Taking pressure off the heart: the ins and outs of atrophic remodelling

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Abstract

Our work on atrophic remodelling of the heart has led us to appreciate the simple principles in biology: (i) the dynamic nature of intracellular protein turnover, (ii) the return to the foetal gene programme when the heart remodels, and (iii) the adaptive changes of cardiac metabolism. Although the molecular mechanisms of cardiac hypertrophy are many, much less is known regarding the molecular mechanisms of cardiac atrophy. We state the case that knowing more about mechanisms of atrophic remodelling may provide insights into cellular consequences of metabolic and haemodynamic unloading of the stressed heart. Overall we strive to find an answer to the question: What makes the failing heart shrink and become stronger? We speculate that signals arising from intermediary metabolism of energy-providing substrates are likely candidates.

Keywords

Cardiac atrophy • Mechanical unloading • Metabolic unloading

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1. Introduction

Dr William Boswell Castle, the famous Harvard haematologist, once said, ‘In all ages the time available in which to think has probably been largely wasted by most.’1 As we set out to review the complex field of atrophic remodelling of the normal and failing heart, we were reminded of his admonition. It is our aim to present the reader with a conceptual framework that accommodates both metabolic and structural remodelling of the heart in response to a decrease in its load.

2. The big picture

Our work on atrophic remodelling of the heart2 has led us to appreciate two simple principles in biology: First, from the cell cycle to the Krebs cycle, there is no life without cycles. The same principle applies to the cycle of intracellular protein synthesis and degradation (Figure 1). Although cellular regeneration of the heart now receives much attention,3 it is almost overlooked that each cardiomyocyte renews itself. This is surprising, because, while stem cells contribute to the replacement of cardiomyocytes after injury, they contribute little to cardiomyocyte renewal during normal ageing.4 Although the dynamic state of body constituents is known since the 1940s, the idea that heart muscle cells continuously renew themselves from within and in response to environmental stimuli (such as metabolic and/or hemodynamic stress) is relatively new.5–7 Second, and equally important, we learned that remodelling of the cardiomyocyte results in a return to the foetal gene programme, no matter whether the heart hypertrophies or atrophies (Table 1) or whether the heart is exposed to the metabolic milieu of diabetes.8–10 Contrary to our original speculation that the failing human heart reverts to the foetal gene programme after mechanical unloading,2 we observed that the foetal gene programme is already activated in the failing human heart.11 Mechanical unloading of the failing heart does not restore the transcript levels of metabolic genes with the notable exception of uncoupling protein 3 (UCP3).12 The perplexing question remains: how does the heart shrink and become stronger (i.e. haemodynamically stronger which is measurable by increased contractile force)? This process seems counterintuitive because atrophied skeletal muscle is always associated with a decrease in contractile strength. In the following sections, we will discuss selected aspects of metabolic and haemodynamic loading and unloading as they relate to atrophic remodelling in both the normal and the stressed heart. Table 2 summarizes the topics we will discuss in our effort to define the complexities of atrophic remodelling of the heart. Because the substrate for atrophic remodelling most often involves a stressed heart, a brief consideration of metabolic and haemodynamic stresses is in order.

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3. Metabolic stresses as modulators of cardiac structure and function

Besides adrenergic and angiotensin receptor activation, the main stressors of the heart are its metabolic and/or haemodynamic load. The beneficial effects of receptor blockade in heart failure management are well known. Modulation of the haemodynamic load is also a well-established concept, which will be discussed later. However, metabolic stresses, including increased nutrient supply, hyper-adrenergic states, or hormonal imbalances as modulators of cardiac structure and function are not always considered (with the notable exception of myocardial ischaemia, of course).

