Calcium release units in heart failure: that’s about the size of it

Fredrik Swift¹,²* and Geir Christensen¹,²

¹Institute for Experimental Medical Research, Oslo University Hospital and University of Oslo, Oslo, Norway; and ²KG Jebsen Cardiac Research Center and Center for Heart Failure Research, University of Oslo, Oslo, Norway

Online publish-ahead-of-print 24 July 2012

This editorial refers to ‘Ultrastructural remodelling of Ca²⁺ signalling apparatus in failing heart cells’ by H.-D. Wu et al., pp. 430–438, this issue.

Cardiac remodelling, often defined as changes in the mass and shape of the whole heart,¹ has been a focus of research over several decades. Despite considerable efforts, the cellular and molecular mechanisms that lead to contractile dysfunction of the remodelled heart are still not clear. Remodelling may also occur at the level of the cardiomyocyte and is then termed ultrastructural remodelling. Studies have revealed substantial ultrastructural alterations in several parts of the cardiomyocytes during cardiac disease, including the sarcoplasmic reticulum (SR)² and transverse (T)-tubules,³,⁴ and in the positioning of ion channels and pumps that are crucial in regulating myocardial contraction and relaxation. Thus, it is likely that ultrastructural remodelling can explain several important aspects of systolic and diastolic heart failure of various aetiologies.

The machinery that couples the electrical activation of the cardiomyocyte to mechanical contraction is set to control transient rises of [Ca²⁺] in the cytosol. Research in the past decades has revealed that the global rise of [Ca²⁺] in the cytosol that activates myofilaments is regulated by mechanisms that are confined within spatially constrained microdomains in the cardiomyocyte. These microdomains occur at sites where Ca²⁺ channels in the T-tubule membrane come very close to Ca²⁺ release channels (RyR) in the membrane of the intracellular Ca²⁺ store, the SR (Figure 1), thus forming a calcium release unit (CRU).⁵ Such an ultrastructural arrangement is thought to be crucial in order to control cardiac contractility through Ca²⁺-induced Ca²⁺ release (CICR).

The reduced contractility of the failing myocardium is in part due to reduced magnitude of the global Ca²⁺ transient. This reduction has been shown to be caused by a decreased SR Ca²⁺ content,⁶ but also by reduced gain of the excitation–contraction coupling.⁷ The trigger for SR Ca²⁺ release, the Ca²⁺ current, is reportedly unchanged in heart failure.⁸ Thus, decreased gain has been explained by Ca²⁺ channel/RyR mismatch and orphaned RyR,⁹ and an increased gap between T-tubules and SR membranes has also been suggested.¹⁰ However, data showing ultrastructural alterations are sparse.

In this issue of Cardiovascular Research, Wu et al.¹¹ reveal an ultrastructural mechanism that could be at the basis of a defective CICR and which may explain a contractile defect in a rat model of heart failure. Using transmission electron microscopy, the authors show that the volume density and the surface area of the junctional sarcoplasmic reticulum (jSR) and those of jSR-coupled T-tubules are decreased in failing hearts (Figure 1). CRUs were found to be displaced or missing from the Z-line areas, and the size of individual T-tubule/SR junctions was reduced. Incorporated into a mathematical model, these experimental findings showed scattered delay of Ca²⁺ release, and the authors conclude that shrinking and the eventual absence of T-tubule/jSR junctions are important mechanisms for decreased contractile strength in heart failure. The authors also present data indicating that the observed remodelling may, at least partly, be caused by loss of a protein named junctophilin-2 (JP2), which is believed to anchor RyR in the SR membrane to the T-tubule membrane.¹²

In the transverse aortic constriction model used in the study of Wu et al.,¹¹ the volume of T-tubules was reduced. This is in good agreement with other studies (for review see Louch et al.).¹³ Interestingly, the authors observed that this reduction was attributed to T-tubules which couple to SR. The amount of T-tubules without associated SR was even increased. Assuming that RyR will stay in the SR membrane even after detachment from T-tubules, this is in good agreement with the findings of Song et al. showing orphaned RyR in the failing heart. Furthermore, the distance between individual T-tubule/SR junctions was increased and the junctions seem to ‘drift’ away from the Z-lines. It is unclear what the functional consequences of such drift would be. However, disruption of a regularly distributed network of CRUs and appearance of orphaned RyRs within the cardiomyocyte could result in uncoupled sites which will not fire or sites which will fire too late during excitation–contraction coupling. This would explain the observed slowing¹³ and diafrequency⁹,¹⁴,¹⁵ of Ca²⁺ release during heart failure and would constitute an ultrastructural basis for slow and weak contractions in heart failure.

An important finding in the study by Wu et al.¹¹ is that the size of individual junctional regions is reduced in heart failure. Although the

¹The opinions expressed in this article are not necessarily those of the Editors of Cardiovascular Research or of the European Society of Cardiology.

*Corresponding author. Tel: +47 23 01 6800; fax: +47 23 01 6799; Email: fredrik.swift@medisin.uio.no

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2012. For permissions please email: journals.permissions@oup.com
contraction coupling. The finding of Wu et al. that T-tubules provide proximity between voltage-sensitive Ca²⁺ channels in the T-tubule membrane and Ca²⁺ release channels in the membrane of the intracellular Ca²⁺ store, the sarcoplasmic reticulum (SR). The junctions formed between T-tubules and the junctional SR (JSR) constitute a calcium release unit. Wu et al. describe in this issue that these junctions become smaller, fewer, and displaced during heart failure. This may cause the slower and weaker contractions observed in heart failure.

Future research should be aimed at discovering how proteins are distributed within CRUs during disease. The discovery of treatment strategies that could repair broken CRUs may lead to major breakthroughs in heart failure treatment. It seems clear that JP2 plays an important role in regulating these structures, but it is likely that other proteins also contribute. The identification of such proteins will provide the groundwork for understanding the ultrastructural remodelling of cardiomyocytes and consequently for a detailed understanding of the molecular mechanisms leading to reduced myocardial contractility in heart failure.

Conflict of interest: none declared.

References