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SHORT REPORT

Molecular and Cellular Physiology of Heart Failure and Cardiomyopathy

Sympathetic neural overdrive and diminished exercise capacity in reduced ejection fraction heart failure related to anthracycline-based chemotherapy

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Abstract

Cardiotoxicity is the most worrying cardiovascular alteration in patients treated with chemotherapy. To improve the understanding regarding the cardiotoxicity, we studied whether *1*) patients with cardiac dysfunction related to anthracycline-based chemotherapy have augmented sympathetic nerve activity and decreased exercise capacity and *2*) these responses are similar to those observed in patients with heart failure caused by other etiologies. Sixteen patients with heart failure with reduced ejection fraction related to anthracycline-based chemotherapy with or without chest radiation (HFrEFCA), 10 patients with heart failure with reduced ejection not related to cancer therapy (HFrEF), and 16 age- and body mass index (BMI)-matched healthy control subjects were studied. Left ventricular ejection fraction (LVEF, echocardiography), peak oxygen consumption (peak $\dot{V}O_2$, cardiopulmonary exercise test), muscle sympathetic nerve activity (MSNA, microneurography), and forearm blood flow (FBF, venous occlusion plethysmography) were measured. We found that peak oxygen consumption peak $\dot{V}O_2$ and LVEF were significantly reduced in patients with HFrEFCA compared with that of control subjects ($P < 0.0001$) but similar to those found in patients with HFrEFCA. The sympathetic nerve activity burst frequency and incidence were significantly higher in patients with HFrEFCA than that in control subjects ($P < 0.0001$). No differences were found between patients with HFrEF and HFrEFCA. Peak $\dot{V}O_2$ was inversely associated with MSNA burst frequency ($r = -0.53$, $P = 0.002$) and burst incidence ($r = -0.38$, $P = 0.01$) and directly associated with LVEF ($r = 0.71$, $P < 0.0001$). Taken together, we conclude that patients who develop heart failure due to anthracycline-based chemotherapy have sympathetic neural overdrive and reduced exercise capacity. In addition, these physiological changes are similar to those observed in patients with HFrEF.

NEW & NOTEWORTHY Patients with heart failure with reduced ejection fraction related to anthracycline-based chemotherapy have increased sympathetic nerve activity and decreased exercise capacity. These alterations in autonomic control and physical capacity are similar to those observed in patients with heart failure due to other etiologies. These findings highlight the importance of special care of oncological patients treated with chemotherapy.

chemotherapy; exercise capacity; heart failure; sympathetic nerve activity

INTRODUCTION

Abnormal neurovascular control has been documented in patients with heart failure with reduced ejection fraction (HFrEF) (1). Muscle sympathetic nerve activity (MSNA) and peripheral vasoconstriction are markedly increased in patients with HFrEF (2, 3), which contributes to skeletal myopathy and decreased exercise capacity (4). In addition, the increased sympathetic nerve activity and reduced muscle blood flow are associated with worse prognosis in this

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population (5). This scenario emphasizes the importance of investigating heart failure.

Drug-induced cardiotoxicity has become an important cause of heart failure. It is well documented that drugs such as anthracyclines, widely used in the treatment of cancer, are associated with 5–48% increase in the incidence of cardiotoxicity (6). Previous studies show that anthracyclines can cause an increase in QT interval, supraventricular and ventricular arrhythmias, acute coronary syndrome, myocarditis, and systolic and diastolic ventricular dysfunction (6). Undoubtedly, systolic ventricular dysfunction resulting in heart failure is the major concern. However, it remains unknown whether sympathetic nerve outflow is altered in patients with heart failure with reduced ejection fraction related to anthracycline-based chemotherapy with or without chest radiation (HFrEFCA). To clarify this issue, we studied the sympathetic neural outflow in patients with HFrEF compared with that of healthy, control subjects. We found that MSNA is increased in patients with HFrEF (1). Based on this finding, we raised an additional question. Are the derangements in sympathetic nerve outflow associated with systemic cardiovascular toxicity different from those associated with other etiologies? To answer this question, we compare the levels of MSNA in patients with HFrEFCA with the levels in patients with HFrEF caused by different etiologies.

