean voltage display as previously described.[22] Muscle sympathetic bursts were expressed as burst frequency (bursts per minute), and burst incidence (bursts per 100 heart beats).

Cardiac autonomic evaluation

The cardiovascular fluctuation of the RR interval was assessed in the frequency domain using autoregressive spectral analysis at rest as described previously.[23,24] In brief, for stationary segments of the time series, autoregressive parameters were estimated via Levinson–Durbin recursion, and the order of the model was chosen according to Akaike's criterion.[23,24] Autoregressive spectral decomposition was then performed. This procedure permitted the automatic quantification of the centre frequency and the power of each relevant component in both absolute normalized units (n.u.). Components of the 0.04–0.15 Hz frequency band were considered to be low-frequency (LF) components that indicated the predominance of sympathetic modulation. The components between the range of 0.15 and 0.4 Hz, which were synchronized with the breathing signals, were considered high-frequency (HF) components that indicate parasympathetic modulation. The normalization procedure was performed by dividing the power of the LF or HF component by the total spectral power from which the power of the very LF component had been subtracted and by multiplying the result by 100.[23,24] Furthermore, the ratio of LF to HF (LF/HF) was calculated as a measure of the cardiac sympathovagal balance.

For the analysis of cardiac autonomic evaluation, five RCM patients were excluded because of atrial fibrillation.

Spontaneous baroreflex sensitivity

The spontaneous BRS evaluation was performed at rest through the sequence method previously described,[25–27] which identifies three or more consecutive increases or decreases in SBP of at least 1 mmHg with concomitant progressive lengthening or shortening of the RR interval of at least 3 ms at rest. This consecutive increase in RR and simultaneous increase in BP represent spontaneous activation of baroreceptors (up sequences; BRS+). The decrease in HR and simultaneous decrease in BP represent spontaneous deactivation of baroreceptors (down sequences; BRS−). Spontaneous BRS obtained from the slope is generated by a linear regression related to the SBP and the RR interval. The measures chosen for analysis were those with a strong linear correlation coefficient (coefficient $r \geq 0.8$). The averages of all inclinations to obtain BRS values were computed.

For the analysis of spontaneous BRS, five RCM patients were excluded because of atrial fibrillation.

Forearm blood flow

The FBF was measured during 10 min of rest by venous occlusion plethysmography as previously described.[28,29] The non-dominant arm was elevated above heart level to ensure adequate venous drainage. A mercury-filled silastic tube attached to a low-pressure transducer was placed around the forearm and connected to a plethysmograph device (Hokanson, Bellevue, WA, USA). Sphygmomanometer cuffs were placed around the wrist and upper arm. At 20-s intervals, the upper cuff was inflated above venous pressure (60 mmHg) for 10 s followed by 10 s of release. The FBF (mL/min/100mL) was determined based on a minimum of four separate readings. Forearm vascular conductance (FVC) was calculated as (forearm blood flow)/(mean blood pressure) × 100 and was expressed in 'units' [100 mL (dL of tissue)$^{-1}$ · min^{-1} · mmHg^{-1}].

Experimental protocol

Day 1 The patients underwent echocardiographic assessment.

Day 2 The patients underwent maximal CPET.

Day 3 The MSNA, FBF, HR, BP, and respiratory rate were evaluated simultaneously with the patient in the supine position. After the electrocardiogram was placed on the chest, the arm was positioned for venous occlusion plethysmography. On the right leg, a tungsten microelectrode was inserted into the peroneal nerve. After that the subject rested quietly for 15 min. The MSNA, FBF, HR, BP, and respiratory rate were recorded during 10 min of rest in a quiet, temperature-controlled (21°C) room.

An automated computer programme (Windaq) with sampling frequency of 500 Hz and with a resolution of 16 bits was used to process the ECG signal to extract the time series of HR (considering the RR interval) and beat-to-beat BP.

On days 1, 2, and 3, the participants were instructed to have the last meal 2 h before the experimental protocol and to avoid caffeine and high-fat food intake for 24 h before measurements. All the experiments were assessed in the morning (between 8 a.m. and 10 a.m.).

Primary endpoint

Our primary endpoint was to evaluate peripheric and cardiac sympathetic activity in patients with RCM compared with DCM and HS. Our secondary endpoints were to evaluate spontaneous BRS, FBF, and functional capacity (peak VO_2).

DOI: 10.1002/ehf2.12142

Statistical analysis

The sample size calculation was based on at least 80% power to detect a mean difference in MSNA (bursts/100 HB) among any three of the groups using one-way ANOVA with a 5% significance level. We calculated a total of 30 patients (10 patients per group) in the present study. Considering possible artefacts or poor quality of the evaluated parameters, 35 patients were included.[30]

The Kolmogorov–Smirnov and Levene's tests were used to assess normality of distribution and homogeneity for each variable.

Significant χ^2 test was used to analyze the distribution of sex, functional class, aetiology, and medications. One-way ANOVA and Scheffé's post-hoc tests were used to compare parametric variables, and Kruskal–Wallis test was used to compare nonparametric variables.

Pearson and Spearman correlations were used to test the association between parametric and nonparametric variables, respectively.

