Reversibility of T-tubule remodelling in heart failure: mechanical load as a dynamic regulator of the T-tubules

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Abstract

The T-tubule system in ventricular cardiomyocytes is essential for synchronous Ca\(^{2+}\) handling, and, therefore, efficient contraction. T-tubular remodelling is a common feature of heart disease. In this review, we discuss whether t-tubular remodelling can be reversed and which factors may be implicated in this process. In particular, we focus on the interaction between mechanical load variation and T-tubule structure and function. What is the evidence of this relationship? What is the role of different degrees and durations of mechanical load variation? In what settings might mechanical load variation have detrimental or beneficial effects on T-tubule structure and function? What are the molecular determinants of this interaction? Ultimately this discussion is used to address the question of whether mechanical load variation can provide an understanding to underpin attempts to induce recovery of the T-tubule system. In reviewing these questions, we define what remains to be discovered in understanding T-tubule recovery.

Keywords

T-tubule • Cardiac recovery • Mechanical load

1. Introduction

The T-tubule network is an extensive series of membrane invaginations which are enriched with proteins essential to excitation–contraction coupling.\(^1\) These intricate membrane structures are disrupted in heart failure (HF), and this appears to be an early and deterministic event (for a review see Song et al. in this issue), especially after chronic mechanical overload.\(^2,3\) The consequences of T-tubule irregularity and loss have been reviewed extensively.\(^1,4–7\) Importantly, such changes include a loss of Ca\(^{2+}\) transient synchrony, with overall slowing of its dynamics. Loss of Ca\(^{2+}\) transient synchrony is spatially colocalized to gaps in the T-tubule network,\(^12,13\) indicating a likely mechanistic link. This is because a central function of the T-tubule membrane is to relay the electrical depolarization signal throughout the depth of the cardiomyocyte.

Data from studies of artificial detubulation (using the osmotic shock agent Formamide) provide the clearest picture of the consequences of T-tubule disruption. Detubulation reduces cell capacitance by 30% and the L-type Ca\(^{2+}\) current (ICa\(_L\)) by \(\sim 80\%\).\(^9\) There is more ICa\(_L\) concentrated in the T-tubule than data from immunocytochemistry experiments would predict, suggesting that the channels in the T-tubule are more active as well as more numerous than those in the surface sarcolemma.\(^4\) Detubulation reduces transmembrane Ca\(^{2+}\) entry by 60%.\(^10\) The percentage reduction in transmembrane Ca\(^{2+}\) entry corresponds to the percentage of NCX localized in the T-tubule.\(^11\) Other currents, such as the Na\(^+\) and K\(^+\) currents, are equally distributed across the surface and T-tubule membrane fractions.\(^12,13\)

Interestingly, inactivation of ICa\(_L\) is slower in detubulated cells, although in the presence of Ryandine (i.e. when SR Ca\(^{2+}\) release is diminished), inactivation of ICa\(_L\) follows a similar time course in detubulated and control cells.\(^14,15\) This possibly suggests that SR Ca\(^{2+}\) release inactivates ICa\(_L\) in the T-tubules more than ICa\(_L\) in the surface sarcolemma.\(^10,15,16\) As noted by Orchard, this has a number of possible implications.\(^5\) First, that the T-tubules contain a large and rapidly inactivating ICa\(_L\), ideal for acting as a Ca\(^{2+}\) release trigger. Secondly, that the more slowly inactivating ICa\(_L\) arising from the surface sarcolemma may function as an SR Ca\(^{2+}\) loading mechanism.\(^14\) The differential inactivation of ICa\(_L\) in the surface sarcolemma and the T-tubules adds weight to the notion of the T-tubule as a specialized site for Ca\(^{2+}\) release. Evidence is rapidly accumulating for the T-tubules as not only a specialized site for Ca\(^{2+}\) entry and efflux, but also as a signalling complex.\(^17\)
The so-called transverse-tubule system is much more intricate than its name suggests and consists of branching transverse and longitudinal elements. Most studies address the transverse elements, but data are emerging that the longitudinal elements may undergo remodelling of either a different nature or at a different timescale. For example, it has been recently shown that proliferation of the longitudinal T-tubules can provide a source of Ca\(^{2+}\) influx in the setting of reduced SERCA2a, although this is not a specific model. Longitudinal T-tubules seem to have a compensatory role during disease, with proliferation of these elements following myocardial infarction in mice, but this remains to be tested specifically. Whether these two compartments respond differently to altered mechanical load is an important question to be determined experimentally.