Obesity, insulin resistance, and diabetes mellitus are characterized by an extracellular milieu of excess fuel supply resulting in metabolic stress on the heart. The effects of obesity on the heart are well known and include impaired diastolic function, decreased cardiac efficiency, and left ventricular hypertrophy. The intramyocardial lipid accumulation in the failing human heart from obese and/or diabetic patients resembles features of the lipotoxic rat heart including oxidative stress, diacylglycerol, and ceramide accumulation. Altogether these characteristics comprise both markers (‘footprints’) and mediators of glucolipotoxicity, a term first used by Marc Prentki and Barbara Corkey in the pancreatic β-cell. The complexities of glucolipotoxicity in the heart include metabolic and functional derangements, which have been reviewed in the context of obesity, and diabetes.

Metabolic disorders stem from several factors, including genetic predisposition on the one hand and the environment on the other hand. Diet is a critical determinant of adaptation and maladaptation of the heart. Along these lines, feeding rats two different obesogenic diets (60% or 45% of caloric intake from fat, 20% from protein and the balance from carbohydrate) resulted in two distinct forms of cardiac responses. High-fat (60% fat, 20% carbohydrate) diet induced futile metabolic cycles allowing the heart to adapt to metabolic overload, while ‘Western’ (45% fat, 35% carbohydrate) diet resulted in heart failure. Maladaptation, revealed by the footprints of glucolipotoxicity in heart and skeletal muscle, is evident in all patients with clinically severe obesity and in all patients with either obesity or type 2 diabetes and advanced heart failure requiring cardiac transplantation.

In short, there are multiple factors, both metabolic and neurohumoral, responsible for myocardial fuel overload. McEwen was probably the first to draw attention to the plasticity of the brain in relationship to stresses, which he collectively called ‘allostatic load’. The collective environmental risk for disease development in any organ has recently been given the term ‘exposome’. We now propose that metabolic loading, like haemodynamic loading, provides a stress to the heart which results in either adaptive or maladaptive, reversible or irreversible structural and functional changes. Reversibility of the process is borne out by the observation that prolonged caloric restriction in obese patients with type 2 diabetes mellitus

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**Figure 1** Protein turnover in the heart. The balance of protein synthesis and degradation determines size and function of cardiomyocytes. Damaged, misfolded, or useless proteins are degraded to amino acids which are used for the synthesis of new, functional proteins. The amino acids phenylalanine and tyrosine (Phe, Tyr) are not metabolized by heart muscle and therefore used as tracers for protein synthesis and degradation in pulse-chase experiments.

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**Table 1** Transcriptional signatures of atrophy and hypertrophy are the same

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<tr>
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<tr>
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<td>c-myc</td>
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<td>Growth factors</td>
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<td>Transcription factors</td>
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<td>Skeletal α-actin</td>
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<td>Ion pumps</td>
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Note: ↑ denotes increase; ↓ denotes decrease; = denotes no change. The pattern is consistent with a return to the foetal gene programme. See text for details. (Adapted from Taegtmeyer.)

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Cardiac mass with physical conditioning and deconditioning. Fur-
heart muscle releases myostatin (not unlike TNFα), and induces muscle wasting in heart failure. Heart-specific over expression of myostatin reduced both heart weight and skeletal muscle weight. Myostatin-induced muscle wasting and cardiac atrophy can be blocked when mice are treated with a soluble receptor of myostatin.49 Another, clinically even more relevant, model is cancer-induced cachexia in mice. Cardiac atrophy due to nutritional unloading is associated with a return to the foetal gene programme, very much a sign of active cardiac remodelling in response to nutritional remodelling.50 Furthermore, cancer-induced cardiac atrophy seems to be regulated by autophagy, not the UPS.51

A third example is the reversal of metabolic overload from dysregulated substrate supply in obesity, insulin resistance, and diabetes, which results in features of glucolipotoxicity. The term ‘glucolipotoxicity’ was first used in the context of metabolic damage to the pancreatic β-cell,18 to denote the damage exerted by non-oxidative glucose and fatty acid metabolites in a variety of tissues including the heart. Virchow12 already described it as the ‘true metamorphosis of the cardiac cell’. Today lipotoxic heart disease is described in obese rats53,54 as much as in obese human patients with advanced heart failure.17 Metabolic unloading of the systemic circulation with the thiazolidinedione (TZD) troglitazone53 or with another, non-TZD compound55 results in complete reversal of both fuel overload and contractile dysfunction of the heart.

