International Journal of Cardiology 265 (2018) 35–37

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Short communication

Is endothelial microvascular function equally impaired among patients with chronic Chagas and ischemic cardiomyopathy?☆

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ARTICLE INFO

Article history:
Received 22 November 2017
Received in revised form 28 February 2018
Accepted 30 April 2018
Available online 1 May 2018

Keywords:
Chagas heart disease
Ischemic heart disease
Coronary artery disease
Endothelial function
Cutaneous vascular conductance
Microvascular flowmetry

ABSTRACT

Background: Chronic Chagas cardiomyopathy (CCC) and cardiomyopathies due to other etiologies involve differences in pathophysiological pathways that are still unclear. Systemic microvascular abnormalities are associated with the pathogenesis of ischemic heart disease. However, systemic microvascular endothelial function in CCC remains to be elucidated. Thus, we compared the microvascular endothelial function of patients presenting with CCC to those with ischemic cardiomyopathy disease.

Methods: Microvascular reactivity was assessed in 21 patients with cardiomyopathy secondary to Chagas disease, 21 patients with cardiomyopathy secondary to ischemic disease and 21 healthy controls. Microvascular blood flow was assessed in the skin of the forearm using laser speckle contrast imaging coupled with iontophoresis of acetylcholine (ACh).

Results: Peak increase in forearm blood flow with ACh iontophoresis in relation to baseline was greater in healthy controls than in patients with heart disease (controls: 162.7 ± 58.4% *vs.* ischemic heart disease: 74.1 ± 48.3% and Chagas: 85.1 ± 68.1%; $p < 0.0001$). Patients with Chagas and ischemic cardiomyopathy presented similar ACh-induced changes from baseline in skin blood flow ($p = 0.55$).

Conclusion: Endothelial microvascular function was equally impaired among patients with CCC and ischemic cardiomyopathy.

1. Introduction

Chagas disease or *American trypanosomiasis* is a complex neglected tropical disease caused by the protozoan *Trypanosoma cruzi*, affecting approximately 11 million people worldwide. From those, up to 30% develop chronic Chagas cardiomyopathy (CCC), which is characterized by ventricular arrhythmias, thromboembolic phenomena, chronic heart failure and sudden cardiac death [1,2].

Despite being an important public health issue, the pathogenesis of CCC is still controversial. Although studies conducted by Rossi et al. [1,3] indicate coronary microvascular abnormalities as an important pathogenic mechanisms leading to CCC, further data confirming this incipient hypothesis are lacking. On the other hand, several studies have been demonstrating that non-Chagas cardiomyopathies are closely associated with systemic microvascular dysfunction, mainly those from ischemic etiology [4,5].

Considering the poor prognosis of patients with CCC in comparison to those with other cardiomyopathies [2,6,7], we hypothesized that microvascular endothelial function among patients with CCC would be worse than those with ischemic cardiomyopathy disease. Recognizing the pathophysiological mechanisms associated with CCC would be crucial to identify which should be the overall aims of drug treatment in Chagas disease, so that therapy may be better targeted and patient outcomes could be improved. In this sense, the endothelial function deserves attention, especially regarding to cardiac remodeling. Accordingly, we sought to compare microvascular endothelial function among healthy individuals with patients presenting with CCC and ischemic cardiomyopathy disease.

2. Methods

The present study is a secondary analysis from two other interventional studies aiming to evaluate the influence of exercise intervention

☆ All above authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcard.2018.04.133
0167-5273/

on microvascular endothelial function. The full description of these intervention studies are described elsewhere [8,9].

We enrolled 42 patients with heart disease and left ventricle ejection fraction lower than 45% and 21 healthy controls. From these 42 patients, 21 had Chagas cardiomyopathy (classification B2 and C) [10] and 21 ischemic cardiomyopathy. Patients with Chagas and ischemic cardiomyopathy were followed at Evandro Chagas National Institute of Infectious Disease (INI) and National Institute of Cardiology (INC), respectively. Both are considered national reference centers for treatment in infectious/tropical diseases and cardiology in Rio de Janeiro, Brazil. Chagas serology was confirmed by two simultaneously tests (enzyme-linked immunosorbent assay – ELISA- and indirect immunofluorescence), while ischemic cardiomyopathy was defined by the presence of obstructive coronary artery disease based on coronary angiography (defined as ≥50% stenosis of any epicardial coronary artery) in patients with angina [11].

Subjects included in the study read and signed an informed consent form. The present study complied with ethical guidelines of the 1975 Helsinki Declaration and was 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).