Importantly, most of our current understanding of the T-tubule system comes from confocal studies of isolated single cardiomyocytes. As stated previously, the results from isolated single cells appear to be replicated by studies of the intact heart. However, confocal microscopy is limited in its ability to study the longitudinal elements of the T-tubule system, and it also provides a snapshot of the whole T-tubule system. The advent of new technologies with nanometer resolution (e.g. stimulated emission depletion live-cell super-resolution imaging) will enhance our understanding of the role of microarchitectural changes of the T-tubule system.

2. Recovering the diseased T-tubule system

Stolen et al. in 2009 made the seminal discovery of the reversibility of the T-tubule defects observed in the setting of diabetic cardiomyopathy. They showed that through exercise training, it is possible to reverse the deterioration of the T-tubule network, without improving the glycaemic profile, indicating a primary effect on the heart. Since this report, a number of groups have documented T-tubule recovery in a number of settings, and achieved by various means. Tomori et al. showed that denervated skeletal muscle underwent remodelling including aberrant t-tubular structure, and that low-intensity direct electrical stimulation could improve the T-tubule architecture. Also employing an electrical stimulation strategy, Sachse et al. showed that the use of cardiac resynchronization therapy in a canine HF model was able to improve T-tubule architecture. This lends support to the possibility of a clinically relevant role for T-tubule reverse remodelling in HF therapy. Xie et al. extended our understanding of the interaction between mechanical load and T-tubule structure by examining the effects of pulmonary hypertension on the right heart, and also of Sildenafil treatment. They showed that Sildenafil, which effectively reduced the afterload on the right heart, was able to significantly improve T-tubule structure. This adds support to the concept of a load-sensitive T-tubule structure. In a highly clinically relevant, if more challenging study to interpret, Chen et al. showed that the beta-adrenoceptor blockade of the infarcted heart prevented T-tubule remodelling. It will be important to understand which of the multiple mechanisms of beta-adrenergic blockade is responsible for this effect. Reversal of T-tubule remodelling has also been observed following molecular interventions. SERCA2a gene therapy of the infarcted, failing heart resulted in enhanced cardiac function. We showed that the normalization of mechanical overload using chronic mechanical unloading of the overloaded, failing heart was sufficient to result in T-tubule recovery (discussed later).

Among the different factors that may be implicated, it appears that reduction of chronic cardiac overload, induced directly or indirectly by the different interventions, is a common feature of all these studies (Table 1). Likewise, the ubiquitous effect of cardiac overload in damaging the T-tubule system is also apparent, secondary to loss of myocardium (myocardial infarction), increased afterload (pulmonary hypertension), or impaired cardiac contractility (diabetic cardiomyopathy, desynchronizing electrical stimulation, JPH2 knockdown). This has been documented in man where HF secondary to dilated, hypertrophic, or ischaemic cardiomyopathy all result in impaired T-tubule structure. We argue therefore that the interventions which impair cardiomyocyte ultrastructure ultimately act on disturbing cardiac load (whether in the positive or negative direction, directly or indirectly) and that likewise interventions which act to enhance T-tubule structure may act via normalizing cardiac load (by reducing the degree of cardiac overload).

