Narrowed lumen of the right coronary artery in chronic chagasic patients is associated with ischemic lesions of segmental thinnings of ventricles.

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Key words: Chagas’ disease, ischemic lesions, steal phenomena, arrhythmia, fibrosis.

Abstract. Thinning of myocardial segments, mainly at the apex and basal posterior region of left ventricle, are frequent lesions in chronic chagasic cardiopathy (CCC), but still without a well determined etiology. Previously we found severe myocardial microvascular dilatation that could cause ischemia in watershed regions. In this study we analyzed whether narrowness in epicardial coronary arteries in CCC might explain these thinned ventricular lesions. Two groups of dilated hearts with similar weights were compared: eleven hearts from patients with CCC versus four hearts from patients with dilated cardiomyopathy (IDCM). As normal controls we studied three non dilated normal weight hearts. There were no atherosclerotic plaques in the main branches of epicardial coronary arteries and cross-sectional luminal areas of proximal and distal segments were histologically measured. It was found that CCC hearts presented a lower mean luminal area in the right coronary artery (RCA) branch than IDCM, in proximal (4.3 ± 1.4 vs 6.6 ± 2.0 mm²; p= 0.02) and in distal (1.6 ± 1.0 vs 3.4 ± 0.9 mm²; p= 0.01) segments, with no statistical differences with normal hearts (2.7 ± 1.3 and 1.5 ± 0.3 mm²) in proximal (p= 0.2) and distal (p=0.11) sections. In conclusion thinning of ventricular wall in CCC patients seems to be ischemic lesions in the peripheral territory irrigated by the right coronary artery, possibly due to a steal phenomenon by the left coronary, induced by micro vessels dilatation.
El lumen estrecho de la arteria coronaria derecha en pacientes chagásicos crónicos está asociado con lesiones de adelgazamientos segmentales de los ventrículos. 

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Palabras clave: Enfermedad de chagas, lesiones isquémicas, fenómeno “steal”, arritmia, fibrosis.

Resumen. Adelgazamientos segmentares del miocardio son frecuentes lesiones en la cardiomiopatía crónica chagásica (CCC), principalmente en el ápice de la región posterior del ventrículo izquierdo, cuya etiopatogenia todavía no está bien conocida. En trabajos anteriores se observó intensa dilatación de la micro circulación que podría llevar a isquemia en regiones de irrigaciones limitrofes. Este estudio analizó si estrechez de las arterias epicárdicas en CCC podrían explicar las lesiones de adelgazamientos ventriculares. Se compararon 2 grupos de corazones con pesos semejantes: 11 corazones de pacientes con CCC versus 4 corazones de pacientes con cardiomiopatía dilatada idiopática (IDCM). Como controles normales fueron estudiados 3 corazones no dilatados y con pesos normales. No estuvieron presentes placas ateroscleróticas en los principales ramos de las arterias coronarias epicárdicas. Las áreas de lumen en cortes transversales de los segmentos proximales e distales arteriales fueran medidas por histología. Los corazones con CCC mostraron una media de lumen menor en el ramo de la coronaria derecha que en los con IDCM, tanto en los segmentos proximales (4,3 ± 1,4 vs 6,6 ± 2,0 mm²; p = 0,02) como en los distales (1,6 ± 1,0 vs 3,4 ± 0,9 mm²; p = 0,01) y ninguna diferencia estadística fue observada cuando se compararon con los corazones normales (2,7 ± 1,3 vs 1,5 ± 0,3 mm²) tanto proximal (p= 0,2) como distal (p=0,11). Adelgazamientos ventriculares en pacientes con CCC parecen ser lesiones isquémicas en territorios distales, irrigados por la arteria coronaria derecha, posiblemente por un fenómeno de sustracción por la coronaria izquierda, debido a vasodilatación de micro circulación.

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INTRODUCTION

Chronic chagasic cardiopathy (CCC) occurs after a long period without symptoms (called “indeterminate form”), following an infection by the hemoflagellate protozoan Trypanosoma cruzi, transmitted by the Triatominae subfamily of insects. Thirty percent of the infected individuals present heart failure in the chronic phase, which is associated with myocarditis and diffuse fibrosis. Segments of ventricular myocardium in CCC are frequently thin, the myocardium substituted by fibrosis. One of these segments is the so called “apical lesion” which is pathognomonic of Chagas disease (1, 2). The posterior-lateral basal region of the left ventricle is also frequently thinned; myocardial wall mostly substituted by fibrosis, and it is associated with development of supraventricular tachycardia (SVT). Complete or partial
atrioventricular (AV) blocks, left anterior bundle branch block and right bundle branch block are associated with replacement of the conducting tissue by fibrosis and/or adipose tissue (3). Intramural reentry is a suggested mechanism of SVT after myocardial infarction (4). Acquatella and co-workers have demonstrated the importance of using M-mode and two-dimensional echocardiography to detect the septal posterior wall pattern and the apex aneurysm in CCC patients (5).