MATERIALS AND METHODS

Sample

Sixteen patients with HFrEFCA, ejection fraction <50%, stable, and undergoing specific treatment for heart failure were enrolled in the study. Ten patients with HFrEF and sixteen aged-paired healthy control subjects from previous studies, which were conducted to study the effects of high-intensity exercise training on sympathetic nerve activity and muscle blood flow in patients with heart failure, and to study the impact of COVID-19 on sympathetic neural activity, endothelial function, and physical capacity in severe COVID-19 survivors, respectively, were also studied (7, 8). Of note, the data of the patients with HFrEF are from the preintervention period with no effect of exercise training. There is no confounding variable in the healthy control group that could influence our findings. During the study, control subjects did not present signals and symptoms of COVID-19, had no nonreactive serological test for antibodies (immunoglobulins G and M), had not been immunized against COVID-19, and were free of cardiovascular or kidney diseases. In addition, the female participants were not pregnant or breastfeeding.

The study was approved by the Human Scientific and Ethical Committee of the Hospital Sírio Libanês (HSL 2014-84), Scientific Research Committee of the Instituto do Coração (InCor), Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil (SDC COP 002/15/002), Ethics Committee of the Instituto do Câncer do Estado de São Paulo (ICESP) and Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo (NP 767/2015), and registered at Clinical Trial [https://clinicaltrials.gov/(NCT04047901)]. All prospectively analyzed patients provided written informed consent before study enrollment. The Ethics Committees from all participating centers provided approval for waiver of consent for patients analyzed retrospectively as part of the study control arms.

Measures and Procedures

The experimental protocol was carried out in two visits in the morning period, in a silent and climate-controlled room (22–24°C), at least 2 h after a standardized light meal. The visits were carried out at the same time of day, with an interval between 2 and 7 days. Before each visit, the participants abstained from alcohol and caffeine for 24 h and from intense physical activity for 48 h. Patients in the HFrEF and HFrEFCA groups were instructed to maintain medications to control heart failure during both experimental visits. On the first visit, all participants underwent cardiac function assessment and cardiopulmonary exercise testing. On the second visit, they underwent neurovascular and hemodynamic assessments at rest.

Cardiac function.

The patients underwent two-dimensional echocardiography assessment (Vivid E9, GE Healthcare; Oslo, Norway). The left ventricular end-diastolic and end-systolic volumes were assessed by apical two- and four-chamber views, which allowed the estimation of ejection fraction by Simpson's biplane method (9).

Exercise capacity.

The exercise capacity was determined through maximum progressive testing on a cycle ergometer (Medifit 400 L, Medical Fitness Equipment), following the ramp protocol with increments of 5–30 W/min at 60 rpm until exhaustion. The metabolic and ventilatory responses (Vmax, Mod. 29 S series YL012278C, Sensor Medics) and the electrocardiogram (Micromed, Cardio PC 13, with 12 simultaneous leads) were registered throughout the test. Peak oxygen consumption (peak $\dot{V}O_2$) was defined as the maximum $\dot{V}O_2$ attained at the end of the exercise period in which the individual could no longer maintain the cycle ergometer speed at 60 rpm.

Muscle sympathetic nerve activity.

MSNA was assessed using the direct multiunit recording technique of the efferent postganglionic pathway of the muscle nervous fascicle, in the peroneal nerve, immediately below the fibular head. The records were obtained through the implantation of a microelectrode in the peroneal nerve. A reference microelectrode was implanted ~1 to 2 cm away from the peroneal nerve microelectrode. The electrodes were connected to a preamplifier, and the nerve signal was fed through a bandpass filter and after that led to an amplitude discriminator to be stored in an oscilloscope. MSNA was assessed through a continuous recording of the sympathetic nerve activity throughout the protocol. The nerve signal was analyzed by the number of bursts per minute and bursts per 100 heartbeats (2, 10).

Forearm blood flow.

