IP$_3$ and Ca$^{2+}$ signals in the heart: Boost them or bust them?

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Cardiac muscle Ca\(^{2+}\) signaling and excitation-contraction coupling rely on a relatively small Ca\(^{2+}\) influx via voltage-dependent L-type Ca\(^{2+}\) channels, which is amplified by a severalfold larger Ca\(^{2+}\) release from the sarcoplasmic reticulum (SR) via ryanodine receptor Ca\(^{2+}\) release channels (RyRs). The Ca\(^{2+}\)-induced Ca\(^{2+}\) release mechanism (CICR) is driving this signal amplification. Besides the RyRs, inositol trisphosphate receptors (IP\(_3\)Rs), a type of Ca\(^{2+}\) release channels with many similarities to the RyRs, are also present in cardiomyocytes. But they are vastly outnumbered by the RyRs (ratios of 1:50 to 1:100). While IP\(_3\)Rs seem important and more abundant during early cardiac development, their relative expression level declines later, as the SR matures and the number of RyRs increases. Why mother nature is perpetuating the presence of the IP\(_3\)Rs at a low density in cardiac muscle has remained a mystery. Several hypotheses have been tested in experimental studies, but the puzzle remains incompletely solved and the role(s) of the IP\(_3\)Rs is not yet clearly defined. In cardiomyocytes, particularly in atrial cells where InsP\(_3\)Rs are more abundant, a modulatory function of InsP\(_3\)Rs on CICR has been recognized (Mackenzie et al., 2002). IP\(_3\)Rs may indeed participate in Ca\(^{2+}\) signaling, secondary to acute or chronic stimulation of membrane receptors linked to the phospholipase C (PLC) - IP\(_3\) signaling pathways, such as endothelin (ET) or angiotensin (AT) II receptors (Horn et al., 2013). Recently, it has been found that IP\(_3\)Rs located in the nuclear envelope are involved in excitation-transcription coupling, thereby participating in the control of gene expression programs. During several pathological conditions, chronic activation of these pathways may engage in cell growth, hypertrophy and the initiation of dedifferentiating gene programs (Nakayama et al., 2010). One notable cardiac condition in which overexpression of IP\(_3\)Rs has been observed is the development of cardiac hypertrophy and failure (Harzheim et al., 2009). In these and related diseases, IP\(_3\)Rs could represent a key element of a slowly developing positive feed-back loop, whereby their maintained activation (in the nucleus) leads to an increase of their own cellular expression via excitation-transcription coupling. How potential Ca\(^{2+}\) signaling complications arising from this constellation could be avoided by spatially targeting the IP\(_3\)R expression and by finely tuning their activity can be conceptualized based on findings published in the present issue of *The Journal of Physiology* (Hohendanner et al., 2014).

In an elegant functional study a wide array of state-of-the art methods was combined (e.g. IP\(_3\) measurements with FIRE, an IP\(_3\) affinity trap, photorelease of IP\(_3\), etc.) to define how IP\(_3\)R and RyR mediated Ca\(^{2+}\) release orchestrates Ca\(^{2+}\) signaling in atrial and ventricular myocytes isolated from normal and heart-failure (HF) rabbits. The first astonishing finding was that in the absence of any IP\(_3\) generating stimuli (i.e. at basal cellular IP\(_3\) levels) and in sharp contrast to the behavior of ventricular myocytes, the Ca\(^{2+}\) transients recorded from HF atrial myocytes were markedly larger than those from control cells. More detailed analysis of this unexpected observation revealed that it was predominantly due to larger and faster centripetal Ca\(^{2+}\) signal propagation, mostly depending on boosted Ca\(^{2+}\) release
via IP3Rs located throughout the cell, with a possible contribution by reduced mitochondrial Ca2+ uptake. The next surprising observation was made when IP3 levels were experimentally elevated above basal, as it might occur in-vivo (e.g. by photolysis of caged IP3 or by ATII). While normal atrial myocytes responded with a slightly increased Ca2+ transient amplitude, the HF cells exhibited dramatically reduced Ca2+ signals combined with slowly rising diastolic Ca2+ concentrations. The reduced amplitudes were particularly evident after prolonged exposure to elevated IP3 levels, and appeared to be caused by a larger SR Ca2+ leak, manifest as a higher frequency of Ca2+ puffs and arrhythmogenic Ca2+ waves, and a corresponding decline of intra SR Ca2+.

The strikingly divergent behavior of the atrial myocyte Ca2+ signaling system under conditions of constitutively low versus stimulated IP3 concentrations is dazzling. These results reveal a new dimension of atrial myocyte Ca2+ signaling modulation by IP3. While in HF atrial cells the overexpressed IP3Rs may contribute to their inotropy at basal IP3 levels, acute stimulation of IP3 generating pathways may be pro-arrhythmogenic (by increasing the propensity for Ca2+ waves) and in the long run curtail atrial Ca2+ signaling, by maintaining an SR Ca2+ leak ultimately lowering its Ca2+ load.

It is well established that patients with HF have elevated levels of circulating ATII. Therefore, the findings of the present study are potentially therapeutically relevant, both for the atrial mechanical performance (atrial kick) and for atrial arrhythmias. However, the effects of cytosolic IP3 seem to be vastly different, if not opposite, in atrial myocytes after remodeling of their Ca2+ signaling during HF. Thus, it will be crucial to define the role of IP3 not only in isolated cell preparations, but to translate these findings to the more complex situation and neurohumoral environment of the organ and even patient, where cytosolic IP3 levels may vary. Such studies seem to be needed to obtain an integrated view of atrial Ca2+ signaling during HF with all of its complexities. This knowledge would appear to be an important pre-requisite to design mechanisms based therapeutical strategies.