Values are presented as mean ± SD or median and interquartile range (IQR, 25–75%). *P* values <0.05 were considered statistically significant. All calculations were developed using SPSS software version 18 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Clinical and physical characteristics

Physical and clinical characteristics are displayed in *Table 1*. Age and sex were similar among the three groups studied. There were no significant differences between RCM and DCM groups in NYHA functional class, etiologies, sodium, potassium, creatinine, and medications, except for spironolactone that was used more frequently in DCM patients. Body mass index was similar among the three groups.

Cardiac function, hemodynamic parameters, and functional capacity

Cardiac function, hemodynamic parameters, and functional capacity are displayed in *Table 2*. The LVEF was significantly higher in RCM compared with that in the DCM group ($P < 0.001$) showing preserved systolic function. As expected, LVEF was lower in RCM and DCM groups compared with that in the HS group ($P < 0.001$). Maximal left ventricular (LV) volume was higher in DCM compared with RCM and HS ($P = 0.03$ and $P = 0.015$, respectively), and minimal LV volume was also higher compared with that in RCM and HS ($P = 0.008$ and $P = 0.002$, respectively). Maximal and minimum LV volumes were also higher in RCM compared with HS ($P = 0.001$ and $P = 0.014$, respectively). The HR, SBP, DBP, and MBP were similar among the three groups. Peak VO_2 and peak HR during cardiopulmonary exercise tesing were similar between both cardiomyopathies (CM) ($P = 0.95$) but lower compared with HS ($P = 0.02$), showing the same reduction in functional capacity between RCM and DCM. All groups had respiratory exchange ratio higher than 1.10, showing that all participants reached their maximal cardiopulmonary exercise test goal.

Muscle sympathetic nerve activity

The MSNA in burst frequency was higher in RCM and DCM (40 ± 8 vs. 44 ± 10 vs. 21 ± 4 bursts/min, $P < 0.001$, *Figure 1A*, respectively), and in burst incidence (57 ± 11 vs. 59 ± 10 vs.

Table 1 Physical and clinical characteristics

Variable	HS ($n = 10$)	RCM ($n = 15$)	DCM ($n = 10$)	*P*
Age, years	51 ± 4	55 ± 9	55 ± 4	0.30
Sex, female/male	8/2	13/2	8/2	0.87
NYHA functional class, II/III	—	11/4	8/2	0.63
BMI, kg/m^2	25.3 ± 2.7	27.5 ± 3.3	27.7 ± 2.8	0.12
Aetiology, n				
Ischemic	—	—	7	0.08
Nonischemic	—	—	3	
EMF	—	15	—	
Medications, n (%)				
Beta-blockers	—	11 (73%)	9 (90%)	0.29
ACEI and ARB	—	10 (67%)	8 (80%)	0.46
Diuretic	—	14 (93 %)	10 (100%)	0.31
Digoxin	—	2 (13%)	2 (20%)	0.66
Spironolactone	—	5 (33%)[b]	9 (90%)	0.003
Biomarkers				
Sodium, mEq/L	141 ± 1	139 ± 5	140 ± 1	0.76
Potassium, mEq/L	4.63 ± 0.54	4.33 ± 0.27	4.42 ± 0.27	0.30
Creatinine, mg/L	0.75 ± 0.11	1.03 ± 0.28	1.06 ± 0.21	0.06

Values are mean ± SD or *n* (%). Significant χ^2 test and one-way ANOVA were used in all comparisons.
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMI, body mass index; DCM, dilated cardiomyopathy; EMF, endomyocardial fibrosis; HS, healthy subjects; NYHA, New York Heart Association; RCM, restrictive cardiomyopathy.
[a]Statistically different from HS group.
[b]Statistically different from DCM group.

Table 2 Cardiac function, hemodynamic parameters, and functional capacity

Variable	HS (n = 10)	RCM (n = 15)	DCM (n = 10)	P
LVEF, %	65±3	55±9[a,b]	33±7[a]	<0.001
Maximal LV volume, mL	40±10	105±57[a, b]	164±72[a]	0.03
Minimal LV volume, mL	22±6	48±31[a, b]	116±69[a]	0.001
HR, beats/min	65±6	70±10	73±13	0.22
SBP, mmHg	128±12	127±13	123±19	0.72
DBP, mmHg	72±6	71±8	71±11	0.98
MBP, mmHg	94±8	92±9	89±13	0.57
Peak VO_2, mL/kg/min	27.5±4.8	13.9±1.9[a]	16.0±3.1[a]	<0.001
RER	1.20±0.08	1.10±0.12	1.16±0.03	0.08
Peak HR during CET, bpm	157±21	125±17[a]	121±25[a]	0.02

Values are mean ± SD or n (%). Significant χ^2 test and one-way ANOVA were used in all comparisons.
CET, cardiopulmonary exercise test; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; HR, heart rate; HS, healthy subjects; LV, left ventricular; LVEF, left ventricular ejection fraction; MBP, mean blood pressure; RER, respiratory exchange ratio; RCM, restrictive cardiomyopathy; SBP, systolic blood pressure; VO2, oxygen consumption.
[a]Statistically different from HS group.
[b]Statistically different from DCM group.

32 ± 6 bursts/100 HB, $P < 0.001$, *Figure 1B*, respectively) compared with HS. Burst frequency and burst incidence were similar between RCM and DCM patients, showing similar sympathetic hyperactivity.