Forearm blood flow (FBF) was measured noninvasively by venous occlusion plethysmography (11). The resting nondominant arm was elevated above the right atrium to ensure adequate venous drainage. A mercury-filled silastic tube attached to a low-pressure transducer was placed around the

forearm, 5 cm distant from the humeral-radial joint, and connected to a plethysmography device (Hokanson 201 AG). Sphygmomanometer cuffs were placed around the wrist and the upper arm. The contralateral arm was used for patients who underwent prior breast resection with lymph node dissection. During the evaluation, the cuff of the wrist was inflated above systolic blood pressure (~ 240 mmHg). At 15-s intervals, the upper arm cuff was inflated above venous pressure for 7–8 s. The FBF was recorded throughout experiments and expressed in mL/min/100 mL of tissue. The forearm vascular conductance was calculated by the ratio between the FBF and the mean arterial pressure multiplied by 100 and expressed in units.

Hemodynamic parameters.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and heart rate (HR) at resting were assessed noninvasively on a beat-by-beat manner, using the digital infrared photoplethysmography method (FinometerPRO; Finapres Medical Systems, Amsterdam, The Netherlands).

Experimental Protocol

After the instrumental, the patient rested for 10 min. After this period, MSNA, FBF, blood pressure, and heart rate were continuously and simultaneously registered for a 15-min period at rest.

Data Analysis

MSNA, BP, HR, and FBF were calculated as mean values of the last 5 min registered. MSNA bursts were identified and confirmed through visual inspection by two independent experienced investigators (A.R.K.S and C.E.N.), who were blinded to the study patients. Echocardiographic and vascular parameters were assessed by experienced investigators who were blinded to the study patients. MBP and FVC were calculated as [2(diastolic BP) + systolic BP]/3 and MAP/FBF, respectively.

Statistical Analysis

The Shapiro–Wilk test was used to verify data distribution and the Mauchly test was used to verify sphericity. The normality and sphericity assumptions were not violated. One-way ANOVA was used to test differences among groups and Bonferroni post hoc test was used to detect differences between groups. Pearson coefficient was used to assess the relationships between outcome variables. Analysis of covariance (ANCOVA) model was used to test whether relevant confounding factors influenced outcome variables. Data are presented as means ± SE. Significance was set at $P < 0.05$. All

Table 1. *Physical and clinical parameters in healthy controls and in HFrEF related to anthracycline-based chemotherapy*

	Healthy	HFrEFCA	HFrEF	*P* Value
Variables				
n	16	16	10	
Age, yr	44.0 ± 2.0	47.0 ± 2.0	51.0 ± 2.0	0.08
BMI, kg/m^2	28.6 ± 1.2	28.4 ± 1.2	28.5 ± 1.5	0.98
Sex, *n* female/male	6/10	15/1	5/5	0.003
Conditions, *n*				
Etiology				
Ischemia		0	7	
Hypertension		0	2	
Idiopathy		0	1	
Cardiotoxicity		16	0	
Medications, *n*				
β-Blocker		15	10	0.42
ACEI/ARB		13	9	0.55
Spironolactone		8	7	0.32
Cardiopulmonary exercise testing				
$\dot{V}O_2$, L/min	2.29 ± 0.1	1.48 ± 0.1	1.42 ± 0.1	<0.0001
$\dot{V}E$, L/min	95 ± 6.0	48 ± 3.0	59 ± 5.0	<0.0001
RER	1.23 ± 0.02	1.14 ± 0.02†	1.16 ± 0.03	<0.006
Weber–Janicki class, *n* (%)				
Class A		2 (12.5)	4 (40)	0.298
Class B		9 (56.3)	3 (30)	
Class C		5 (31.3)	3 (30)	
Central hemodynamic variables				
SBP, mmHg	130 ± 3.0	129 ± 4.0	131 ± 4.0	0.92
DBP, mmHg	75 ± 2.0	75 ± 3.0	73 ± 2.0	0.86
MAP, mmHg	93 ± 2.0	93 ± 2.6	92 ± 3.2	0.98
HR, beats/min	69 ± 2.5	72 ± 3.0*	63 ± 3.0	0.045
Peripheral hemodynamic variables				
FBF, mL/min/100 mL	2.0 ± 0.1	1.8 ± 0.1	1.7 ± 0.2	0.16
FVC, U	2.2 ± 0.1	2.0 ± 0.1	1.9 ± 0.2	0.29

Values are means ± SE and *n* (%). HFrEFCA, reduced ejection fraction related to anthracycline-based chemotherapy with or without chest radiation; HFrEF, heart failure with reduced ejection not related to anthracycline-based chemotherapy with or without chest radiation; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitors. $\dot{V}O_2$, oxygen uptake; $\dot{V}E$, ventilation; RER, respiratory exchange ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; FBF, forearm blood flow; FVC, forearm vascular conductance. *$P < 0.05$ vs. HFrEF. †$P < 0.05$ vs. healthy group.