Cutaneous microvascular reactivity was assessed always in the morning after a 20-minute rest with individuals in the supine position in a temperature-controlled room (23 ± 1 °C). Microcirculatory tests were performed as previously described [4,5]. Briefly, systemic 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) for noninvasive and continuous measurements of cutaneous microvascular perfusion changes in the forearm (in comparison to baseline, %) [5,12]. ACh (2% w/v; Sigma Chemical Co., St. Louis, MO, USA) iontophoresis was performed using a microphramacology 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-second intervals spaced 1 min apart (total charges were 0.3, 0.6, 0.9, 1.2, 1.5 and 1.8 mC, respectively). Skin blood flow was also divided by the mean arterial pressure to yield the cutaneous vascular conductance (CVC) and expressed as the peak response to ACh minus baseline. Images were analyzed using the manufacturer's software (PIMSoft, Perimed, Järfälla, Sweden).

Differences between groups were assessed with a one-way analysis of variance (ANOVA) and post-hoc testing with the Newman-Keuls correction. Results are expressed as the mean ± SD and significance level was set at $p < 0.05$. All calculations were performed using a commercially available computer based statistical package (GraphPad Prism 5 for Windows, version 5.01; La Jolla, USA).

3. Results

Table 1 shows baseline clinical characteristics of subjects. Age, gender, systolic, mean and diastolic blood pressure were similar across groups. Also, there was no difference in left ventricle ejection fraction among patients with Chagas and ischemic cardiomyopathy.

Fig. 1 depicts the results for the changes in skin microvascular reactivity expressed in percentage (A) and cutaneous vascular conductance (B). Not surprisingly, peak increase in forearm blood flow with ACh iontophoresis in relation to baseline was greater in healthy controls than in patients with heart disease expressed either in percentage (controls: 162.7 ± 58.4% *vs*. ischemic heart disease: 74.1 ± 48.3% and Chagas: 85.1 ± 68.1%; $p < 0.0001$) or cutaneous vascular conductance (controls: 0.35 ± 0.16 *vs*. ischemic heart disease: 0.23 ± 0.15 and Chagas: 0.24 ± 0.17 APU/mmHg; $p = 0.03$). Patients with Chagas and ischemic cardiomyopathy presented similar ACh-induced changes from baseline in skin blood flow ($p = 0.55$).

4. Discussion

The present study compared the microvascular endothelial function among patients with CCC and ischemic cardiomyopathy with healthy subjects matched for age. Our main finding was that microvascular endothelial function was equally impaired in patients with CCC and ischemic cardiomyopathy.

Prior research indicates that patients presenting with coronary artery disease exhibit a reduction on systemic microvascular blood flow response to ACh compared with healthy controls, which suggests that microvascular abnormalities are involved in the pathogenesis of ischemic heart disease [4,12]. However, the existence of microvascular endothelial changes and its role in pathophysiological pathways of non-ischemic heart diseases remains to be elucidated. In this sense, Chagas disease deserves attention due to some particular clinical features in comparison to cardiomyopathies secondary to other etiologies, including a specific autonomic imbalance, lower survival rate and a more aggressive cardiac remodeling [2,7,8]. Together, these features indicate a worse prognosis for CCC than ischemic cardiomyopathy due to differences in pathophysiological pathways, such as a possible greater impairment of microvascular endothelial function.

Although microvascular abnormalities have been suggested by others as a potential mechanism associated to the pathogenesis of CCC [1,3], the present study demonstrated that cardiomyopathy secondary to chronic Chagas disease is not related to additional damages on systemic microvascular endothelial function than those observed in ischemic heart disease. Therefore, the discrepancies in pathophysiological pathways between CCC and ischemic etiology does not seem to be due to a greater microvascular endothelial dysfunction. A potential explanation for this difference could be the greater inflammatory milieu generated by parasite and host defenses in Chagas disease [13]. As a result, regardless of microvascular changes, greater endothelial activation could occur and cause a higher local recruitment of cell adhesion molecules, such as *E*-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule-1 (ICAM-1) through a mechanism involving NF-κB activation [14]. Therefore, although the microvascular reactivity is the same between CCC and ischemic heart disease, the degree of endothelial activation may be different and induce a faster progression of the cardiac structural damage, which leads to more frequent and severe ventricular arrhythmias and heart dysfunction [7,15,16]. Evidently, microvascular function participates but is not central to the pathogenesis of the disease and further research on this

Table 1
Baseline clinical characteristics of study subjects.