Based on the hypothesis that normalization of mechanical load might ameliorate overload-induced T-tubule remodelling, we tested whether mechanical unloading of failing, chronically overloaded hearts could improve T-tubule structure. HF was induced in rats using left coronary artery ligation for a period of 12 weeks, at which point the hearts were transplanted into the abdomen of a recipient for a period of 4 weeks to induce chronic mechanical unloading. To investigate the effect of mechanical unloading on the T-tubule system, we used heterotopic abdominal heart transplantation in rats. This model involves transplanting a syngeneic cardiac graft into the abdominal position of a second animal via an aorto-aortic anastomosis and a pulmonary artery-inferior vena cava anastomosis. This results in perfusion of the cardiac graft, without blood flow through the ventricles which are substantially unloaded, in an analogous manner to the condition of the left ventricular assist device (LVAD)-supported left ventricle (discussed later).

We observed the recovery of the cell surface architecture (imaged using scanning ion conductance microscopy), T-tubule density, and regularity and also T-tubule microarchitecture studied using electron microscopy. This also improved Ca\(^{2+}\) transient synchrony and other features of the Ca\(^{2+}\) transient, partly through restoration of the sarcoplasmic reticulum Ca\(^{2+}\) content. A part of this improvement is also mediated through recoupling of L-type Ca\(^{2+}\) channels and ryanodine receptors following restoration of T-tubule network structure. This implies that substantial reduction of chronic mechanical load may improve T-tubule structure. It is challenging to know whether the T-tubule system is undergoing reverse remodelling in response to reduced loading conditions, or whether more general reverse remodelling enhances cardiac function, which subsequently improves subcellular architecture. The interacting pathways between the phenomenon of unloading-induced cardiac recovery, its molecular sequelae and the whole heart effects of directly altering the molecular phenotype of the failing heart remains to be tested, but promises an enhanced understanding of the pathogenesis of HF as well as fruitful means to induce cardiac recovery.

3. Is the T-tubule network load sensitive?

Chronic mechanical overload has been directly modelled using thoracic aortic constriction, commonly in the rat. A number of studies
show T-tubule disruption, at various durations following the institution of chronic mechanical overload (which can be of varying degrees depending on the degree of stenosis). In the setting of chronic HF with its essential component of chronic mechanical overload, a large number of studies show T-tubule dysfunction in both animals and humans, a subject which has been reviewed extensively.1,7 Perhaps the most compelling evidence for an effect of mechanical overload per se on the T-tubule network comes from the whole heart study of T-tubule structure following mechanical overload by Wei et al.2 Using thoracic aortic constriction and a method to examine the T-tubules in the whole heart, changes to the T-tubule network are observed in response to pressure overload prior to the onset of overt myocardial failure.2 This implies that chronic myocardial overload (and not general HF remodelling) alters the T-tubule network. If the T-tubule network is responsible for the optimization of Ca$^{2+}$ handling in the normally loaded heart, then such alterations must be maladaptive. The fact that under these specific experimental conditions, they are not associated with cardiac dysfunction implies the presence of compensatory mechanisms. We recently provided evidence that augmented sarcoplasmic reticulum Ca$^{2+}$ content may play a role in this at the cellular level. What is particularly noteworthy is that the degree of T-tubule dysfunction appears to correlate with the degree of myocardial dysfunction, as quantified by the ejection fraction.2 Could this be related to the degree of mechanical overload? Presumably, the most overloaded hearts are those that develop the most severe T-tubule remodelling, and it is tempting to speculate that this is really a relationship between degree of overload and T-tubule structure. This remains to be formally tested. What this result now establishes beyond doubt is that (i) T-tubule remodelling is an early, possibly deterministic, event in the pathogenesis of HF; should be reviewed extensively.1,7 In the setting of chronic mechanical overload, a large number of studies show T-tubule dysfunction in both animals and humans, a subject which has been reviewed extensively.1,7 Perhaps the most compelling evidence for an effect of mechanical overload per se on the T-tubule network comes from the whole heart study of T-tubule structure following mechanical overload by Wei et al.2 Using thoracic aortic constriction and a method to examine the T-tubules in the whole heart, changes to the T-tubule network are observed in response to pressure overload prior to the onset of overt myocardial failure.2 This implies that chronic myocardial overload (and not general HF remodelling) alters the T-tubule network. If the T-tubule network is responsible for the optimization of Ca$^{2+}$ handling in the normally loaded heart, then such alterations must be maladaptive. The fact that under these specific experimental conditions, they are not associated with cardiac dysfunction implies the presence of compensatory mechanisms. We recently provided evidence that augmented sarcoplasmic reticulum Ca$^{2+}$ content may play a role in this at the cellular level.2 What is particularly noteworthy is that the degree of T-tubule dysfunction appears to correlate with the degree of myocardial dysfunction, as quantified by the ejection fraction.2 Could this be related to the degree of mechanical overload? Presumably, the most overloaded hearts are those that develop the most severe T-tubule remodelling, and it is tempting to speculate that this is really a relationship between degree of overload and T-tubule structure. This remains to be formally tested. What this result now establishes beyond doubt is that (i) T-tubule remodelling is an early, possibly deterministic, event in the pathogenesis of HF;
(ii) the changes observed in vitro in dissociated cells are relevant to the intact heart and (iii) that mechanical load regulates T-tubule structure.