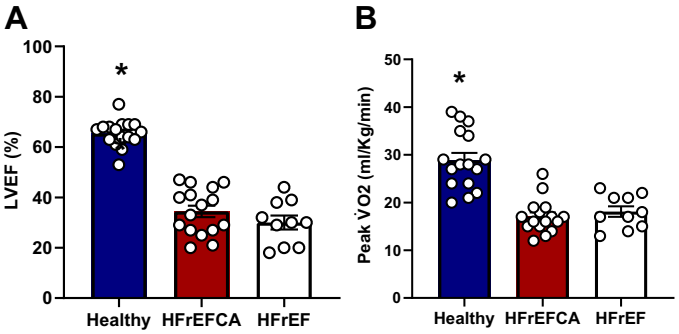

Figure 1. Cardiac function and exercise capacity in patients with heart failure with reduced ejection fraction related to anthracycline-based chemotherapy (HFrEFCA, $n = 16$), patients with heart failure with reduced ejection fraction not related to cancer therapy (HFrEF, $n = 10$), and healthy control subjects (healthy, $n = 16$). *A*: left ventricular ejection fraction (LVEF). *B*: peak oxygen consumption ($\dot{V}O_2$). Note that LVEF and peak $\dot{V}O_2$ were significantly reduced in both groups of patients with heart failure compared with healthy control subjects (healthy). *$P < 0.0001$.

analyses and the figures were performed in GraphPad Prism 8.0 and Statistical 12.0.

RESULTS

The physical and clinical characteristics of patients with HFrEFCA, patients with HFrEF, and healthy control subjects are shown in Table 1. There were no differences in age and BMI among groups. The Weber–Janicki class showed no differences between patients with HFrEFCA and patients with HFrEF. Likewise, medications were similar between heart failure groups. Absolute peak oxygen consumption and peak pulmonary ventilation were significantly reduced in patients with HFrEFCA and HFrEF than in healthy control subjects ($P < 0.0001$). Respiratory exchange ratio was lower in the heart failure groups relative to healthy control subjects ($P < 0.001$). No significant differences were observed in SBP and DBP and MBP across groups. HR was higher in patients with HFrEFCA compared with patients with HFrEF ($P = 0.045$). No significant differences were found between patients with HFrEFCA and healthy control subjects. No differences were found in FBF and FVC among groups. All patients with HFrEFCA received anthracycline-based chemotherapy, and nine of them also received some type of chest radiation.

The LVEF was significantly lower in patients with HFrEFCA and patients with HFrEF compared with healthy control subjects (Fig. 1*A*, $P < 0.0001$). No differences were found between patients with HFrEFCA and patients with HFrEF.

The relative peak $\dot{V}O_2$ was significantly reduced in patients with HFrEFCA and patients with HFrEF compared with healthy control subjects (Fig. 1*B*, $P < 0.0001$).

The MSNA levels are shown in Fig. 2. The original recordings from one patient with HFrEFCA, one patient with HFrEF, and one healthy control subject are shown in Fig. 2*A*. MSNA burst frequency ($P < 0.0001$) and burst incidence ($P < 0.0001$) were significantly greater in patients with HFrEFCA and patients with HFrEF compared with healthy control subjects (Fig. 2, *B* and *C*). MSNA was similar between patients with HFrEFCA and patients with HFrEF ($P > 0.05$).

Relative peak $\dot{V}O_2$ was inversely associated with MSNA burst frequency (Fig. 3*A*, $r = -0.53$, $P = 0.002$) and burst incidence (Fig. 3*B*, $r = -0.38$, $P = 0.01$), and HR (Fig. 3*C*, $r = -0.33$, $P = 0.03$).