	Healthy controls (n = 21)	Ischemic heart disease (*n* = 21)	Chagas heart disease (n = 21)	p-Value
Age (years)	56.1 ± 4.7	58.9 ± 9.3	59.9 ± 11.5	0.38
Male [n (%)]	21 (100)	16 (76)	16 (76)	0.06
Left ventricle ejection fraction (%)	–	38.1 ± 9.0	35.1 ± 10.5	0.33
Systolic blood pressure (mmHg)	121.5 ± 6.0	120.7 ± 14.6	114.1 ± 13.0	0.10
Diastolic blood pressure (mmHg)	74.8 ± 5.1	72.2 ± 8.2	72.4 ± 7.7	0.44
Mean blood pressure (mmHg)	90.2 ± 4.4	88.3 ± 9.6	86.4 ± 8.3	0.29

The results are expressed as the mean ± SD.

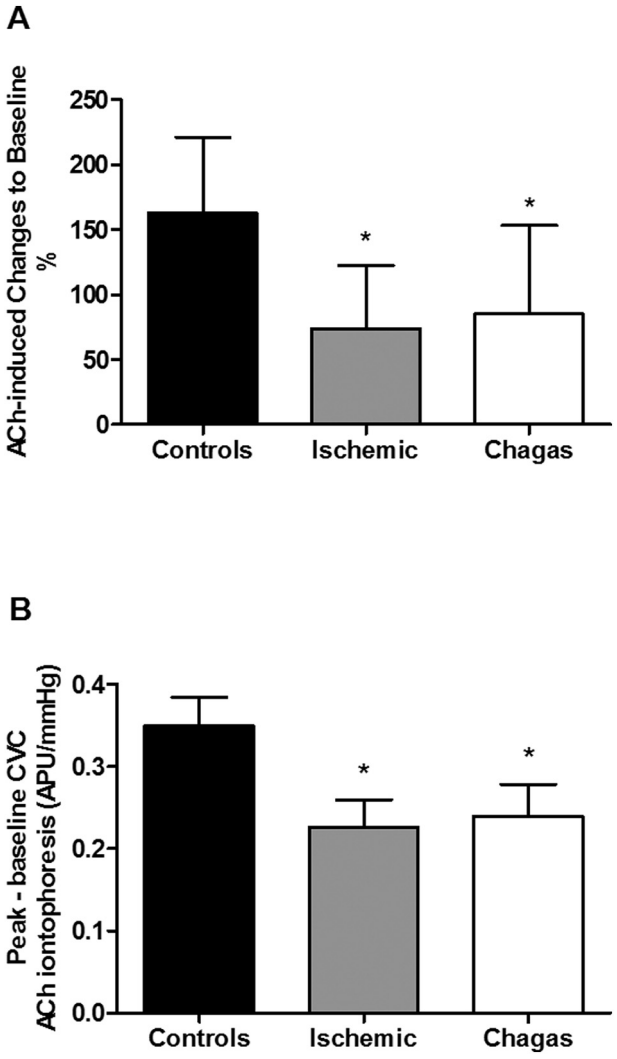

Fig. 1. Percentage (A) and cutaneous vascular conductance (B) acetylcholine-induced changes to baseline in skin blood flow among healthy controls and patients with ischemic and Chagas cardiomyopathy. Values represent means ± SDs.*p ≤ 0.05 *vs* Controls.

issue is warranted in patients with heart disease, particularly in patients presenting with CCC.

The cross sectional design is an important limitation of the present study that precludes the establishment of a causal relationship. Secondly, microvascular endothelial function was assessed solely by iontophoresis of ACh, a method in which the drug delivery depends on the intensity and duration of the current applied and on the diffusional and electrical characteristics of the skin. Actually, the thickness of the upper layer of the skin, the stratum corneum, is supposed to be the major obstacle to iontophoretic transport. Nevertheless, both study groups were submitted to the same experimental protocol of ACh iontophoresis. In other words, magnitude and duration of the current applied were identical for all subjects, which may have minimized any potential variation between groups due to the method. Importantly, to the best of our knowledge, this is the first study evaluating the microvascular endothelial function of patients with CCC and could serve as the basis for future investigations in this area.

To conclude, endothelial microvascular function was equally impaired among patients with chronic Chagas and ischemic cardiomyopathy. Studies evaluating the potential mechanisms associated to the pathogenesis of CCC are warranted in order to develop more specific therapeutic strategies.

Grant support

This work was partially supported by grants from CNPQ (#303328/2013-4 and #407742/2012-3) (National Council of Scientific and Technological Research, Brasilia, Brazil) and FAPERJ (#E-26/102.981/2011) (Research Support Foundation of the State of Rio de Janeiro, Rio de Janeiro, Brazil).

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments

The authors would like to thank Marcio Marinho Gonzalez for his excellent technical assistance.

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