Using a normal cardiac allograft, transplanted for a period of 4 weeks, we showed that chronic mechanical unloading alone resulted in impaired T-tubule structure. This consisted in an intact T-tubule density (the percentage of the cell where T-tubules were detectable) but a reduced periodicity of the T-tubule network (as measured by the peak of the Fourier transformation). This was associated with an impaired Ca\(^{2+}\) transient synchrony, with an overall slowing of the Ca\(^{2+}\) transient time to peak, and time to 50 and 90% decline, as well as reduced Ca\(^{2+}\) transient amplitude. These changes occurred despite a normal SR Ca\(^{2+}\) content.33 Interestingly, these changes mirror those found in HF secondary to mechanical overload (and other aetiologies), where there is also T-tubule disruption. As in the case of mechanical overload-induced remodelling, presumably the changes in T-tubule structure are not isolated but come about as a part of a programme of subcellular remodelling. In this sense, it can be challenging to determine the causality of phenomena in this setting. This is particularly the case for the Ca\(^{2+}\) transient changes. We observed an increase in Ca\(^{2+}\) transient frequency, mirroring effects in HF and overload, and believe it may also be related to the degradation of the T-tubule network. Meethal et al.34 showed that increased Ca\(^{2+}\) transient frequency occurred at gaps in the T-tubules where diastolic Ca\(^{2+}\) levels were higher. This suggests that orphaned RyR show more activity than coupled dyads, possibly pointing to a direct effect of detubulation on local RyR activity. An important unresolved question is how T-tubule disruption leads to increased Ca\(^{2+}\) transient frequency, since the displacement of the ICa,L might be expected to reduce (not enhance) RyR activation. Evidence suggests that factors more complex than simple Ca\(^{2+}\) influx through ICa,L are involved35–37 and that the interaction between ICa,L and RyR, regulated heavily by the T-tubules, appears to be critical. Thus, complex consequences of T-tubule irregularities might be expected, and not necessarily reduced Ca\(^{2+}\) transient frequency. Following myocardial infarction, Ca\(^{2+}\) transient frequency appears to increase in areas of delayed activation during the Ca\(^{2+}\) transient, where T-tubules would be disrupted.38 Irregularities in the T-tubule membrane might result in mislocalization of NCX also, which could locally elevate [Ca\(^{2+}\)] and promote Ca\(^{2+}\) sparks through either directly activating RyR or via CaMKII.39 This mislocalization of NCX could also account for the increased length of Ca\(^{2+}\) sparks.38

These experimental findings show that both extremes of mechanical load variation can impact upon T-tubule structure deleteriously. They suggest that mechanical load variation is a regulator of the T-tubule system and also pose the hypothesis that there is a limited, moderate range of chronic myocardial loading conditions which are compatible with an intact T-tubule system. In the setting of the sometimes profound reverse remodelling observed following mechanical unloading of chronically overloaded hearts, it raises the possibility that normalization of mechanical load might promote the conditions for normalization of the T-tubule system during cardiac disease, as we have documented.27

4. Myocardial loading conditions as a regulator of T-tubule structure

We recently tested the hypothesis that a range of physiologically relevant cardiac loading conditions regulated T-tubule structure more directly. To do this, we used a model which induces a moderate degree of mechanical unloading by transplanting the cardiopulmonary circulation into the abdomen of a syngeneic recipient using a single aorta-aortic anastomosis. This allows an investigation of the effect of mechanical unloading over a longer time frame than the drastic effects induced by standard heart-only transplantation. Mechanical overloading was induced by thoracic aortic constriction.

