Reduced abundance of transverse tubules and L-type calcium channels: another cause of defective contractility in failing ventricular myocytes

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See article by He et al. [1] (pages 298–307) in this issue.

1. Introduction

Congestive heart failure (CHF) is a complex syndrome that is the leading cause of death in Western society. A central feature of this syndrome is reduced cardiac contractility and blunted adrenergic responsiveness that together cause poor pump performance and limit exercise tolerance. Depression of myocardial contractility is thought to be a principle cause of the progressive decline in cardiac function that is a hallmark feature of end-stage CHF. The cellular and molecular basis of dysfunctional myocyte contractility in CHF is currently being studied in many laboratories in the hope that novel therapeutic targets can be identified. The manuscript by He et al. [1] in the current issue of Cardiovascular Research focuses on changes in transverse (T)-tubules and L-type Ca channel abundance in the contractile defects of ventricular myocytes from a canine model of CHF induced by rapid pacing.

T-tubules are specialized invaginations of the surface membrane that serve to rapidly transmit the cardiac action potential deep into the core of large muscle cells, thereby producing synchronous contraction throughout the cell. L-type Ca channels are thought to be localized in high density within the T-tubules [2]. Depolarization of the T-tubules causes opening of L-type Ca channels [3], which elevates the [Ca] in the subsarcolemmal space where the T-tubules and the junctional sarcoplasmic reticulum (SR) are in close proximity. This elevation in subsarcolemmal Ca activates the calcium release channel (ryanodine receptor, RYR) to induce SR Ca release via calcium-induced calcium release (CICR) [4]. Reductions in the density of T-tubules and L-type Ca channels [1] should reduce the effectiveness of excitation-contraction coupling (ECC), slow the overall rate of SR Ca release and decrease the rate and magnitude of contraction.

The cellular basis of contractile dysfunction in CHF is a complex and puzzling problem. Most studies of the failing human heart have shown that there is reduction in the rate and magnitude of peak force (muscles) or shortening (myocytes) [5]. An important observation in a number of these studies is that the magnitude and nature of the contractile defects varies with the beating rate. At slow rates of stimulation (30 beats/min) contractile properties and Ca transients of non-failing and failing myocytes are similar [6]. When the heart rate is increased, there is an associated increase in force (or shortening) and Ca in non-failing muscle (positive force frequency). In failing muscles increasing the heart rate causes a decrease or no change in contraction and Ca [7]. These studies show that the processes that are responsible for abnormal Ca regulation in failing myocytes produce the most profound defects at faster, more physiological heart rates.

The scope of this editorial is to consider how the new observations presented by He et al. help us to better understand abnormal ECC and associated changes in contractility in the failing myocyte. In this context I will discuss the idea that contractile dysfunction in most forms of CHF is not likely to be a problem of a single or even a few genes or gene products. Instead myocyte functional defects in CHF appear to be best explained by orchestrated changes in myocyte structure and in the abundance, location and regulation of myocyte proteins [8].

2. Do alterations in the structure of failing cardiac myocytes cause abnormal ECC?

A major finding of the study by He et al. is that there are significant reductions in the abundance of T-tubules in...
myocytes isolated from failing hearts and that these changes are heterogeneous within and among failing cells. Defects of this type would have a negative impact on EC coupling and should make Ca release heterogeneous within and among failing myocytes. A related study by Gomez et al. [9] suggests that the defective ECC of failing rat ventricular myocytes is caused by changes in the structure (widening) of the T-tubular SR junction. This may be a related or earlier version of the T-tubular defects observed by He et al. in canine myocytes. New studies are needed to determine the relationship (if any) between these observations and to determine the nature of the Ca handling defects of myocytes with an aberrant distribution or absence of T-tubules. In the future it will also be important to prove that the aberrant T-tubular abundance also exists in myocytes in the intact failing heart, thereby ruling out the possibility that aberrant T-tubule abundance results from damage to failing myocytes that can occur during their isolation.

There are few quantitative studies of changes in T-tubular density in diseased cardiac myocytes. An older study from Page’s laboratory [10] quantified changes in T-tubules in hypertrophied rat myocytes using transmission electron microscopy. This study showed that T-tubular area increases in hypertrophy and the membrane surface area to volume ratio is maintained. There is good evidence for cellular hypotrophy in the canine tachycardia CHF model [11], however T-tubular density was not measured in this study. Importantly there are new approaches for quantifying T-tubular morphology in live cells using confocal microscopy [12]. Application of these techniques to other CHF models and to samples from failing human hearts should determine if loss of T-tubules is a consistent finding in myocytes with poor contractility.

