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Short Communication

Exercise training improves microvascular function in patients with Chagas heart disease: Data from the PEACH study

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ABSTRACT

Background: Chagas heart disease (CHD) impairs the systemic microvascular function. We investigated the effects of exercise training on cutaneous microvascular function among patients with CHD.
Methods: Patients from the PEACH study were randomly assigned to a supervised exercise training 3 times/week for 6 months (Trained; $n = 10$) or a control group (Untrained; $n = 8$). Both groups underwent evaluation of microvascular function before, and at 3- and 6-months of follow-up. Cutaneous vascular conductance (CVC) was assessed in the skin of the forearm using laser speckle contrast imaging coupled with iontophoresis of acetylcholine (ACh), sodium nitroprusside (SNP) and during post-occlusive reactive hyperemia (PORH).
Results: At 3-months of follow-up, no difference was detected between groups in CVC responses to ACh ($p = 0.50$), SNP ($p = 0.26$) and HRPO ($p = 0.65$). However, at 6-months of follow-up, trained vs. untrained patients improved CVC induced by SNP-iontophoresis (0.19 ± 0.10 vs. 0.14 ± 0.15 APU.mmHg^{-1}; $p = 0.05$) and PORH (0.63 ± 0.15 vs. 0.48 ± 0.18 APU.mmHg^{-1}; $p = 0.05$). CVC response to ACh-iontophoresis was similar between groups (0.19 ± 0.11 vs. 0.22 ± 0.17 APU.mmHg^{-1}; $p = 0.38$).
Conclusion: Exercise training performed during 6 months improved the cutaneous microvascular function of CHD patients. Further studies evaluating the mechanism involved in this response are warranted.

1. Introduction

Chagas disease is a tropical parasitic disease caused by *Trypanosoma cruzi* that affects over 6 million people worldwide World Health Organization (2020, #37). Approximately 30% of those patients develop Chagas heart disease (CHD) that involves progressive myocardial fibrosis, ventricular arrhythmias, congestive heart failure and sudden cardiac death, which is the main cause of death among patients with Chagas disease (Echavarria et al., 2019).

We have demonstrated by using laser speckle contrast imaging that patients with CHD exhibit reduced cutaneous microvascular blood flow response to acetylcholine compared to healthy controls (Borges et al., 2016). This feature deserves attention, since cutaneous microvascular reactivity has been proposed as a surrogate of poor prognosis (Tibirica et al., 2018).

Exercise training is a well-established non-pharmacological strategy for the management of chronic diseases (Pedersen and Saltin, 2015) that improves microvascular function in several cardiometabolic diseases (Borges et al., 2018b; de Moraes et al., 2016). However, its impact on microvascular function among patients with CHD has not been previously investigated. Considering that CHD presents a complex pathophysiology that differs from those of cardiac diseases of other etiologies (Bonney and Engman, 2008), studies on this field are needed. Therefore, we aimed to evaluate the effect of an exercise training program upon

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microvascular reactivity in patients with CHD.

2. Methods

The present study is a secondary analysis from the PEACH study, a single-center, superiority randomized clinical trial of exercise training versus an untrained control group (Clinicaltrials.gov register NCT02517632) performed at Evandro Chagas National Institute of Infectious Disease (INI), a national reference center for treatment and research in infectious and tropical diseases in Rio de Janeiro, Brazil. The full description of the PEACH study design has been previously published (Mendes Fde et al., 2016), as well as its results on maximal functional capacity and cardiac function (de Souza Nogueira Sardinha Mendes et al., 2020).

For this secondary analysis, we included 18 patients with CHD (left ventricular ejection fraction <45% with or without heart failure) (Dias et al., 2016) of both sexes from the PEACH study that were randomly assigned into an exercise trained ($n = 10$) or untrained ($n = 8$) group. Exclusion criteria were major comorbidities or limitations that could interfere with exercise training, pregnancy, unavailability to attend exercise sessions 3 times a week, practice of regular exercise training at baseline (>1 time per week in the previous 3 months), smoking, or evidence of associated non-CHD.

All procedures described in the present study were conducted in accordance with the Declaration of Helsinki of 1975 as revised in 2000 and approved by Evandro Chagas National Institute of Infectious Disease Institute Institutional Review Board (CAAE 38038914.6.0000.5262) and National Institute of Cardiology Institutional Review Board (CAAE 38701614.8.0000.5272). All patients provided written informed consent to participate in the study.

Both groups received nutritional and pharmaceutical counseling monthly. In addition, patients underwent regular medical appointments with the same cardiologist during the follow-up based on standard medical treatment of the Brazilian consensus on Chagas disease recommendations (Dias et al., 2016). Trained group performed 3 supervised exercise sessions per week for 6 months, in which patients walked on treadmill for 30 min and performed 20 min of strength exercises for the major muscle groups (sit-ups, push-ups, and pull-ups) and 10 min of stretching. The target heart rate (HR) was defined according to cardiopulmonary exercise testing (CPET) and corresponded to 90–100% of the baseline anaerobic threshold during the first month and to 100–110% thereafter.