We found that chronic overload resulted in a time-dependent degradation of the T-tubule system, with no changes at 6 weeks but a loss of T-tubule density and regularity at 10 weeks following aortic constriction.27 On the other hand, mechanical unloading resulted in a slow loss of T-tubule regularity, with no changes at 4 weeks but the loss of regularity at 8 weeks (Figure 1). This is in contrast to the effects of profound unloading induced by heart-only transplantation, where there was marked the loss of T-tubule regularity at 4 weeks.29 This implies that, at least in the setting of mechanical unloading, the T-tubule system is sensitive to the degree, as well as the duration, of mechanical load variation.

To summarize some of the most direct evidence relating to the influence of mechanical load on T-tubule structure, we here briefly summarize our work with surgical models of graded mechanical unloading and overload. Our main hypothesis is that there is an optimal range of physiological loading conditions which are compatible with normal T-tubule structure. Reducing this mechanical load in a modest manner initially has little effect on the structure and function of the T-tubule system. However, excessively prolonged or severe mechanical unloading induce abnormal remodelling to the T-tubules.29,32 Conversely, mechanical overload can also impair T-tubule structure,32 supporting the concept of a range of intermediate degrees of load which are compatible with normal T-tubule structure. Meethal et al.33–35 showed that increased Ca\(^{2+}\) transient frequency occurred at gaps in the T-tubules where diastolic Ca\(^{2+}\) levels were higher. This suggests that orphaned RyR show more activity than coupled dyads, possibly pointing to a direct effect of detubulation on local RyR activity. An important unresolved question is how T-tubule disruption leads to increased Ca\(^{2+}\) transient frequency, since the displacement of the ICa,L might be expected to reduce (not enhance) RyR activation. Evidence suggests that factors more complex than simple Ca\(^{2+}\) influx through ICa,L are involved35–37 and that the interaction between ICa,L and RyR, regulated heavily by the T-tubules, appears to be critical. Thus, complex consequences of T-tubule irregularities might be expected, and not necessarily reduced Ca\(^{2+}\) transient frequency. Following myocardial infarction, Ca\(^{2+}\) transient frequency appears to increase in areas of delayed activation during the Ca\(^{2+}\) transient, where T-tubules would be disrupted.38 Irregularities in the T-tubule membrane might result in mislocalization of NCX also, which could locally elevate [Ca\(^{2+}\)] and promote Ca\(^{2+}\) sparks through either directly activating RyR or via CaMKII.39 This mislocalization of NCX could also account for the increased length of Ca\(^{2+}\) sparks.38

5. The molecular mechanisms mediating the regulation of the T-tubule system

A large number of molecules have been described which influence T-tubule structure.30 These include BIN1 (implicated in the formation of mechanical unloading by transplanting the cardiopulmonary circulation into the abdomen of a syngeneic recipient using a single aorta-aortic anastomosis. This allows an investigation of the effect of mechanical unloading over a longer time frame than the drastic effects induced by standard heart-only transplantation. Mechanical overloading was induced by thoracic aortic constriction.

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of tubular invaginations and the shuttling of the L-type Ca\textsuperscript{2+} channel to the T-tubule\textsuperscript{42–44}, JPH2 and Tcap. Tcap and JPH2 have been investigated in the setting of mechanical load variation.