3. Do changes in protein abundance cause dysfunctional ECC?

Many studies have examined the idea that changes in the abundance of Ca handling proteins underlies abnormal Ca transients in CHF [13]. Changes in the abundance of L- and T-type Ca channels, RYR channels, SR Ca ATPase (SERCa), phospholamban (PLB) and the sodium-calcium exchanger (NCX) have been observed in animal models and in failing human hearts [14–16]. Most of these studies support the idea that SR function is depressed in CHF and produces reduced SR Ca loading. However, there have also been a number of reports in which abnormal contractility could not be related to changes in Ca handling protein abundance or activity [17].

The idea that reduction in the L-type Ca channel density is involved in dysfunctional contractility in CHF has been examined in more than 20 studies [8,18] and either no change or a small reduction in current density has been found. The exciting feature of the new study by He et al. is that while there was no change in Ca current density in failing myocytes the total number of sarcolemmal Ca channels (as measured by charge movement) was significantly reduced. This suggests that the Ca channels in these failing myocytes were more likely to open with depolarization than those from normal myocytes. Single channel measurements of L-type Ca channels in failing human myocytes by Schroder et al. [19] are consistent with this idea. These results point out that measurement of whole cell Ca current is insufficient to determine if the total number of available Ca channels is altered in CHF.

With respect to EC coupling, the relevant L-type Ca channels are those at the junction of the T-tubules and the SR because these are the ones that trigger SR Ca release. Future studies need to determine if the number of L-type Ca and RYR channels co-localized to these junctional regions is altered in CHF (to reduce EC coupling effectiveness or gain), or if the number of junctional contacts is reduced in CHF because of T-tubular dropout or some other process.

4. Does abnormal protein regulation cause defective ECC?

One of the most exciting features of the study by He et al. is that the activity of individual L-type Ca channels appears to be significantly and persistently altered in CHF. Phosphorylation of L-type Ca channels (via protein kinase A) is known to increase their activity [20]. Therefore, increased phosphorylation of the L-type Ca channel might explain the results of He et al. and Schroder et al. [19]. These results are consistent with the findings of Marx et al. [21] who showed that there is ‘hyperphosphorylation’ of RYR in failing dog (and human) ventricular myocytes. These independent investigations support the hypothesis that abnormal regulation of EC coupling proteins is likely to be centrally involved in the contractile abnormalities of the failing heart. In future studies it will be interesting to see if the well-known blunting of adrenergic responsiveness in the failing heart [22] is not simply a signaling problem [23,24] but also results from the fact that target proteins are persistently phosphorylated. Hyperphosphorylation of molecules in the T-tubule SR junction during the transition from compensated hypertrophy to CHF could also partially explain the experiments of Gomez et al. [9] in which PKA activation rescued EC coupling defects in hypertrophied (compensated) but not in failing rat myocytes.

Not all previous studies support the idea that there is hyperphosphorylation of PKA target proteins in CHF. A few have found that PLB phosphorylation is reduced in CHF [25,26]. Directly contradicting the results of the report by He et al. is a recent study by Litwin and Bridge [27] that shows that abnormal Ca transients in myocytes from infarcted rabbit hearts are a result of heterogeneous
SR Ca release. SR release was resynchronized with the PKA-activator isoproterenol, eliminating the possibility that it resulted from a fixed structural defect such as reduced T-tubular density and also suggesting that reduced rather than enhanced levels of phosphorylation of ECC proteins are involved in the dysfunctional Ca transients of these cells. More studies into the localization and compartmentation of key proteins involved in EC coupling and their regulatory molecules are warranted.

5. Final considerations

There is now substantial evidence for the idea that the amount of Ca released from the SR of failing myocytes is smaller than normal. In human CHF these defects become greater at faster heart rates. It seems unlikely that a fixed structural defect (such as a reduced T-tubular abundance) can explain rate-related Ca handling defects. Reduction in the number of Ca channels involved in ECC however, could be involved if recovery from inactivation was sufficiently slow at fast heart rates to cause failure or inefficiencies in ECC.

It also seems unlikely that there is a common defect responsible for defective Ca handling or ECC in animal models of CHF because each model has a variable amount of hypertrophy and failure and each of the species used has unique Ca regulatory processes. A single, common defect will also probably not be sufficient to explain abnormal EC coupling in human CHF because the disease has multiple etiologies and is multifactorial. The challenge is to find the most common causes of aberrant Ca handling in human CHF and then determine if correcting these defects rescues or further depresses the failing heart.

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