The pathogenesis of CCC remains controversial. According to some authors, autoimmunity has an important role (6), but antigens from the parasite were associated with myocardial inflammation (7, 8), and intense immunological response would injury noninfected myocardial fibers (9).

Idiopathic dilated cardiomyopathy (IDCM) has many similarities with chronic Chagas’ cardiopathy, however with less interstitial fibrosis (10) and without segmental areas of myocardial wall thinning as described in CCC.

Ischemia due to vascular obstruction and abnormalities in the myocardial microcirculation have been proposed in CCC (11-13). Focal microvascular spasm associated with direct or indirect injury to endothelial cells by the parasite also has been imputed (14). However, none of these findings explain the extensive segmental fibrosis present in particular regions of chagasic hearts.

In a previous study, we observed severe dilatation of microcirculation in CCC compared with normal or IDCM hearts, which was interpreted as a factor for the development of ischemic injuries in the ‘watershed’ regions (15). Here we investigated if luminal areas of epicardial coronary arteries would be diminished in CCC that might be contributing for the development of ischemic lesions.

MATERIAL AND METHODS

The Scientific and Ethic Committee of Heart Institute (InCor) of Sao Paulo University Medical School on human research approved this study and an informed consent approving the use of necropsy material for research was signed for the patient’s families before admission of the autopsy.

We analyzed hearts obtained at autopsy from the following three groups: Group 1 (CCC): eleven patients who presented with heart failure and arrhythmia (nine males and two females; mean age: 44 ± 16 years; median age: 43 years); Group 2 (IDCM) – four patients who presented with heart failure without arrhythmias (three males and one female; mean age: 54 ± 13 years; median age: 49 years; and Group 3 (controls): three patients who died of sudden or accidental death without associated cardiomyopathy (two males and one female); mean age: 37 + 10 years; median age: 38 years. Following cannulation, the coronary arteries in the hearts were perfused with 2% paraformaldehyde at a constant (80 mmHg) pressure for 30 min; fixation of the hearts was completed by immersing them in 10% saline-buffered formalin for 24 h. The first and last centimeters of the right coronary (RCA), left anterior descending (LAD), posterior descending (PD), and circumflex (CX) coronary arteries were then cross-sectioned for histological examination. The coronary artery samples were routinely processed for paraffin-embedded histological examination, and 4-µm thickness sections were stained with hematoxylin and eosin (H&E). Transmural myocardial samples from the right lateral ventricular wall, basal posterior wall, left lateral ventricular wall, and left ventricular apex also were stained using the H&E, Masson’s trichrome methods. The image analysis system (Leica, Benfheim, Ger-
many) was used to measure the cross-sectional luminal areas of the main epicardial coronary arteries and thickness of myocardium wall of right ventricles.

Statistical analysis was done comparing the vessel diameters from three groups G1, G2 and G2 by one way of variance (ANOVA) followed by Tukey test (pairwise multiple comparison procedure) or one way analysis of variance on ranks (Kruskal-Wallis) followed by Dunn’s method when normality test failed (p<0.05 was considered statistically significant).

RESULTS

The mean weights of the hearts were respectively G1 (CCC) 559g ± 129, (median 530g); G2 (IDCM) 531g ± 28. (median 533g) and G3 (control) 386 g ± 90 (median 350g), without difference between CCC and IDCM hearts, both higher than controls (p= 0.05).

Macroscopic evaluation revealed the characteristic increase of heart size and thinning of the lateral-posterior basal wall, as well as a left apical aneurysm in all CCC hearts (Fig. 1). Histological examination detected extensive replacement of the myocardium by fibrous tissue in the basal posterior left ventricular wall, with islands of viable myocardial fibers among the fibrosis accompanied by mononuclear inflammatory infiltration. The fibrosis extended irregularly from the endocardium to the subepicardial region and reaches the His bundle (Fig. 2). The borders between viable myocardial region and the fibrotic area were irregular. Surviving myocardial fibers exhibited cytoplasmatic edema and myocytolysis (Fig. 3). Three hearts in the CCC group also exhibited wide replacement of the right ventricular wall by adipose tissue. The IDCM group did not show ventricular segmental fibrosis as the hearts of patients with CCC, but presented small and wide-
spread foci, atrophy and myocytolysis of myocardial fibers.