Perhaps the most impressive reversal of cardiac dysfunction and hypertrophy in response to metabolic stress occurs, however, in severely obese patients following bariatric surgery. Here the early normalization of hormone and substrate levels (and insulin resistance) is followed by a dramatic improvement in left ventricular diastolic function,74 as well as a progressive decrease in left ventricular mass.16 The left ventricle becomes smaller and stronger with the removal of the systemic metabolic pressure (Figure 3). To the contrary, increased fatty acid metabolism using a pharmacological activator of the nuclear receptor, peroxisome proliferator-activated receptor, (PPARα) in the hypertrophied heart promotes fuel overload and results in contractile failure.56 We conclude that the removal of an excess nutrient supply to the heart, in contrast to cachexia, is beneficial for both size and function of the heart.

7. Haemodynamic unloading

The functional and structural changes of the heart to haemodynamic unloading are complex. There is little doubt that in the failing human heart mechanical unloading improves, or even normalizes, Ca2+ cycling in the cardiomyocyte;57 remodels the extracellular matrix,58 reduces interstitial fibrosis, and decreases the size of heart muscle cells.12 In contrast to this pattern of structural and functional improvement with mechanical unloading of the failing human heart, no consistent pattern has been apparent at the transcriptional level.59 In the normal heart, we have drawn attention to the fact that the common feature of both pressure overload-induced hypertrophy and atrophy is a reactivation of the foetal gene programme (Table 1).2 Moreover, the metabolic consequences for the heart, including impaired insulin-responsiveness, are also the same for the hypertrophied and atrophied heart.60 In concurrence with this trend, El-Armouche et al.61 recently reported that microRNA signature patterns are also common in the unloaded and overloaded heart.

Figure 3 Progressive regression of left ventricular mass after metabolic unloading by bariatric surgery. Drastic reduction in metabolic parameters (glucose, insulin, HOMA, leptin, CRP) occurs early after surgery and plateau after 9 months (metabolic unloading). Left ventricular mass continues to regress 24 months after surgery (HOMA, homeostasis model of assessment; LVM, left ventricular mass; CRP, C-reactive protein). (With permission from Algahim et al., Am J Med 2010.56)
Many studies have reported the improvement of pathological hypertrophy with placement of a LVAD when used as a 'bridge to transplantation' in heart failure patients. Patients with LVAD support exhibit a reduced ventricular mass as a result of regression in myocyte hypertrophy. Mechanical unloading with LVADs may also improve the ejection fraction and reduce left ventricular end-diastolic dimensions, improve myocyte contractility, and increase β-adrenergic responsiveness. Although great strides have been made, more studies are still necessary in order to understand the mechanisms regulating 'reverse remodelling' of the failing heart.

Similar to the failing heart, the normal heart can also be haemodynamically unloaded, as is the case of prolonged bed rest and space-flight, or 'deconditioning' of the heart. Cardiac atrophy, resulting from extended periods of bed rest, is in part due to hypovolaemia and can be reversed with exercise and by inducing lower body negative pressure. Likewise, space-flight leads to decreased stroke volume and decreased systemic oxygen uptake due to decreased blood volume, collectively termed 'microgravity-induced deconditioning'. Cardiac atrophy due to space-flight can be reversed with supine cycling exercises combined with plasma volume restoration.

7.1 Unloading of the normal heart

A well-established experimental model of cardiac atrophy is the heterotopic transplantation of the mammalian heart. Initially introduced in the early 1930s in dogs, this method has more recently been adapted for rat heart transplantation studies. Additional modifications such as 'pressure-loaded' and 'volume-loaded' preparations of the unloaded heart have confirmed that alterations in cardiac structure and function are load-dependent. Heterotopic transplantation of the mouse heart has also been employed to investigate mechanisms of atrophic remodelling. We have utilized this model in transgenic animals to investigate gain- and loss-of-function studies as they relate to cardiac atrophy.

