Microvascular disturbances in Chagas’ heart disease

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A considerable amount of clinical and experimental data gives support to the concept that transitory ischemic events caused by functional disturbances of coronary blood flow regulation is a relevant pathogenetic mechanism in chronic Chagas’ cardiomyopathy. In fact, atypical precordial chest pain, usually prolonged and recurrent, but with no clear provocative factors, is a frequent and disabling complaint by chagasic patients. Sometimes the symptom assumes an acute coronary syndrome presentation, masquerading as acute myocardial infarction or unstable angina, but with normal coronary arteries at angiographic studies. It’s worth to note that investigations of esophagus, an organ often involved in Chagas’ disease digestive tract manifestation, as a possible alternative source of these angina-like symptoms has produced no conclusive results. Thus, considering the association between chest pain and laboratory documentation of myocardial ischemia with normal coronary arteries, it’s conceivable to suppose the participation of functional alterations of the arterial coronary bed in the genesis of that clinical set. This hypothesis is primarily based on reports of hystopathological studies showing small coronary artery lesions, and has been recently reinforced by experimental model observations and some scarce clinical reports.

Chronic Chagas’ myocarditis is characterized, fundamentally, by focal mononuclear inflammatory infiltrates associated to reactive interstitial fibrosis and myocytolytic necrosis. Myocytolysis is a particular form of cell degeneration apparently related to hypoxia secondary to low intensity repetitive ischemic episodes as it has been observed in ischemia and reperfusion experimental models. Moreover, the occurrence of flow disturbances at the microcirculatory level is quite conceivable as the tissue lesion is focal, encompassing discrete cellular groups, and the associated reparative interstitial fibrosis seems to be characteristic of chronic hypoxic damage. These hystopathological aspects give support to the participation of myocardial ischemia, depending on microvascular abnormalities, in the pathogenesis of chronic Chagas’ myocardopathy. Early pathological observations have already documented inflammatory lesions of small coronary vessels in humans, both in heart and digestive tract, and similar findings were also reported in murine experimental models. The topographic distribution of myocardial capillary chagasic vessels, in comparison to normal individuals, has shown areas of reduced vascularization. This named “mesenchymal-reactive decapillarization” seems to be secondary to extra-luminal compression, being responsible for the myocytolysis found in these hearts.

The course of the murine model of acute and chronic Chagas’ myocarditis reproduces quite closely the main pathological features seen in human disease. Platelet aggregation generating occlusive thrombi has been reported in small epicardial and intra-mural coronary vessels. Further studies in murine model, employing histochemical methods has shown evidence of myocardial hypoxic alterations related to foci of myocytolytic necrosis. Furthermore, morphological studies of the microcirculation in mice with acute T. cruzi infection have demonstrated areas of focal vascular constriction, microaneurysm formation, dilatation, and proliferation of microvessels. In addition, the use of verapamil, a calcium channel blocker (with vasodilatory action in small vessels and anti-platelet activity), achieved significant reduction in mortality and ameliorated myocardial tissue lesions in mice infected with T. cruzi.

The usage of the scintigraphic method for myocardial blood flow distribution assessment in humans has also yielded results consonant with this hypothesis. Rest Thallium-201 studies has shown marked heterogeneity in radiotracer distribution in the majority of patients, that was significantly improved after prolonged treatment with dipyridamole. These findings were confirmed by myocardial perfusion studies in Chagas’ heart disease patients employing rubidium-86 that showed reduced myocardial blood flow at rest and poor increment during stress. More recently, these observations were extended to patients with chronic Chagas’ cardiomyopathy presenting precordial
chest pain and angiographically normal coronary arteries by Thallium–201 myocardial perfusion studies at stress and rest. A high frequency of perfusion defects in areas with normal left ventricular wall motion was detected. All patients in that report had at least one segment of left ventricular wall showing perfusion defects. Transient perfusion defects, ischemic or paradoxical (both potentially related to abnormalities in regional blood flow) were predominantly found. The evaluation of myocardial perfusion using scintigraphic images after intracoronary injection of 99mTc-labeled-microspheres in chagasic patients with chest pain also yielded positive results of prominent perfusion disturbances with normal coronary arteries. Most recently, additional evidence for abnormal coronary blood flow regulation was obtained by assessment of flow responses to pharmacologic stimuli employing intra-coronary doppler studies. Paradoxical responses of flow reduction to acetylcholine, and attenuated vasodilation to adenosine were documented. These results indicate endothelial dysfunction as responsible for abnormal coronary vasodilation capacity. Furthermore, abnormal vasoconstrictor behavior of epicardial coronary artery vessels was observed in chagasic patients with precordial chest pain submitted to the hyperventilation stimulus.

The time course relationship between myocardial ischemia and development of regional myocardial contraction disturbances has been recently addressed. In this study three groups of patients with progressive severity of Chagas’ disease myocardial damage were studied with stress-rest Thallium-201 myocardial scintigraphy. A high incidence of perfusion defects was documented even in patients asymptomatic with normal EKG, and global and segmental normal LV function. About 40% of perfusion defects in each group were ischemic and occurred with normal coronary arteries. Figure A shows an example of one patient of this series with reversible perfusion defect in the inferior and lower septal regions. In each projection, the top, middle and lower panels represent respectively the stress, redistribution and rest reinjection of the tracer. More extensive perfusion defects were found in groups with more severe heart disease and global LV dysfunction. A significant positive correlation was found between the total area of abnormal myocardial perfusion and decrease in LV ejection fraction. Furthermore, a very significant topographic relationship was found between ischemic defects and abnormal segmental contraction. These findings strongly suggest that myocardial ischemia depending on functional coronary blood flow regulation participates in the genesis of myocardial damage in CHD.

However, the actual interpretation of these findings should consider the disease main pathogenic process, namely the inflammatory process. In this sense, most probably the functional disturbances in flow regulation may happen secondarily to action of vasoactive substances produced by the inflammatory infiltrate, like cytokines, and
Thromboxan-\(A_2\), delivered by platelets aggregation. Ultra-structural studies have suggested that the aggression to small vessels wall is also related to immune effector cell aggression. So, even though the myocardial ischemia constitutes conspicuous phenomena, it likely plays an ancillary role in the pathogenetic complex of chronic Chagas’ myocarditis and most probably acts as an amplification factor in producing myocardial damage.

Bibliography