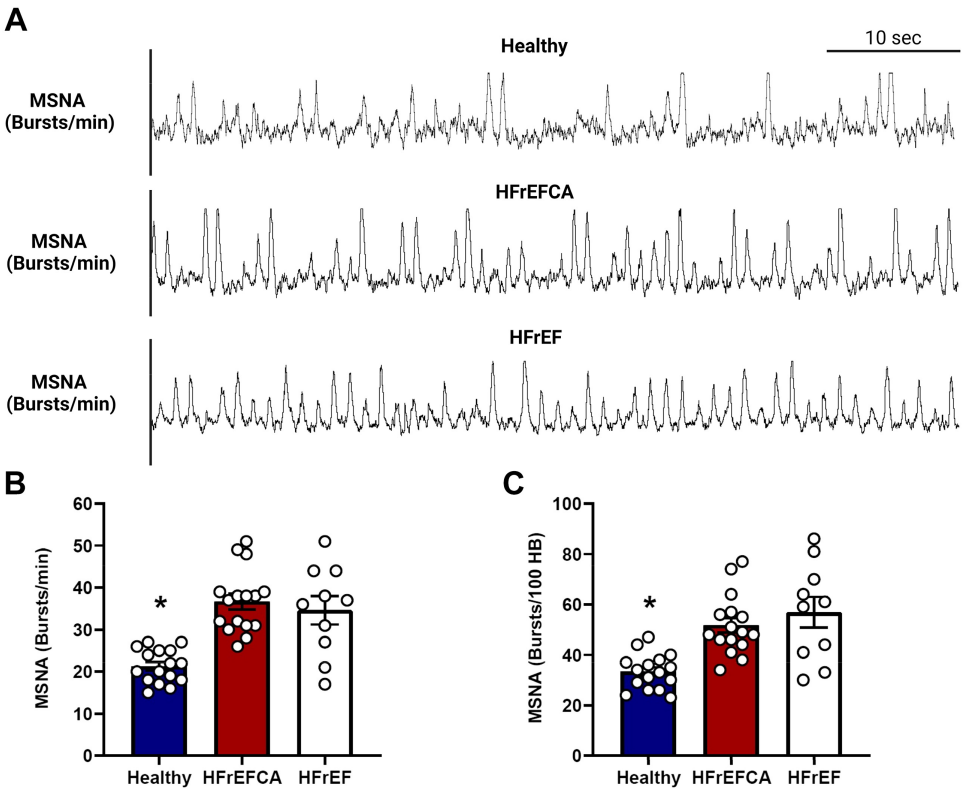

Figure 2. Muscle sympathetic nerve activity (MSNA) in patients with heart failure with reduced ejection fraction related to anthracycline based chemotherapy (HFrEFCA, $n = 16$), patients with heart failure with reduced ejection fraction not related to related to cancer therapy (HFrEF, $n = 10$), and healthy control subjects (healthy, $n = 16$). *A*: examples of nerve recordings. *B* and *C*: mean values of MSNA bursts frequency (*B*) and bursts incidence (*C*). Note that MSNA was significantly increased in both patients with HFrEFCA and HFrEF compared with healthy control subjects (healthy). *$P < 0.0001$.