The mean cross-sectional luminal areas of epicardial coronary artery branch from G1, G2 and G3 in proximal and distal segments are shown in Table I. G1 and G2 groups of dilated hearts had similar increased weights and were expected to have enlarged epicardial coronary arterial lumen. However, it occurred only in G2, in the right coronary artery (RCA): p=0.01, by analysis of variance.

Right coronary artery (RCA) of chagasic hearts (G1) exhibited significantly lower mean luminal areas than IDCM (G2), both in proximal (4.3 ± 1.4 vs 6.6 ± 2.0 mm²) p=0.05 and distal segments (1.6 ± 1.0 vs 3.4 ± 0.9 mm²), p=0.01 (Tukey test). G1 luminal areas did not differ with the control (G3), in both proximal (2.7 ± 1.3 mm²), p=0.2 and distal (1.5 ± 0.3 mm²) segments (p=0.11, Tukey test).

LAD in proximal segment presented higher means (7.4 ± 4.2) in IDCM than CCC (4.5 ± 1.8) and controls (5.0 ± 0.7), but were not statistically significant (p=0.15, Kruskal-Wallis test). In distal segments the values did not differ: G1 (1.0 ± 0.6; G2 (1.1 ± 0.7) and G3 (1.4 ± 1.0), p=0.7. The posterior descending artery (PD) in CCC hearts had the smallest mean luminal area (0.48 ± 0.31), but without statistic difference between groups (p=0.51). The sums of the mean cross-sectional luminal areas of the all proximal coronary segments were in G1, G2 and G3, re-

**TABLE I**

**MEAN (SD) VALUES OF LUMINAL AREAS (mm²) OF DISTAL AND PROXIMAL SEGMENTS OF EPICARDIAL CORONARY ARTERY BRANCHES**

<table>
<thead>
<tr>
<th>Artery</th>
<th>Segment</th>
<th>G1 (CCC) n=11</th>
<th>G2 (IDCM) n=04</th>
<th>G3 (control) n=03</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCA</td>
<td>Proximal</td>
<td>4.3 (1.4)</td>
<td>6.6 (2.0)</td>
<td>2.7 (1.3)</td>
<td>0.10*</td>
</tr>
<tr>
<td></td>
<td>Distal</td>
<td>1.6 (1.0)</td>
<td>3.4 (0.9)</td>
<td>1.5 (0.3)</td>
<td>0.01*</td>
</tr>
<tr>
<td>LAD</td>
<td>Proximal</td>
<td>4.5 (1.8)</td>
<td>7.4 (4.2)</td>
<td>5.0 (0.7)</td>
<td>0.15**</td>
</tr>
<tr>
<td></td>
<td>Distal</td>
<td>1.0 (0.6)</td>
<td>1.1 (0.7)</td>
<td>1.4 (1.0)</td>
<td>0.68*</td>
</tr>
<tr>
<td>CX</td>
<td>Proximal</td>
<td>2.8 (1.5)</td>
<td>4.9 (2.6)</td>
<td>4.8 (3.3)</td>
<td>0.16*</td>
</tr>
<tr>
<td></td>
<td>Distal</td>
<td>1.6 (1.4)</td>
<td>2.1 (2.1)</td>
<td>1.9 (0.8)</td>
<td>0.80**</td>
</tr>
<tr>
<td>PD</td>
<td>Distal</td>
<td>0.5 (0.3)</td>
<td>1.2 (1.1)</td>
<td>0.8 (0.7)</td>
<td>0.51**</td>
</tr>
</tbody>
</table>

spectively: 11.6 ± 3.7; 18.9 ± 8.0 and 12.4 ± 3.0. No atheromatose plaques were seen in CCC.

The measures of length of coronary artery branches are showed at Table II and we observe no difference (all p > 0.05) in the length of these branches among groups.

DISCUSSION

Segments with thin myocardial wall, where the myocardium is substituted by fibrosis, are seen in the apex and posterior-basal regions of the left ventricle in CCC. In previous works in CCC necropsies we observed that the myocardium presented severe microvessel dilatation, in association with severe myocarditis; we proposed that such arteriolar dilatation could lead to a low blood pressure perfusion and ischemic lesions in watershed regions (11, 15) (Fig. 4). The ventricular tachycardia is the most important arrhythmia and may cause death in CCC, and it has been associated with the presence of fibrosis at the posterior basal region of left ventricle (16, 536 Sambiase y col.