Cardiac autonomic control

Cardiac parasympathetic activity was decreased in RCM and DCM (HF, n.u.; 29 ± 14 vs. 27 ± 13 vs. 50 ± 20%, P = 0.005, *Figure 2A*, respectively) compared with HS. In addition, RCM and DCM displayed increased cardiac sympathetic activity (LF, n.u.) (71 ± 14 vs. 73 ± 13 vs. 50 ± 20%, P = 0.005, *Figure 2B*, respectively), and increased cardiac sympathovagal balance (LF/HF) (2.4 [2.2–4.2] vs. 3.0 [1.6–5.2] vs. 0.8 [0.6–1.7] $P < 0.02$, *Figure 2C*, respectively) compared with HS.

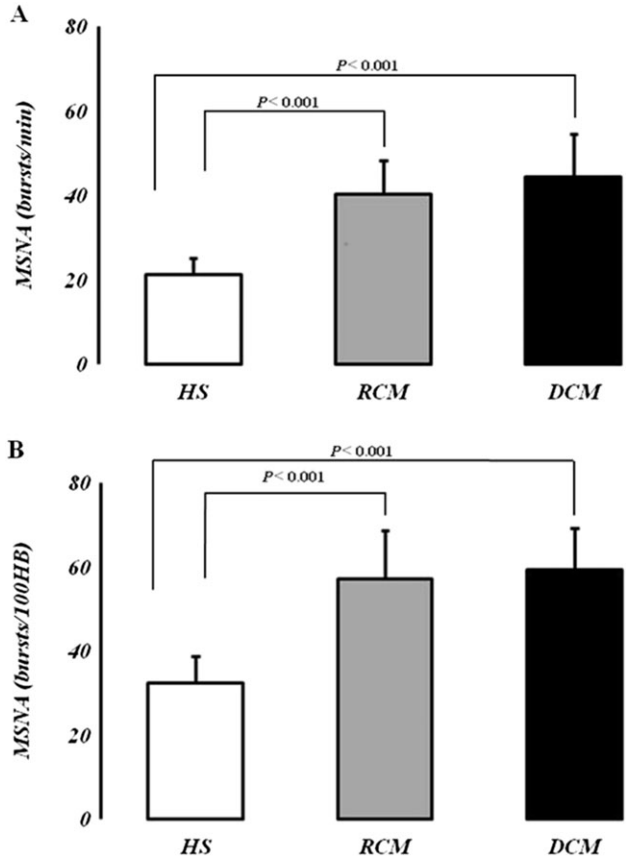
Spontaneous baroreflex sensitivity

The RCM and DCM groups displayed lower spontaneous BRS+ (3.3 ± 2.6 vs. 4.3 ± 3.0 vs. 7.6 ± 1.5 mmHg/ms, P = 0.002, *Figure 3A*, respectively) and BRS− (5.0 ± 4.1 vs. 4.2 ± 3.8 vs. 9.6 ± 1.1 mmHg/ms, P = 0.002, *Figure 3B*, respectively) compared with HS. There were no significant differences between RCM and DCM for spontaneous BRS+ and BRS− (P = 0.67 and P = 0.85, respectively). In addition, RCM and DCM had a decreased total number of BRS sequences compared with HS (15 ± 15 vs. 28 ± 29 vs. 57 ± 31 ramps, P = 0.004, *Figure 3C*).

Forearm blood flow and forearm vascular conductance

Finally, RCM and DCM displayed lower FBF (1.43 ± 0.54 vs. 1.86 ± 0.55 vs. 2.69 ± 0.87 mL/min/100mL, $P < 0.001$, *Figure 4A*, respectively) compared with HS. Likewise, FVC was lower in RCM and DCM compared with HS (1.59 ± 0.67 vs. 2.13 ± 0.64 vs. 2.88 ± 1.00 units, $P < 0.002$, *Figure 4B*, respectively). The FBF and FVC were similar between RCM and DCM.

Figure 1 Muscle sympathetic nerve activity (MSNA). (A) The restrictive cardiomyopathy (RCM) and dilated cardiomyopathy (DCM) patients had increased MSNA in burst frequency compared with HS ($P < 0.001$). (B) The RCM and DCM patients had increased MSNA in burst incidence ($P < 0.001$) compared with healthy subjects (HS). Note that there were no significant differences between the two groups with cardiomyopathies. One-way ANOVA was used in all comparisons.



Associations

All associations between peripheral and cardiac sympathetic activity, BRS, peripheral vasoconstriction, and functional capacity are displayed in *Table 3*.

Discussion

The present study was conducted to investigate the cardiac and peripheral autonomic dysfunctions, baroreflex modulation, and its neurovascular repercussion in patients with RCM. We found that both peripheral and cardiac sympathetic

Figure 2 Cardiac autonomic evaluation. (A) Cardiac parasympathetic activity [high-frequency (HF) normalized units (n.u.), $P = 0.005$]. (B) Cardiac sympathetic activity [low-frequency (LF) n.u., $P = 0.005$]. (C) Cardiac sympathovagal balance [sympathovagal balance (LF/HF), $P = 0.02$]. Note that restrictive cardiomyopathy (RCM) and dilated cardiomyopathy (DCM) had lower HF n.u., higher LF n.u., and higher LF/HF compared with healthy subjects (HS). For the analysis of cardiac autonomic evaluation, five RCM patients were excluded because of atrial fibrillation. One-way ANOVA and Kruskal–Wallis test were used in all comparisons.