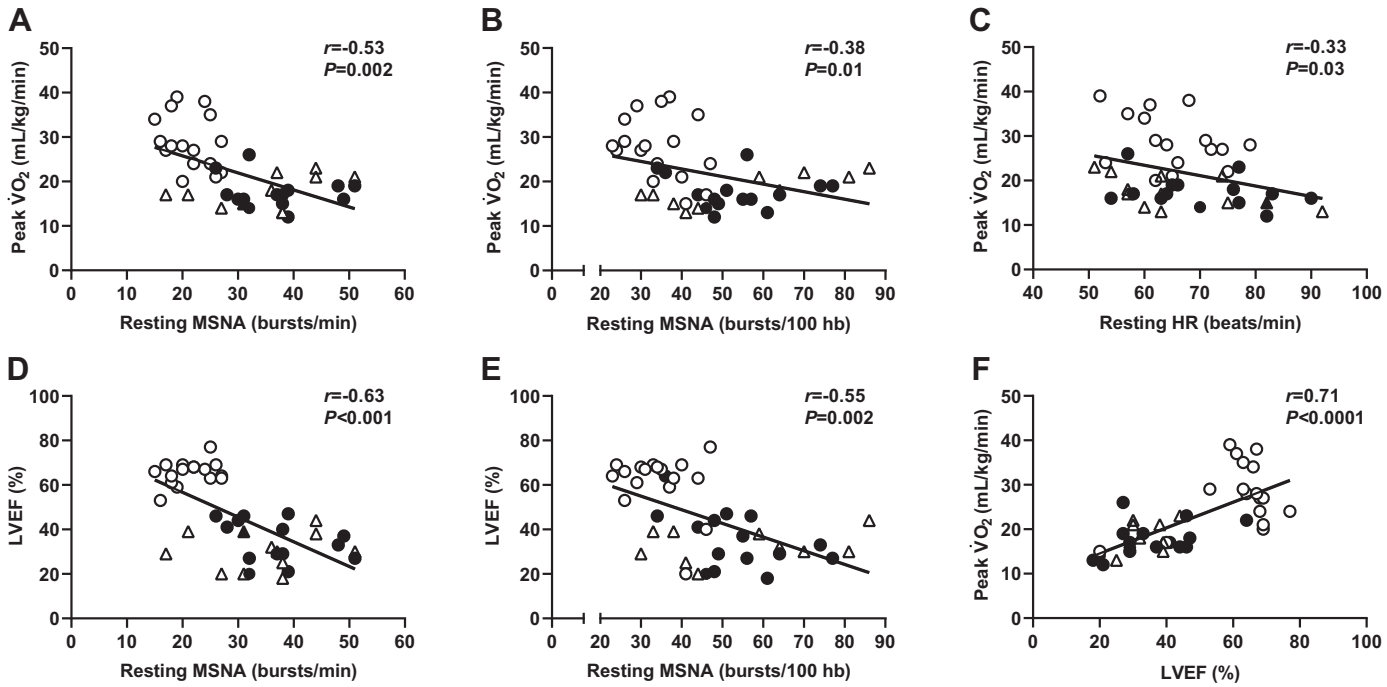

Figure 3. Diminished exercise capacity and cardiac dysfunction are related to neurovascular changes at-rest patients with heart failure with reduced ejection fraction related to anthracycline-based chemotherapy with or without chest radiation (HFrEFCA). *A–C*: correlation between peak oxygen consumption ($\dot{V}O_2$) and muscle sympathetic nerve activity (MSNA), burst frequency (*A*) and burst incidence (*B*), and heart rate (HR, *C*). *D* and *E*: correlations between left ventricular ejection fraction (LVEF) and muscular sympathetic nerve activity (MSNA), burst frequency (*D*) and burst incidence (*E*). *F*: correlation between peak oxygen consumption ($\dot{V}O_2$) and left ventricular ejection fraction (LVEF). Note that MSNA burst frequency and burst incidence were inversely associated with LVEF and with peak $\dot{V}O_2$, whereas LVEF was significantly correlated with peak $\dot{V}O_2$. ○, control healthy subjects; ●, HFrEFCA; △, heart failure with reduced ejection fraction (HFrEF).

LVEF was inversely associated with MSNA bursts frequency (Fig. 3*D*, $r = -0.63$, $P < 0.001$) and burst incidence (Fig. 3*E*, $r = -0.55$, $P = 0.002$). Relative peak $\dot{V}O_2$ was directly associated with LVEF (Fig. 3*F*, $r = 0.71$, $P < 0.0001$).

DISCUSSION

The main and novel findings of this study are as follows. First, patients with HFrEFCA have augmented MSNA levels compared with heathy control subjects. Second, this response is similar to that observed in patients with HFrEF. Third, exercise capacity is equally decreased in patients with HFrEFCA and patients with HFrEF. Finally, there is an inverse association between peak $\dot{V}O_2$ levels and MSNA levels in patients with HFrEFCA.

Sympathetic activation is the hallmark of heart failure. Increased circulatory catecholamine (12), cardiac vagal and sympathetic imbalance in favor of the later, increased cardiac and renal norepinephrine spillover (13, 14), and increased MSNA bursts frequency and bursts incidence (15) have been reported in heart failure. The present study shows for the first time that patients with HFrEFCA have increased MSNA bursts frequency and bursts incidence. These findings are relevant and have immediate clinical implication since MSNA is an independent predictor of mortality in patients with HFrEF (10). The mechanisms involved in the sympathetic activation in patients with HFrEFCA are complex. To uncover this issue, future studies should focus on afferent controls of sympathetic nerve activity. The potential mechanisms for these thoughts are the decreased baroreflex control, the increased muscle mechanoreflex control, and the sensitized chemoreflex control that have been convincingly documented in patients with HFrEF (4). It is possible that the same derangements occur in patients with HFrEFCA.

