Editorial

Associating Chagasic Cardiomyopathy With Abnormal Diastolic Calcium Handling

Asociación de la miocardiopatía chagásica con el comportamiento anormal del calcio diastólico

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Calcium is a central player in the regulation of cardiac contraction and rhythm, and predominant cardiac pathologies have been associated directly or indirectly with changes in intracellular calcium handling.1-4 A feature common to many diseases involving either rhythm disturbances or impaired cardiac function is that they are linked to genetic mutations5-8 or abnormal phosphorylation of one or several calcium handling proteins9-7 that alter their activity. In patients with heart failure, multiple alterations in calcium handling have been reported that may account for the impaired contraction and relaxation3,8 as well as the propensity of these patients to present ventricular arrhythmia.4 It is therefore natural to speculate that the tropical disease known as Chagas disease caused by the hemoflagellate Trypanosoma cruzi, which eventually induces dilated cardiomyopathy, systolic and diastolic dysfunction, arrhythmias, and sudden cardiac death,9 also induces changes in the calcium metabolism in cardiac myocytes from chagasic patients.

So far, studies on potential effects of chagasic infection on calcium handling have been carried out in noncardiac preparations from animal models. Therefore, to address this important issue in humans, in the article published in Revista Española de Cardiología, López et al.10 have undertaken the difficult task of determining the diastolic calcium concentration in ventricular myocytes from patients infected with Trypanosoma cruzi, at different stages of the progression of this disease.

Since the development of fast responding fluorescent calcium indicators with high quantum efficiency,11 these compounds have been widely used to measure and visualize changes in cytosolic calcium levels in isolated cardiomyocytes and multicellular preparations. However, it is commonly overlooked that the chemical properties of most fluorescent calcium indicators make them unsuited for impalement of human ventricular myocytes from patients at different stages of the progression of Chagas disease. The diastolic calcium level in these same 30 myocytes was 111 ± 4 nM. This value also agrees with estimations of the diastolic calcium level in human ventricular myocytes using the fluorescent calcium indicator fluo-3,2 affirming that calcium-selective microelectrodes is a useful technique to simultaneously record the resting membrane potential and diastolic calcium levels in human ventricular myocytes. The calcium-selective microelectrodes were therefore used to impale human ventricular myocytes from patients at different stages of the progression of Chagas disease, and the results provide evidence that progression of the disease is associated with a parallel increase in the diastolic calcium concentration. Although not directly addressed in the study of López et al.,10 this is likely to cause calcium overloading of the sarcoplasmic reticulum and it may contribute to the propensity of chagasic patients to suffer cardiac arrhythmia. The higher diastolic calcium level in ventricular myocytes from these patients is also expected to reduce the dynamic range for modulation of the cardiac transient amplitude and this likely contributes to promote diastolic and systolic dysfunction. Furthermore, the concurrent loss of the resting membrane potential, which reduces excitability, may exacerbate the effects of diastolic calcium overload in patients with Chagas disease.

To determine whether the abnormal diastolic calcium handling in chagasic patients is associated with changes in inositol...
triphosphate (IP$_3$) signaling. López et al.\textsuperscript{10} used pharmacological manipulation of cellular IP$_3$ production and IP$_3$ receptor activation. Their results show that blockade of IP$_3$ production (with the β-phospholipase C inhibitor U73122) selectively reduced the diastolic calcium concentration in chagasic patients without changing the resting membrane potential, while stimulation of IP$_3$ production with phenylephrine had the opposite effect on diastolic calcium. IP$_3$ receptor blockade (with 2-APB) reduced the elevated diastolic [Ca$^{2+}$]$_i$ in functional class I and II chagasic patients towards concentrations observed in control patients, and reversed the stimulatory effect of phenylephrine, suggesting that there is an upregulation of IP$_3$ receptor-mediated signaling in ventricular myocytes from patients with Chagas disease.

Together, these findings suggest that upregulation of IP$_3$ receptor-mediated signaling and abnormal diastolic calcium handling are novel mechanisms that may contribute to promote diastolic dysfunction in patients with Chagas disease. The study also opens new lines of research needed to 1) address the molecular mechanism underlying the progressive loss of the resting membrane potential in these patients, 2) determine if abnormal diastolic calcium handling is associated with the loss of the membrane potential, and 3) establish how the observed elevation of the diastolic [Ca$^{2+}$]$_i$ is linked to upregulation of IP$_3$ receptor activation. Another finding of the study by López et al. that deserves further investigation is the dramatic elevation of the diastolic [Ca$^{2+}$]$_i$ observed in class III patients (922 ± 33 nM) without any apparent cell contracture. The authors discuss different explanations for this observation but a tempting hypothesis is that there is a parallel decrease in the calcium sensitivity of the myofilaments during progression of Chagas disease.

The importance of the findings reported by López et al.\textsuperscript{10} is unquestionable, and as mentioned above their results provide a foundation for future research on the mechanisms underlying abnormal diastolic calcium handling in chagasic diseased cardiomyocytes. However, I find it of particular merit that the authors have taken the effort to use the best-suited, albeit experimentally most demanding technique, to measure the diastolic [Ca$^{2+}$]$_i$ in human ventricular myocytes – a highly relevant but technically difficult experimental preparation.

CONFLICTS OF INTEREST
None declared.

REFERENCES

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