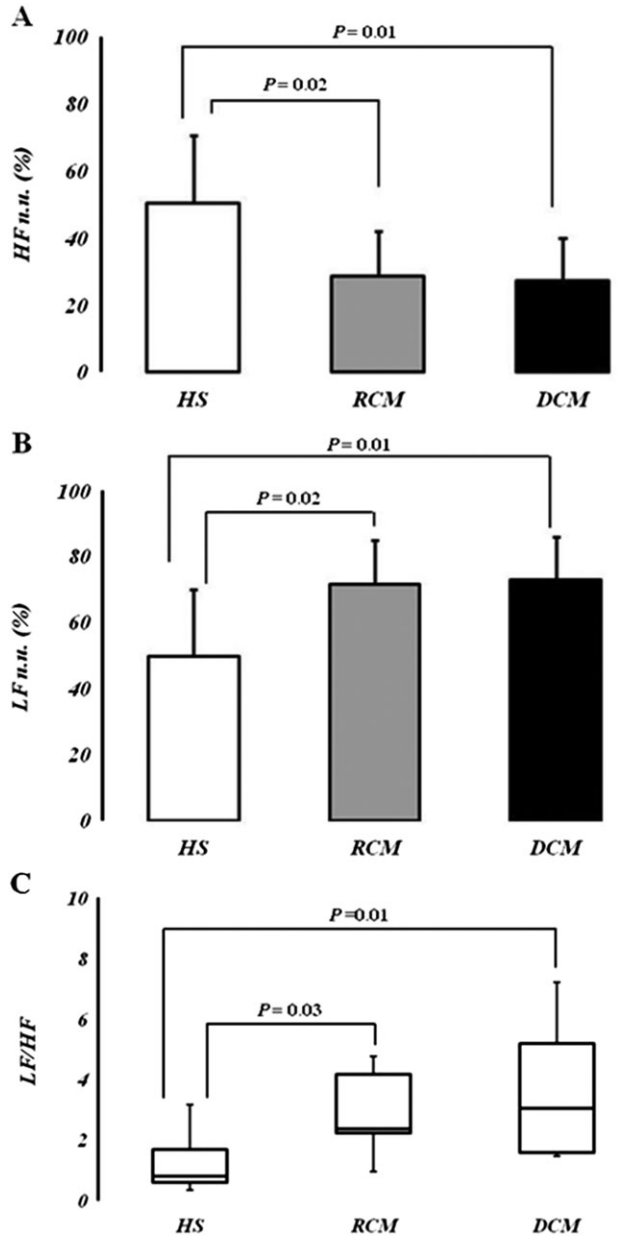
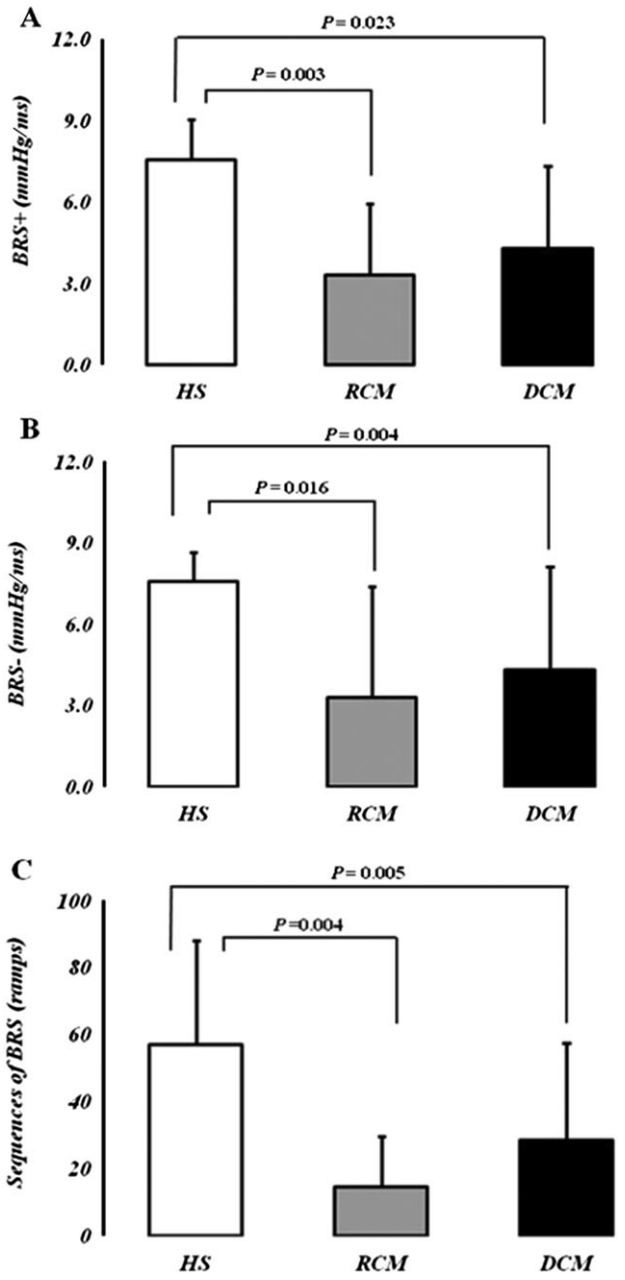


