Cardiac and peripheral autonomic control in restrictive cardiomyopathy

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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

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.¹⁻⁵ The RCM is a cardiomyopathy that affects up to 5% of the population worldwide¹,⁴ 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.\textsuperscript{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) etiology; (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 recommendations of the STROBE statement.\textsuperscript{15}

**Measures and procedures**

**Echocardiography**

Echocardiography was performed on all participants for cardiac functional evaluation according to the American Society of Echocardiography recommendations\textsuperscript{16} with a Sequoia 512 ultrasound machine (Acuson, Mountain View, CA, USA) and a 2.5 MHz harmonic imaging transducer.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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., Brasilia—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.\textsuperscript{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 bandpass 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 ≥ 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/100 mL) 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 · 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 VO₂).
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 χ² 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 VO₂ and peak HR during cardiopulmonary exercise testing 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/m²             | 25.3 ± 2.7        | 27.5 ± 3.3        | 27.7 ± 2.8        | 0.12 |
| Aetiology, n (%)       | —                 | —                 | —                 |      |
| Ischemic               | —                 | —                 | —                 |      |
| Nonischemic            | —                 | —                 | —                 |      |
| EMF                    | —                 | —                 | —                 |      |
| 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%)
| 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 χ² 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.

*Statistically different from HS group.

*Statistically different from DCM group.
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.

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

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**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 VO2, 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 \( \chi^2 \) 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.

*Statistically different from HS group.

**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.
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 | 0.532 | 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 \( (r = 0.532 \text{ between MSNA frequency and LF/HF}; r = 0.522 \text{ and between MSNA incidence and LF/HF}) \). 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 LF/HF; \( r = -0.503 \text{ and BRS− and LF/HF; } r = -0.487 \)). 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, \( r = -0.543 \text{ and BRS− and MSNA incidence, } r = -0.524 \)). 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.

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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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{48} In the present study, we also observed 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\textsubscript{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.\textsuperscript{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.\textsuperscript{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.

\section*{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.

\section*{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.

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\section*{Conflict of interest}

None declared.

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