Our study shows that arterial blood pressure is not different between patients with HFrEFCA and healthy control subjects. Moreover, arterial blood pressure is similar in patients with HFrEF and patients with HFrEF. These findings do not surprise because previous studies (16, 17) demonstrate that SBP and DBP at rest are similar between patients with heart failure and normal control subjects. The higher heart rate levels in patients with HFrEF compared with patients with HFrEF are somewhat unexpected. Based on this response, someone could argue that patients with HFrEF have more β-blockade than patients with HFrEFCA. This explanation seems unlikely because β-blockers' usage was not different between groups (Table 1). Moreover, the MSNA levels were similar between patients with HFrEF and patients with HFrEFCA. In a previous study, we found that carvedilol decreases MSNA in patients with heart failure (18). Finally, further analysis of covariance shows that resting HR does not influence our findings.

Since the regional blood flow is highly influenced by sympathetic outflow, someone could expect that the muscle blood flow was diminished in patients with HFrEFCA. Surprisingly, this was not the case. We found no difference in muscle blood flow between healthy subjects and patients

with HFrEFCA. One possible explanation for such a response is that sympathetic nerve activity was measured in the leg, whereas muscle blood flow was measured in the forearm. The sympathetic nerve outflow is not uniform in different sites. Some elegantly reported that there is a dissociation of arm and leg sympathetic nerve activity in response to mental stress (19). Others demonstrated different vascular control between the arm and leg during mental stress, which is not associated with muscle sympathetic nerve activity [neurovascular responses to mental stress (20)].

Of course, the similarity in muscle blood flow does not rule out that other vascular beds undergo vasoconstriction in patients with HFrEFCA. The peripheral vasoconstriction is a marker of heart failure (21).

Exercise intolerance is one of the major issues in heart failure. Patients with heart failure have decreased physical capacity, which is associated with poor quality of life and increased mortality (22, 23). Cancer survival rate is also associated with physical capacity (24). Previous studies have also shown that patients with cancer have a 25% reduction in physical capacity after adjuvant systemic cancer therapy, even in the absence of heart failure (25). Our study extends this knowledge to patients with cardiomyopathy caused by anthracycline-based chemotherapy with or without chest radiation. Peak $\dot{V}O_2$ is remarkably reduced in patients with HFrEFCA when compared with healthy individuals. Moreover, our study shows a negative association between peak $\dot{V}O_2$ levels and MSNA levels. Taken together, these findings suggest that both the decreased peak $\dot{V}O_2$ and the increased MSNA contribute to poor prognosis in patients with HFrEFCA.

Alterations in skeletal muscle secondary to cardiac dysfunction play a key role in the exercise intolerance in patients with heart failure. Muscle atrophy due to protein catabolism has been described in heart failure (26). Myofilament and mitochondrial proteins undergo quantitative and qualitative changes in heart failure. These skeletal muscle alterations contribute to loss in functionality, exercise intolerance, and poor quality of life in patients who suffer from heart failure (27). More recently, we learned that chronic cardiac dysfunction causes changes in skeletal myocytes in the microRNA environment (28), and that nonpharmacological therapy based on physical training upregulates microRNA-1, decreasing the expression of the homologous protein of phosphatase and tensin (PTEN), resulting in activation of phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT), associated with skeletal muscle trophism (29). Whether these mechanisms also occur in patients with HFrEFCA and contribute to the reduction in physical capacity in these patients remain unknown.

Perspectives and Significance

Patients who develop heart failure due to anthracycline-based chemotherapy have sympathetic neural overdrive and reduced physical capacity. These findings highlight the necessity of special care in oncological patients treated with chemotherapy and chest radiation. Therapeutic interventions, such as exercise rehabilitation, should be considered to improve long-term cardiac clinical outcomes in this set of patients.

DATA AVAILABILITY

Data will be made available upon reasonable request.

GRANTS

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

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

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