Tcap is a member of the stretch-sensitive complex of the cardiomyocyte, and is mutated in muscular dystrophy (Limb-girdle muscular dystrophy type 2G).\textsuperscript{45–48} Mutations in the heart can lead to hypertrophic or dilated cardiomyopathy, and it has been suggested that this is related to the degree of stretch-sensation.\textsuperscript{49} In zebrafish skeletal muscle, Zhang et al.\textsuperscript{50} showed that T-tubules were formed in response to increased stretch, but that this required normal Tcap expression. We recently investigated the role of Tcap in regulating cardiac T-tubules.\textsuperscript{40} Using a Tcap KO mouse model, we showed that there were subtle, progressive defects in the T-tubule system. These changes were pronounced following the institution of mechanical overload using thoracic aortic constriction, indicating a critical role for Tcap in the regulation of the T-tubule system during altered mechanical load (the T-tubule remodelling was worse in Tcap KOs). Lyon et al.\textsuperscript{51} recently showed that following reverse remodelling induced by SERCA2a gene therapy, the recovery of the T-tubule system was associated with augmented Tcap expression. The full details of the relationship between cardiac loading conditions, Tcap expression and cardiac T-tubule structure is a critical step in developing our understanding of this system.

JPH2 is a linker molecule at the level of the dyad.\textsuperscript{52} JPH2 has been shown to be reduced during the progression of hypertrophy to HF, possibly as a result of increasing cardiac overload.\textsuperscript{23} Xie et al.\textsuperscript{23} showed that JPH2 expression was also reduced during pulmonary hypertension-induced right ventricular failure, with loss of normal T-tubule structure. Importantly, following the administration of Silde nafil, which reduces right ventricular afterload, JPH2 recovered. Recovery of JPH2 expression has also been documented by the same group following the amelioration of T-tubule disruption in the setting of beta-adrenoceptor blockade following myocardial infarction.\textsuperscript{24} Van Oort et al.\textsuperscript{26} have also provided convincing evidence that JPH2 is sufficient for the recovery of the T-tubules (and augmented cardiac function) by rescuing JPH2 expression in the context of JPH2-knockdown-induced cardiomyopathy. Xu et al.\textsuperscript{52} have recently dissected an additional tier of bioregulation, whereby miR-24 expression is dynamically altered during overload and disease which influences JPH2 expression.

It is necessary to develop a more interconnected understanding of how these molecules are coordinated to regulate the T-tubule

**Figure 1** Time and degree dependent changes following mechanical overload and unloading. This figure shows effects of chronic overload induced by thoracic aortic constriction (TAC) and mechanical unloading (UN) of the heart on the T-tubule structure at different time points. The lower left graph indicates T-tubule density (% membrane staining). The lower right graph shows the ‘power’ or the peak of the Fourier transform used to assess T-tubule regularity. A higher power indicates more organized T-tubules. For more details see Ibrahim et al.\textsuperscript{29}
Mechanical overload increases ventricular size, and disrupts T-tubule structure in a load-dependent manner. Mechanical unloading reduces ventricular size and disrupts T-tubule structure in a load dependent manner. Small or short durations of mechanical load variation are associated with normal T-tubule structure despite alterations in ventricular size.

Table 2 Degree and duration of mechanical load variation and its impact on T-tubule structure

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<thead>
<tr>
<th>Study</th>
<th>Finding</th>
<th>Implication</th>
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<tr>
<td>Study 1: chronic mechanical unloading of a normal heart (4 weeks)</td>
<td>Disrupted T-tubule regularity but intact density</td>
<td>T-tubule remodelling is implicated in atrophic remodelling</td>
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<td>Study 2: chronic mechanical unloading of a failing heart (4 weeks)</td>
<td>Recovery of T-tubule regularity and density with relocalization of DPHR-RyR receptors</td>
<td>Normalization of mechanical load results in reversal of T-tubule remodelling</td>
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<td>Study 3: chronic mechanical overload alone</td>
<td>6 weeks: no changes</td>
<td>Hypertrophy can initially be associated with no or minor changes to the T-tubule network As overload-induced remodelling progresses, the T-tubule network becomes disrupted</td>
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<td>10 weeks: disrupted T-tubule regularity and density</td>
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<td>8–12 weeks: heart failure was associated with worse T-tubule structure than hypertrophy</td>
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<td>Study 4: chronic moderate mechanical unloading</td>
<td>4 weeks: short-term, moderate mechanical unloading does not alter T-tubule structure</td>
<td>Mechanical load variation modulates T-tubule structure in a time and degree dependent manner</td>
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<td>8 weeks: long-term moderate mechanical unloading achieves similar effects (loss of T-tubule regularity) to more severe unloading, over a longer timeframe</td>
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system, which factors (biochemical and biophysical) regulate them and which are most amenable to therapeutic intervention.