<table>
<thead>
<tr>
<th>Coronary branch</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCA</td>
<td>11.8 (2.3)</td>
<td>12.2 (2.4)</td>
<td>10.7 (1.5)</td>
<td>0.65 *</td>
</tr>
<tr>
<td>LAD</td>
<td>12.2 (2.1)</td>
<td>12.0 (1.8)</td>
<td>11.3 (0.6)</td>
<td>0.79 *</td>
</tr>
<tr>
<td>CX</td>
<td>4.7 (1.4)</td>
<td>4.5 (1.7)</td>
<td>6.0 (2.6)</td>
<td>0.47 *</td>
</tr>
<tr>
<td>PD</td>
<td>7.2 (2.2)</td>
<td>6.7 (2.1)</td>
<td>6.3 (1.5)</td>
<td>0.81 *</td>
</tr>
</tbody>
</table>

RCA: right coronary artery. LAD: left anterior descending. CX: circumflex artery. PD: posterior descending artery. * One Way Analysis of Variance. p values <0.05 considered significant.

Fig. 4. Schematic representation of blood flow in coronary arteries and microcirculation. Schematic purpose of ischemia in watershed region that may explain wide ischemic lesions in chagasic hearts.
Sustained ventricular tachycardia (SVT) in ischemic hearts is mainly due to the electrical reentry phenomenon in myocardial infarction or scar regions (18). Interconnected islands of surviving myocardial fibers in the middle of fibrotic tissue results in slowed myocardial conduction and development of SVT (19-21). Reentrant circuits also seem to be responsible for ventricular tachycardia in chagasic patients (22). Severe SVT in CCC was successfully treated with radio-frequency ablation of an aneurysmatic lesion located in the basal inferior wall (17).

Favoring our hypothesis that substitution by fibrosis in posterior lateral regions is a frequent complication in CCC (23), delayed contrast magnetic resonance image (24) showed the same lesion in vivo. In this study we confirmed these findings as all CCC hearts present fibrotic thinning of the lateral-posterior basal wall and apex of left ventricle, with an aspect of healed ischemic lesion.

As it is expected for hypertrophic dilated hearts (with increased weight), the IDCM group had increased lumen diameters of epicardial coronary arteries, mainly the RCA and LAD as compared with normal hearts. However, in CCC, the mean luminal areas did not present any difference with the normal weight hearts and, compared with IDCM, the RCA had significant lower diameters. Then, we concluded that a diffuse narrowing of the right coronary artery is present in CCC and it may contribute to distal ischemia, mainly in the watershed regions of the descending posterior and descending anterior coronary branches. It would induce myocardium fibrotic thinning of the apex of left ventricle. The watershed region between distal right coronary and circumflex branches may cause ischemia at the basal inferior of left ventricular wall. In addition, the first septal artery (originating from the descending artery) irrigates the conduction system in a double irrigation with AV node artery (originating from RCA at the crux cordis). The lack of irrigation by the RCA may lead to fibrosis at the right part of the conduction system. Also, narrowing of the RCA may cause fibrosis and adipose tissue replacement of the right ventricle resembling arrhythmogenic right ventricle dysplasia; an aspect described in CCC (25).

Trying to understand why there is a particular decreased luminal area in one arterial epicardial branch, we formulate a hypothesis of steal phenomenon (see schematic representation at right in Fig. 4). As we have already reported, these hearts usually present dilatation of microcirculation (10), with lack of pressure control for a good blood flow distribution and a steal phenomenon may occur during the diastole. When the aortic valve leaflets close, the blood flow would be sucked by the left branch orifice as this branch has a descending trajectory. Differently, the right branch orifice has a perpendicular trajectory to the heart position.

Torres and co-works have demonstrated that CCC patients have an abnormality of the coronary endothelium–dependent vasodilatation and this could play a role in the symptoms of myocardial ischemia (chest pain) and segmental wall motion abnormalities (26). The cause of this abnormal vessel wall response may be related to the parasite. It has been proposed that infective forms of the T cruzi can chemically modify the surfaces of myocardial and vascular endothelial cells by parasite neuraminidase cause desialylation (27).

In conclusion, the present work shows that CCC patients present decreased luminal area in RCA. We suggest that thin segments of the myocardial wall with substitution by fibrosis, frequently present in these patients, may be related to chronic
ischemia due to a decreased luminal area of the right coronary artery and steal phenomenon induced by microvessel dilatation.

Our findings may explain similarities referring to arrhythmias observed between post-MI and CCG patients. Further studies with higher number of cases and in vivo studies are needed to validate our hypothesis.

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