Cutaneous microvascular reactivity was evaluated at baseline, after 3- and 6-months of intervention, as previously described (Borges et al., 2016), by the same technician who was not aware of the experimental condition of each patient. Briefly, microcirculatory tests were performed after a 20-min rest with the patients in the supine position in a temperature-controlled room (23 ± 1 °C) approximately 1 h after a light breakfast. Microvascular reactivity was evaluated using a laser speckle contrast imaging system with a laser wavelength of 785 nm (PeriCam PSI system, Perimed, Järfälla, Sweden) coupled to iontophoresis of acetylcholine (ACh) and sodium nitroprusside (SNP) for noninvasive and continuous measurements of increases in forearm cutaneous microvascular perfusion (peak minus baseline) (Cordovil et al., 2012). ACh and SNP (2% *w/v*; Sigma Chemical Co., St. Louis, MO, USA) iontophoresis were performed using a microphamacology system (PF 751 PeriIont USB Power Supply, Perimed, Sweden) with increasing anodal currents of 30, 60, 90, 120, 150 and 180 μA applied in 10-s intervals spaced 1 min apart (total charges were 0.3, 0.6, 0.9, 1.2, 1.5 and 1.8 mC, respectively). Post-occlusive reactive hyperemia (PORH) was assessed after arterial occlusion with supra-systolic pressure (50 mmHg above systolic arterial pressure) by means of a sphygmomanometer applied to the right arm during 3 min. Maximum flow was measured after releasing the pressure. Skin blood flow, in arbitrary perfusion units, was divided by the mean arterial pressure to yield the cutaneous vascular conductance (CVC).

Statistical analyses were performed using Stata 13.0. Patient characteristics were summarized using mean and standard deviation for continuous variables and frequencies; and percentages for categorical variables. Linear mixed models were fitted to evaluate longitudinal changes for repeated measures during the follow-up. Model included time, treatment and the interaction term (time X treatment) to estimate the rate of changes between groups in the outcomes (represented as β coefficient for trained vs untrained). All models were adjusted for the baseline values of each outcome and age. All patients regardless of losses to follow-up or noncompliance to exercise were included in the intention-to-treat analysis. *P*-values of ≤0.05 were considered statistically significant.

3. Results

One patient in the trained group did not perform the 3-month test, while another in the untrained group died before the 6-month test due to complications of a femur fracture. Table 1 depicts baseline clinical characteristics of the patients. No differences were observed between trained and untrained groups at baseline. Of the 18 patients included, 94% were treated with beta-blockers (carvedilol), 94% with angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers (47% losartan, 44% enalapril, and 6% captopril), 50% with aldosterone antagonist (spironolactone), 11% with isosorbide and 6% with hydralazine. No differences were observed between groups for the used medication at baseline and during the follow-up.

As demonstrated in Table 2, no differences were detected between groups at 3 months of follow-up for increases in CVC induced by ACh- and SNP-iontophoresis and PORH. At 6 months of follow-up, although ACh-induced increases in CVC were similar between groups, responses in CVC to SNP-iontophoresis and PORH were greater in trained versus untrained group. Moreover, although changes in peak VO_2 were similar between groups after 3 months of follow-up ($\beta = +1.90$; $p = 0.41$), trained patients exhibited greater responses in peak VO_2 after 6 months of follow-up ($\beta = +6.00$; $p < 0.01$). No significant differences for left ventricular ejection fraction were detected between groups at 3- ($\beta = +3.95$; $p = 0.19$) and 6-months follow-up ($\beta = +1.87$; $p = 0.54$).

4. Discussion

The main finding of the present study was that patients with CHD submitted to exercise training improved cutaneous vascular responsiveness to reactive hyperemia and SNP, but not to ACh, in comparison to those who did not perform exercise. Additionally, exercise-induced changes in vasoreactivity of those patients seem to occur only after longer exercise programs (i.e. 6 months), as 3 months of physical training were not enough to provide such changes.

Our findings may have clinical significance as coronary microvascular derangements are acknowledged to contribute to the complex pathogenesis of CHD, as well as abnormal autonomic regulation and low-grade chronic inflammation (Nunes et al., 2018). Although central microcirculation was not presently assessed, cutaneous blood flow seems to represent well the coronary microvascular function (Khan et al., 2008). Prior research have already evidenced by using laser

Table 1
Crude means (standard deviation) for clinical parameters at baseline.

