Editorial

Associating Chagasic Cardiomyopathy With Abnormal Diastolic Calcium Handling

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

Leif Hove-Madsen*

Centro de Investigación Cardiovascular CSIC-ICCC, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Article history:
Available online 20 April 2011

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 mutations5,6 or abnormal phosphorylation of one or several calcium handling proteins5–7 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 measuring 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 it difficult to use them for quantification of the cytosolic calcium concentration. Thus, the fluorescent calcium indicators represent exogenous calcium buffers with calcium affinities that typically fall between the diastolic and systolic calcium levels. This is bound to affect the cellular calcium homeostasis, and the problem is aggravated by the fact that common calcium indicators such as fura-2, indo-1 and fluo-3 are known to bind extensively to cellular proteins, which increases their effective calcium buffering capacity dramatically.12 Moreover, the binding of these compounds to cellular proteins substantially alters their calcium affinity,12,13 further complicating their use for quantitative purposes. In contrast to this, calcium selective electrodes have the virtues that make them ideal for measurements of static calcium concentrations; i.e., they have a wide dynamic range, they do not interfere with the cytosolic calcium level, and their calibration is fairly uncomplicated. The drawbacks that have pushed the calcium electrodes into the shadow of the fluorescent calcium dyes is their slow response time and the necessity of impaling the myocyte under study, making it a demanding experimental technique with a limited success rate.14 However, for quantitative purposes in quiescent preparations calcium selective electrodes remain superior to the fluorescent dyes. A further advantage of this technique is that it allows simultaneous determination of the resting membrane potential.

Using calcium-selective microelectrodes, López et al.10 measured a resting membrane potential of ~83 ± 2 mV in 30 ventricular myocytes from 4 control patients, a value that compares well to determinations in multicellular human ventricular preparations.15 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-3,3 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 calcium 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

SEE RELATED ARTICLE:


* Corresponding author: Centro de Investigación Cardiovascular CSIC-ICCC, Hospital de la Santa Creu i Sant Pau, St. Antoni M. Claret 167, 08025 Barcelona, Spain.

E-mail address: lhove@csic-iccc.org

1885-5857/5 – see front matter © 2011 Sociedad Española de Cardiología. Published by Elsevier España, S.L. All rights reserved.
myofilaments during progression of Chagas disease. There is a parallel decrease in the calcium sensitivity of the
explanations for this observation but a tempting hypothesis is that
any apparent cell contracture. The authors discuss different
abnormal diastolic calcium handling in chagasic diseased cardi-
unquestionable, and as mentioned above their results provide a
deservest further investigation is the dramatic elevation of the
diastolic $[\text{Ca}^{2+}]$ observed in class III patients (922
The importance of the findings reported by López et al.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 cardi-
omycocytes. 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 $[\text{Ca}^{2+}]$ in
human ventricular myocytes – a highly relevant but technically
difficult experimental preparation.

CONFLICTS OF INTEREST
None declared.

REFERENCES


14. Hove-Madsen L, Baudet S, Bers DM. Making and using calcium-selective mini-