Figure 3 Spontaneous baroreflex sensitivity (BRS). (A) The BRS for increase in blood pressure ($P = 0.003$), (B) BRS for decrease in blood pressure ($P = 0.004$), and (C) sequences of BRS ($P = 0.001$). Note that restrictive cardiomyopathy (RCM) and dilated cardiomyopathy (DCM) had lower spontaneous BRS and fewer sequences of BRS compared with healthy subjects (HS). One-way ANOVA was used in all comparisons. BRS+, BRS for increase in blood pressure; BRS−, BRS for decrease in blood pressure.



activities are increased in patients with RCM. Furthermore, RCM patients had a reduction in cardiac parasympathetic activity. This autonomic imbalance was directly associated with impaired spontaneous BRS and increased peripheral vasoconstriction. More interestingly, these autonomic and neurovascular dysfunctions were similar to those found in patients with DCM, despite the fact that patients with RCM had preserved left ventricular function.

Sympathetic hyperactivity is well documented as one of the main mechanisms leading to morbidity and mortality in

Figure 4 Forearm blood flow (FBF) and forearm vascular conductance (FVC). (A) The restrictive cardiomyopathy (RCM) and dilated cardiomyopathy (DCM) patients had decreased FBF compared with HS ($P < 0.001$). Note that there were no significant differences between the two groups with cardiomyopathies. (B) The RCM and DCM patients had decreased forearm vascular conductance (FVC) compared with healthy subjects (HS) ($P < 0.001$). There were no significant differences between RCM and DCM. One-way ANOVA was used in all comparisons.

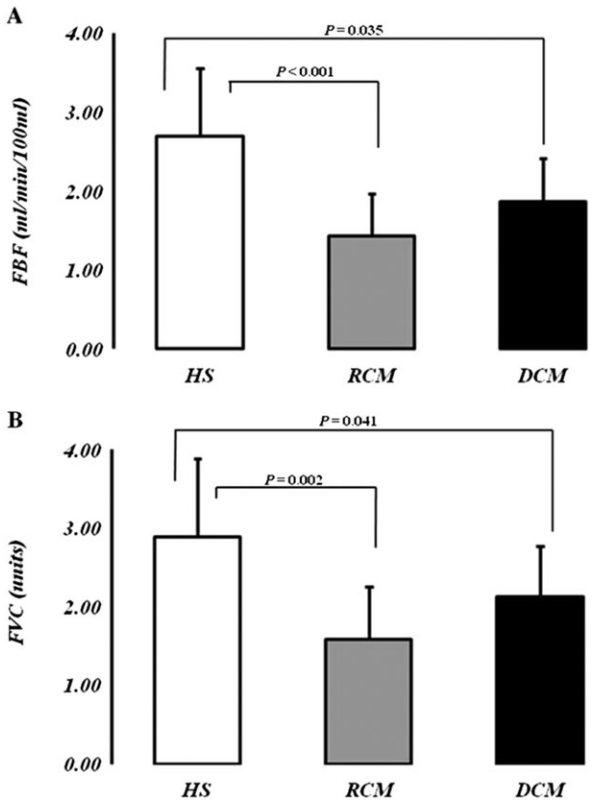


Table 3 Associations between peripheral and central sympathetic nervous activity, baroreflex sensitivity, and functional capacity

Association	*r*	*P*
BRS+ and MSNA frequency	−0.609	0.001
BRS− and MSNA frequency	−0.648	<0.001
BRS+ and MSNA incidence	−0.543	0.004
BRS− and MSNA incidence	−0.524	0.006
BRS+ and LF/HF	−0.503	0.03
BRS− and LF/HF	−0.487	0.04
MSNA frequency and LF/HF	00.532	0.03
NA incidence and LF/HF	0.522	0.04
FBF and LF/HF	−0.646	0.005
FVC and LF/HF	−0.566	0.02
FBF and peak VO_2	0.645	<0.001

BRS+, baroreflex sensitivity for increase in blood pressure; BRS−, baroreflex sensitivity for decrease in blood pressure; FBF, forearm blood flow; FVC, forearm vascular conductance; LF/HF, low frequency/high frequency; MSNA, muscle sympathetic nerve activity; *r*, correlation coefficient; VO_2, oxygen consumption.
Pearson and Spearman correlations were used in all comparisons.

heart failure patients.[9,31,32] We found that RCM patients have increased peripheral sympathetic activity (MSNA) and cardiac sympathovagal balance (LF/HF), and both are associated with each other (r = 0.532 between MSNA frequency and LF/HF; r = 0.522 and between MSNA incidence and LF/HF). However, the mechanisms involved in the sympathoexcitation in RCM patients are unknown.

Several studies in heart failure patients show that sympathetic hyperactivity is triggered by lower BRS.[33–35] We observed that spontaneous BRS is decreased either BRS+ or BRS− in patients with RCM. Our results contradict previous studies that show that young patients with RCM have preserved BRS compared with healthy individuals.[36] However, Singh and collaborators studied unspecified etiologies of RCM patients, and in our study, we included only EMF patients with endocardial resection surgery.