6. Clinical correlates

HF is the result of a wide range of myocardial insults which either impair cell function or reduce cell number, and commonly both. This ultimately results in fewer, damaged cells which are forced to take over the work of a larger number of healthy cardiomyocytes, resulting in chronic mechanical overload. Such chronic overload further impairs cardiomyocyte function and number, resulting in a self-sustaining, progressive process which result in an inability to perfuse the tissues at a normal filling pressure—HF. The central role which mechanical overload plays in the progression of HF has long been realized. Mechanical overload does not uniformly result in HF, and a range of increased loads are associated with compensatory adaptation (centred around cardiac hypertrophy), which enhance cardiac function to cope with increased workload. Such a relationship is also true for changes in the acute setting where initial increases in cardiac loading are handled with increased contractility, but beyond a physiological range of loads, cardiac output no longer increases. On the other hand, chronic reductions in cardiac load, for example, by prolonged bed rest result in adaptation to diminished cardiac workload, including cardiac atrophy. Whether such adaptations can also occur within a physiological range prior to becoming maladaptive is much less clear at present.

In an attempt to sustain the circulation of patients with end-stage HF, LVADs, which support the work of the left ventricle, were developed. Use of LVADs as a bridge to recovery from HF involves the use of the profound pressure and volume unloading afforded by LVAD therapy to encourage reversal of the pathological remodelling in HF to a degree at which cardiac function is sufficient to sustain the circulation. The seminal discovery of the phenomenon of cardiac recovery challenged the paradigm of HF as irreversible and blurs the distinction between physiological and pathological hypertrophy. It also offers unprecedented opportunity to study the response of the myocardium to chronic mechanical unloading. Such studies have elucidated a number of pertinent points. Importantly, mechanical unloading regulates cardiac function in a graded manner. Maybaum et al showed that following LVAD implantation, native cardiac function improved, but that with prolonged mechanical unloading, these functional improvements regress. This indicates that there is a biphasic response to chronic mechanical unloading in the setting of HF, with initial beneficial effects due to relief of overload, followed by maladaptation to the state of chronic unloading. Further evidence for such a biphasic relationship is provided by studies showing that augmentation of physiological hypertrophy (with the use of the beta-agonist drug, Clenbuterol) following mechanical unloading is effective in greatly increasing the rate of cardiac recovery. It is noteworthy that the pattern of load-dependent changes observed following LVAD implantation mirror those determined in studies of T-tubule structure-function following chronic mechanical load variation (Table 2).

The mechanisms by which mechanical load variation influences myocardial function are multiple. These are enacted at the systemic, whole heart, cellular, and subcellular levels, and have been reviewed extensively for the setting of LVAD therapy. One particular cluster of activity is that of excitation—contraction coupling, and in this subsystem multiple elements are changed. Our work suggests that the dynamic relationship between mechanical load variation and T-tubule structure (which impacts on cellular Ca2+ handling and contractility) underlies a part of reverse remodelling and atrophic remodelling observed following LVAD implantation. This hypothesis requires direct testing, which is ongoing.

7. Conclusions

The T-tubule system is a dynamic, tightly regulated membrane structure which has a major impact on regulating the Ca2+ dynamics of cardiomyocytes, and in turn cardiac contractility. Its normal structure and function appears to depend on normal cardiac loading conditions (Figure 2). The expansion of knowledge of its molecular regulation will help us better understand the specificity of this interaction, its overall role with respect to the other changes that occur during disease, and whether it would serve as effective therapeutic target.

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References