Initial studies on atrophic remodelling of the normal heart focused on the structural and functional changes that occur in the absence of a load. Over a period of 28 days, cardiomyocyte cross-sectional area progressively decreases, with the earliest structural changes, including disarray of myofilaments, visible 1 day after unloading the feline papillary muscle. After 1 week, large areas of non-specific cytosol devoid of organelles are evident (Figure 2B). Surgically reloading the papillary muscle demonstrates the reversibility of atrophic remodelling; contractile filaments, mitochondria, and protein concentrations are restored, and the cytosol is replaced with organized myofibrils (Figure 2C). Additional studies in vitro using isolated adult feline myocytes verified that structural and biochemical changes observed in vivo are load-dependent. In the unloaded rat heart, an overall decrease in cardiac size and mass results from decreased cardiomyocyte number, and cardiomyocytes within the left ventricular endomyocardium respond most drastically to unloading. Furthermore, decreased phospholipid concentrations in the sarcolemma occur in response to unloading, which may be due, at least in part, to decreased lipid incorporation. After long-term unloading there is increased ventricular stiffness, likely caused by increased extracellular matrix remodelling, which can be reversed with reloading. Despite the gross structural changes, normal functional capillary density is maintained in the unloaded heart.

7.2 Ca\(^{2+}\) homeostasis in atrophic remodelling

Although atrophic remodelling significantly decreases myocyte area and volume, hearts maintain normal systolic function after 4 weeks of unloading. Cardiomyocytes from unloaded hearts have decreased sodium currents and increased calcium currents, while total calcium concentration in the myocyte remains unchanged. Cardiomyocytes have preserved fractional shortening and peak systolic [Ca\(^{2+}\)], at baseline, but have prolonged time to 50% relengthening and time to 50% decline in [Ca\(^{2+}\)], after unloading. Alterations in calcium handling may be, at least partially, due to increased phospholamban protein levels. Although isometric contraction and calcium-stimulated ATPase activity is not affected, decreased calcium uptake in the sarcoplasmic reticulum occurs with unloading, which may contribute to a decreased relaxation phase. Cardiomyocytes from hearts unloaded for 2 weeks have preserved fractional shortening and time to peak contraction and relaxation times, but papillary muscles develop less maximal force. When taking into account a decrease in myocyte size, however, there is no difference in maximal force per area in the unloaded heart.

7.3 Substrate metabolism and growth signalling

Early studies in the transplanted mammalian heart focused on structural and functional changes that occur in cardiomyocytes after unloading; however, the molecular mechanisms regulating these changes are still largely unclear. We demonstrated that in both atrophy and hypertrophy, the heart is less responsive to insulin and prefers glucose as substrate, consistent with the observed foetal pattern of energy consumption. Switch in substrate utilization in the unloaded heart is also reflected in the decreased expression of PPARα and the PPARα-regulated genes pyruvate dehydrogenase kinase 4 (PDHK4), and malonyl-CoA decarboxylase (MCD). Downregulation of PPARα in unloaded hearts is likely due to the activation of the IKKβ/p65/p50 pathway. We also investigated the role of growth factors, the mitogen-activated protein (MAP) kinase pathway, and the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway in the unloaded heart. Atrophic remodelling was associated with increased IGF-1 and FGF-2 mRNA expression and increased ERK1, p70S6K, and STAT3 phosphorylation. As is the case with the foetal gene programme, changes in growth factor expression are the same in both atrophy and hypertrophy, suggesting that directionality of change in cardiac size does not necessarily correlate with the corresponding changes in transcript levels. The activation of cardiac growth signalling in atrophic remodelling is not readily explained other than by the remodelling process itself. In short, active remodelling occurs with increased or decreased load indicating that myocardial protein turnover is a critical regulator of cardiac mass.