Moreover, there is a strong association between spontaneous BRS and MSNA, as well as between spontaneous BRS and cardiac sympathovagal balance (LF/HF). We found that baroreflex dysfunction may explain at least about 50% of cardiac sympathovagal imbalance (BRS+ and LH/HF; r = −0.503 and BRS− and LH/HF; r = −0.487). In addition, the peripheral sympathetic hyperactivity (MSNA frequency) can be explained, at least in part, by the reduction in BRS+ (r = −0.609) and BRS− (r = −0.648). These results remain even when MSNA was corrected for HR (BRS+ and MSNA incidence, r = −0.543; and BRS− and MSNA incidence, r = −0.524). Therefore, these findings suggest an alteration in arterial baroreflex modulation in peripheral and cardiac sympathetic activation. Indeed, this reciprocal relationship between arterial baroreceptor and sympathetic outflow has been reported,[33,37] and it is known that reduced BRS is associated with a poor prognosis in heart failure patients.[38,39]

Some of the possible causes of BRS reduction in general physiopathologic conditions include the baroreceptors' desensibilization, decreased compliance of the carotid sinus wall, and alteration in central modulations of the baroreceptors or even in the efferent via the reflex arch.[39–41] Therefore, it is evident that baroreceptors play a very important role in the normal regulation of the circulatory system and exert a major inhibitory influence on sympathetic outflow.[42,43] Decreased BRS, even in the presence of beta blockade,[44] has been directly associated with worsening outcomes in patients with cardiovascular disease.[45] Besides that previous studies support the idea that the decreased number of BRS sequences is indicative of lower carotid distensibility,[46] and in our study, BRS sequences were lower in RCM patients (*Figure 3C*). Thus, we could speculate that the decreased BRS increases cardiovascular risk in patients with RCM. The explanation for the reduction in BRS is a complex issue and is out of the scope of our study. Moreover, sympathetic hyperactivity triggered by baroreflex dysfunction could provoke cardiovascular alterations like an increase in peripheral vasoconstriction.

In fact, we observed that RCM patients had decreased FBF and FVC. This can be justified by the peripheral blood flow alterations already observed in these patients.[47] The left ventricle fibrotic involvement may decrease diastolic suction and restrict the increase of end-diastolic volume, which reduces ventricular filling and hinders the Frank–Starling mechanism.[17] In an attempt to maintain normal cardiac output, RCM patients may experience a reflex vasoconstriction to improve blood flow redistribution. Acutely, the peripheral vasoconstriction caused by sympathetic hyperactivity is a compensatory mechanism that can improve venous return and maintain an adequate cardiac output in RCM patients. Chronically, the reduction in muscle blood flow is an independent predictor of mortality and contributes to exercise intolerance in patients with DCM.[48] In the present study, we also obsverved that lower FBF may contribute to exercise intolerance in RCM patients, because we found that the reduction in FBF was associated with a reduction of peak VO_2 ($r = 0.645$). This intensification of peripheral vasoconstriction found in RCM patients could also be explained by the increased sympathetic nerve activity. As a matter of fact, RCM patients showed an inverse association between FBF and LF/HF ($r = -0.646$) and between FCV and LF/HF ($r = -0.566$).

Currently, the treatment for RCM patients is focused on symptomatic relief, with the use of diuretics, aldosterone antagonists, and vasodilators. Beta-blockers are recommended as a class I, level of evidence A for the treatment of DCM patients; however, beta-blockers demonstrated a modest reduction in all-cause mortality or cardiovascular hospitalization in patients with heart failure with preserved ejection fraction.[49] Beta-blockers may not be as effective in patients with RCM, once they have impaired ventricular filling caused by endomyocardial fibrosis. Additionally, elevated ventricular filling pressure might be needed for adequate stroke volume and cardiac output to prevent clinical decompensation.[1] Despite that, in our study, 73% of EMF patients were treated with beta-blockers. Therefore, it is important to understand the physiopathology involved in RCM patients and to look for better selective pharmacological treatment to improve quality of life and reduce poor outcomes.

Conclusion

The RCM patients had cardiac and peripheral autonomic dysfunctions associated with peripheral vasoconstriction and a reduction in exercise capacity. Nonetheless, the presence of normal ejection fraction underestimates the evolution of the disease and makes clinical treatment difficult. These alterations could lead to similar cardiovascular risks observed in DCM patients.

Limitations

The present study has several limitations. We only studied patients with EMF, which is the most prevalent form of primary RCM. Therefore, we do not know whether alteration in autonomic and neurovascular control also occurs in other etiologies of RCM. Also, all patients had undergone fibrosis resection surgery; therefore, we do not know whether the ET effects would occur in patients before a fibrosis resection procedure. Finally, the number of patients only represents a fraction of our own population. Therefore, we do not know if other populations would have the same results.

Acknowledgement

We would like to thank Miss Sara Rodrigues for her support during data collection.

Conflict of interest

None declared.

Funding

This work was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP #2009/17529-9). ALCS was supported by Conselho Nacional de Pesquisa (CNPq #141856/2012-2). MRS was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Conselho Nacional de Pesquisa (CNPq #234052/2014-7). FRS and ACDBM were supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). ASO was supported by Conselho Nacional de Pesquisa (CNPq #142179/2013-2).VMCS was supported by Conselho Nacional de Pesquisa (CNPq # 305304/2014-3).