	Trained (n = 10)	Untrained (*n* = 8)
Age (yrs)	57.0 (10.1)	59.8 (12.7)
Male [n (%)]	9 (90)	6 (75)
Body mass index (kg/m^2)	23.5 (4.0)	24.5 (3.4)
Peak oxygen uptake (ml/kg·min)	17.8 (4.6)	17.3 (7.5)
Systolic blood pressure (mm Hg)	115.0 (20.2)	102.5 (17.4)
Heart rate (bpm)	68.2 (12.0)	60.6 (9.3)
Ejection fraction (%)	31.2 (9.2)	36.1 (4.1)

Table 2
Increases in forearm cutaneous vascular conductance [in APU.mmHg^{-1}] induced by the iontophoresis of Acetylcholine [ACh] and Sodium Nitroprusside [SNP] and post-occlusive reactive hyperemia [PORH] before and at 3 and 6-month of follow-up.

	Baseline	3 months				6 months			
	Mean (sd)	Mean (sd)	Δ[a]	β	*P*[b]	Mean (sd)	Δ[a]	β	*P*[b]
ACh									
Trained	0.26 (0.30)	0.20 (0.16)	−0.6	−0.06	0.50	0.19 (0.11)	−0.7	−0.08	0.38
Untrained	0.20 (0.18)	0.23 (0.13)	+0.3			0.22 (0.17)	+0.2		
SNP									
Trained	0.17 (0.08)	0.19 (0.08)	+0.2	+0.06	0.26	0.19 (0.10)	+0.2	+0.11	0.05
Untrained	0.22 (0.15)	0.18 (0.14)	−0.4			0.14 (0.15)	−0.8		
PORH									
Trained	0.56 (0.17)	0.53 (0.17)	−0.3	−0.03	0.65	0.63 (0.15)	+0.7	+0.15	0.05
Untrained	0.54 (0.21)	0.55 (0.15)	+0.1			0.48 (0.18)	−0.6		

[a] Changes from baseline.
[b] *P*-values for time × treatment interaction using linear mixed models.

speckle contrast imaging that patients presenting with CHD exhibit abnormal vasodilatation of cutaneous microcirculation (Borges et al., 2018a), which suggests a poor prognosis (Tibirica et al., 2018). Thus, manageable strategies to mitigate such functional damages in CHD are paramount.

Although never tested in CHD, cutaneous vascular responsiveness increased after exercise training performed during 3 months or less in patients with cardiometabolic diseases, such as coronary artery disease (CAD) (Szyguła et al., 2020) and diabetes (de Moraes et al., 2016). Our results partially agree with those findings, as we observed that 3 months of exercise training were insufficient to enhance microcirculation function in patients with CHD. Although skin microvascular function may be equally impaired among patients with cardiac disease secondary to Chagas disease and ischemic cardiomyopathy (Borges et al., 2018a), their adaptive responses to exercise training at the microcirculatory level may be different, requiring a longer duration of exercise training to achieve benefits. One possible explanation for this would be the discrepancies between the pathogenesis of CHD and ischemic cardiomyopathies (Echavarria et al., 2019). Further studies are warranted to better elucidate the time-course of exercise-induced adaptation in microcirculation and its underlying mechanisms in CHD.

We observed that exercise training improved the vasodilation due to SNP iontophoresis in comparison to untrained. SNP is an endothelium-independent relaxant agent and therefore its effect is attributed to a direct action on vascular smooth muscle (Souza et al., 2014). Hence, it is feasible that exercise training improved the smooth muscle function of patients with CHD. Curiously, unlike vasoreactivity to SNP and PORH, ACh-induced increases in forearm blood flow were unchanged after exercise training, regardless of its duration. Although both ACh- and PORH-induced responses are considered to be endothelium-dependent, our results suggest that distinct vasomotor pathways contribute to their effects. In fact, prior research suggests that PORH-mediated responses are more dependent on total plasma antioxidant capacity, sensory nerves and BKCa channels, while those of ACh seem to involve nitric oxide and cyclooxygenase-derived prostanoids (Simmons et al., 2011). However, endothelium-dependent pathways of vasodilatation in the skin are complex and only partially understood; and thus it remains unclear which of these pathways are affected by exercise training in CHD.

Unlike untrained patients, in those submitted to exercise training the microvascular results were accompanied by maintenance of maximal exercise capacity. However, no association was found between these two outcomes ($r < 0.10$). A previous study from our group support this premise, as patients with CAD who attended cardiac rehabilitation for 6 months increased endothelium-dependent reactivity without improvements in peak VO_2 (Borges et al., 2018b). It is therefore possible that different underlying mechanisms mediate exercise-related effects on exercise capacity and microcirculation.

The major limitation of this study regards the small sample size, which is common in studies involving pathologies with low prevalence (Marino et al., 2018). Future studies with larger sample size investigating microcirculation responses to exercise training in CHD and their underlying mechanisms are necessary. Moreover, the behavioral feature of intervention precluded the blinding of patients and research personnel during exercise training. However, cutaneous microvascular reactivity was performed and analyzed by the same blinded evaluator.

In conclusion, exercise training performed during 6 months improved the cutaneous microvascular function of CHD patients. Further studies evaluating the mechanism involved in this response are warranted.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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