7.4 Pathways of protein turnover

The pathways regulating protein synthesis have been well characterized in the heart, while protein degradation in the heart, by comparison, has been less studied. The three major pathways regulating protein degradation in the heart have been previously reviewed.
and include the calcium-dependent calpain system, lysosomal proteolysis and autophagy, and the UPS. The UPS degrades proteins in a specific manner. Ubiquitin ligases confer the specificity of the system by tagging the target proteins to be degraded with ubiquitin, and the tagged proteins are then degraded by the proteasome. The role of the UPS, specifically the ubiquitin ligases Atrogin-1 and MuRF1, in regulating cardiac mass is well documented during cardiac hypertrophy and in skeletal muscle atrophy. In the unloaded heart, we observed an increase in polyubiquitinated proteins and increased levels of a ubiquitin conjugating enzyme, UbcH2, suggesting that the UPS is an important regulator of cardiac mass during atrophic remodelling. Unexpectedly, we found a decrease in the transcript levels of the ubiquitin ligases Atrogin-1 and MuRF1 after 7 days of unloading, although these data are consistent with the increase in IGF-1, as both ligases are negatively regulated by the insulin signalling pathway. Although surprising, our findings do not rule out the importance of Atrogin-1 and MuRF1 during early atrophic remodelling of the heart.

To further define the role of protein degradation in the unloaded heart, we also investigated the calcipan system and autophagy during atrophic remodelling. We found that the transcript levels and activities of both Calpain 1 and 2 were increased in the unloaded heart. However, in unloaded hearts overexpressing the endogenous calpain inhibitor calpastatin, atrophy was not inhibited, suggesting that more than one proteolysis pathway is involved in the atrophic remodelling process.

In ongoing work, we also postulate that autophagy is an important mechanism regulating protein degradation in the unloaded heart. We found that markers of autophagy including LC3, Atg5, and Atg12 are increased at both the RNA and protein levels in the unloaded heart. However, in failing heart already expresses elevated levels of autophagy markers but when implanted with an LVAD, autophagy markers are downregulated. These data suggest that autophagy could be an adaptive mechanism in the failing heart; however, they do not rule out the possibility that autophagy in end-stage heart failure could be maladaptive. More studies, including gain- and loss-of-function studies will be necessary to clearly define the role of autophagy in atrophic remodelling of the heart.

Skeletal muscle atrophy due to disuse, or unloading, is caused by increased protein degradation and a decreased protein synthesis. We therefore reasoned that in the heart, protein synthesis would be decreased during atrophy. We unexpectedly found, however, that the mTOR pathway is activated with unloading. When the mTOR pathway is inhibited with rapamycin, there is a further decrease in cardiac mass in the unloaded heart. Simultaneous activation of protein synthesis (mTOR pathway) and protein degradation (the UPS, the calpain system, and autophagy) provides evidence that active remodelling occurs in the unloaded heart. To further understand the mechanisms involved in this process, we are currently investigating the hypothesis that metabolic signals regulate protein turnover during atrophic remodelling of the heart.

8. Outlook

A new paradigm is needed to assess the causes and consequences of atrophic remodelling of the heart. We have reviewed, in broad strokes, the consequences of metabolic and haemodynamic overload, the consequences of unloading the heart, and the many levels of complexity of atrophic remodelling. The latter include changes in gene expression, changes in protein abundance and activity, and changes in metabolites and metabolic fluxes. The powerful tools of discovery research and systems biology continue to add to the large pool of information. Great strides have been made in the field of cardiovascular proteomics giving rise to a more comprehensive understanding of the dynamics involved in disease pathogenesis, an example being the identification of novel posttranslational modifications of mitochondrial proteins. Advancements in the analysis and quantitation of protein biomarkers will continue to improve clinical diagnosis. Coupled with proteomics, metabolomics becomes a valuable resource to elucidate the link between cellular metabolism and cardiac function. In short, new analytical methods will help to find an answer to the question: How does the heart shrink and become stronger at the same time?

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Atrophic cardiac remodelling


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