References

1. Abelmann WH, Lorell BH. The challenge of cardiomyopathy. *J Am Coll Cardiol* 1989; **13**: 1219–1239.
2. Mogensen J, Kubo T, Duque M, Uribe W, Shaw A, Murphy R, Gimeno JR, Elliott P, McKenna WJ. Idiopathic restrictive cardiomyopathy is part of the clinical expression of cardiac troponin I mutations. *J Clin Invest* 2003; **111**: 209–216.

3. Sorajja P. Invasive hemodynamics of constrictive pericarditis, restrictive cardiomyopathy, and cardiac tamponade. *Cardiol Clin* 2011; **29**: 191–199.
4. Sanchez Torres RJ, Calderon R. The cardiomyopathies, a review for the primary physician. *P R Health Sci J* 2004; **23**: 285–292.
5. Salemi VM, Leite JJ, Picard MH, Oliveira LM, Reis SF, Pena JL, Mady C. Echocardiographic predictors of functional capacity in endomyocardial fibrosis patients. *Eur J Echocardiogr* 2009; **10**: 400–405.
6. Mady C, Salemi VM, Ianni BM, Fernandes F, Arteaga E. Relation between left atrial dimension and exercise capacity in endomyocardial fibrosis. *Arq Bras Cardiol* 2005; **84**: 222–224.
7. Mocumbi AO, Yacoub S, Yacoub MH. Neglected tropical cardiomyopathies: II. Endomyocardial fibrosis: myocardial disease. *Heart* 2008; **94**: 384–390.
8. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *J Am Coll Cardiol* 2009; **54**: 375–385.
9. Barretto AC, Santos AC, Munhoz R, Rondon MU, Franco FG, Trombetta IC, Roveda F, de Matos LN, Braga AM, Middlekauff HR, Negrao CE. Increased muscle sympathetic nerve activity predicts mortality in heart failure patients. *Int J Cardiol* 2009; **135**: 302–307.
10. Mostarda C, Moraes-Silva IC, Moreira ED, Medeiros A, Piratello AC, Consolim-Colombo FM, Caldini EG, Brum PC, Krieger EM, Irigoyen MC. Baroreflex sensitivity impairment is associated with cardiac diastolic dysfunction in rats. *J Card Fail* 2011; **17**: 519–525.
11. Lohmeier TE, Iliescu R. The baroreflex as a long-term controller of arterial pressure. *Physiology (Bethesda)* 2015; **30**: 148–158.
12. Kienbaum P, Karlssonn T, Sverrisdottir YB, Elam M, Wallin BG. Two sites for modulation of human sympathetic activity by arterial baroreceptors? *J Physiol* 2001; **531**: 861–869.
13. Pinna GD, Maestri R, Capomolla S, Febo O, Robbi E, Cobelli F, La Rovere MT. Applicability and clinical relevance of the transfer function method in the assessment of baroreflex sensitivity in heart failure patients. *J Am Coll Cardiol* 2005; **46**: 1314–1321.
14. Binkley PF, Nunziata E, Haas GJ, Nelson SD, Cody RJ. Parasympathetic withdrawal is an integral component of autonomic imbalance in congestive heart failure: demonstration in human subjects and verification in a paced canine model of ventricular failure. *J Am Coll Cardiol* 1991; **18**: 464–472.
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–1457.
16. Cohen GI, Pietrolungo JF, Thomas JD, Klein AL. A practical guide to assessment of ventricular diastolic function using Doppler echocardiography. *J Am Coll Cardiol* 1996; **27**: 1753–1760.
17. Salemi VM, Picard MH, Mady C. Assessment of diastolic function in endomyocardial fibrosis: value of flow propagation velocity. *Artif Organs* 2004; **28**: 343–346.
18. Brindeiro Filho D, Cavalcanti C. Value of Doppler echocardiography in the diagnosis and management of endomyocardial fibrosis. *Arq Bras Cardiol* 1996; **67**: 279–284.
19. Groehs RV, Toschi-Dias E, Antunes-Correa LM, Trevizan PF, Rondon MU, Oliveira P, Alves MJ, Almeida DR, Middlekauff HR, Negrao CE. Exercise training prevents the deterioration in the arterial baroreflex control of sympathetic nerve activity in chronic heart failure patients. *Am J Physiol Heart Circ Physiol* 2015; **308**: H1096–H1102.
20. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010; **122**: 191–225.
21. Fagius J, Wallin BG. Long-term variability and reproducibility of resting human muscle nerve sympathetic activity at rest, as reassessed after a decade. *Clin Auton Res* 1993; **3**: 201–205.
22. Roveda F, Middlekauff HR, Rondon MU, Reis SF, Souza M, Nastari L, Barretto AC, Krieger EM, Negrao CE. The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. *J Am Coll Cardiol* 2003; **42**: 854–860.
23. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991; **84**: 482–492.
24. Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A. Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. *Circulation* 1994; **90**: 1826–1831.
25. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998; **351**: 478–484.
26. Parati G, Di Rienzo M, Mancia G. How to measure baroreflex sensitivity: from the cardiovascular laboratory to daily life. *J Hypertens* 2000; **18**: 7–19.
27. Trombetta IC, Somers VK, Maki-Nunes C, Drager LF, Toschi-Dias E, Alves MJ, Fraga RF, Rondon MU, Bechara MG, Lorenzi-Filho G, Negrao CE. Consequences of comorbid sleep apnea in the metabolic syndrome—implications for cardiovascular risk. *Sleep* 2010; **33**: 1193–1199.
28. Fraga R, Franco FG, Roveda F, de Matos LN, Braga AM, Rondon MU, Rotta DR, Brum PC, Barretto AC, Middlekauff HR, Negrao CE. Exercise training reduces sympathetic nerve activity in heart failure patients treated with carvedilol. *Eur J Heart Fail* 2007; **9**: 630–636.
29. Alves MJ, Dos Santos MR, Dias RG, Akiho CA, Laterza MC, Rondon MU, Moreau RL, Negrao CE. Abnormal neurovascular control in anabolic androgenic steroids users. *Med Sci Sports Exerc* 2010; **42**: 865–871.
30. Antunes-Correa LM, Melo RC, Nobre TS, Ueno LM, Franco FG, Braga AM, Rondon MU, Brum PC, Barretto AC, Middlekauff HR, Negrao CE. Impact of gender on benefits of exercise training on sympathetic nerve activity and muscle blood flow in heart failure. *Eur J Heart Fail* 2010; **12**: 58–65.
31. Malpas SC. Sympathetic nervous system overactivity and its role in the development of cardiovascular disease. *Physiol Rev* 2010; **90**: 513–557.
32. Grassi G, Seravalle G, Quarti-Trevano F, Scopelliti F, Dell'Oro R, Bolla G, Mancia G. Excessive sympathetic activation in heart failure with obesity and metabolic syndrome: characteristics and mechanisms. *Hypertension* 2007; **49**: 535–541.
33. Macefield VG, Henderson LA. Real-time imaging of the medullary circuitry involved in the generation of spontaneous muscle sympathetic nerve activity in awake subjects. *Hum Brain Mapp* 2010; **31**: 539–549.
34. Sundlof G, Wallin BG. Human muscle nerve sympathetic activity at rest. Relationship to blood pressure and age. *J Physiol* 1978; **274**: 621–637.
35. Charkoudian N, Joyner MJ, Johnson CP, Eisenach JH, Dietz NM, Wallin BG. Balance between cardiac output and sympathetic nerve activity in resting humans: role in arterial pressure regulation. *J Physiol* 2005; **568**: 315–321.
36. Singh M, Juneja R, Bali HK, Varma JS. Autonomic functions in restrictive cardiomyopathy and constrictive pericarditis: a comparison. *Am Heart J* 1998; **136**: 443–448.
37. Kennedy GA, Coleman GJ, Armstrong SM. Restricted feeding entrains circadian wheel-running activity rhythms of the kowari. *Am J Physiol* 1991; **261**: R819–R827.
38. Mortara A, La Rovere MT, Pinna GD, Prpa A, Maestri R, Febo O, Pozzoli M, Opasich C, Tavazzi L. Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications. *Circulation* 1997; **96**: 3450–3458.

39. Mirizzi G, Giannoni A, Bramanti F, Ripoli A, Varanini M, Bernardi L, Emdin M, Passino C. A simple method for measuring baroreflex sensitivity holds prognostic value in heart failure. *Int J Cardiol* 2013; **169**: e9–11.
40. Chapleau MW, Li Z, Meyrelles SS, Ma X, Abboud FM. Mechanisms determining sensitivity of baroreceptor afferents in health and disease. *Ann N Y Acad Sci* 2001; **940**: 1–19.
41. Chapleau MW, Cunningham JT, Sullivan MJ, Wachtel RE, Abboud FM. Structural versus functional modulation of the arterial baroreflex. *Hypertension* 1995; **26**: 341–347.
42. Grassi G, Seravalle G, Colombo M, Bolla G, Cattaneo BM, Cavagnini F, Mancia G. Body weight reduction, sympathetic nerve traffic, and arterial baroreflex in obese normotensive humans. *Circulation* 1998; **97**: 2037–2042.
43. Laterza MC, de Matos LD, Trombetta IC, Braga AM, Roveda F, Alves MJ, Krieger EM, Negrao CE, Rondon MU. Exercise training restores baroreflex sensitivity in never-treated hypertensive patients. *Hypertension* 2007; **49**: 1298–1306.
44. La Rovere MT, Pinna GD, Maestri R, Robbi E, Caporotondi A, Guazzotti G, Sleight P, Febo O. Prognostic implications of baroreflex sensitivity in heart failure patients in the beta-blocking era. *J Am Coll Cardiol* 2009; **53**: 193–199.
45. Grassi G, Seravalle G, Cattaneo BM, Lanfranchi A, Vailati S, Giannattasio C, Del Bo A, Sala C, Bolla GB, Pozzi M. Sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. *Circulation* 1995; **92**: 3206–3211.
46. Di Rienzo M, Parati G, Castiglioni P, Tordi R, Mancia G, Pedotti A. Baroreflex effectiveness index: an additional measure of baroreflex control of heart rate in daily life. *Am J Physiol Regul Integr Comp Physiol* 2001; **280**: R744–R751.
47. Kushwaha SS, Fallon JT, Fuster V. Restrictive cardiomyopathy. *N Engl J Med* 1997; **336**: 267–276.
48. Drexler H. Reduced exercise tolerance in chronic heart failure and its relationship to neurohumoral factors. *Eur Heart J* 1991; **12**(Suppl C): 21–28.
49. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines. ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**: e147–e239.