

# Cellular metabolic and structural changes in heart failure

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## Abstract

The myocardium undergoes dramatic metabolic and structural changes in patients with heart failure. These metabolic and structural changes can be major contributors to the contractile dysfunction seen in heart failure. These changes include dramatic alterations in mitochondrial function and energy metabolism, as well as structural changes in the myocyte itself and the collagen matrix. Alterations in calcium handling and excitation-contraction coupling are also hallmarks of the failing heart. Part of these alterations result from accelerated apoptosis, autophagy, mitochondrial production of reactive oxygen species, mitophagy, and mitofission that occur in heart failure. This Refresher Corner paper provides a review of some of the metabolic and structural changes in the failing heart. ■ *Heart Metab.* 2017;74:32-36

**Keywords:** apoptosis; autophagy; excitation-contraction coupling; mitochondria; mitofission; mitophagy

## Introduction

Despite the differing etiologies involved in the development of heart failure, there are a number of common metabolic and structural changes that can occur in the failing heart (*Figure 1*). These include: (i) changes in cardiac energy metabolism; (ii) changes in myocardial structure (eg, increased cardiomyocyte hypertrophy, increased fibrosis, and alterations in the collagen network); (iii) alterations in cardiac contractile proteins and calcium handling; (iv) alterations in myocardial signaling pathways; and (v) alterations in apoptotic, autophagic, and mitophagic pathways. Many of these metabolic and structural changes are an initial attempt to allow the heart to adapt to the underlying etiology causing the heart failure; however, these changes can also result in an adverse remodeling of the myocardium that can

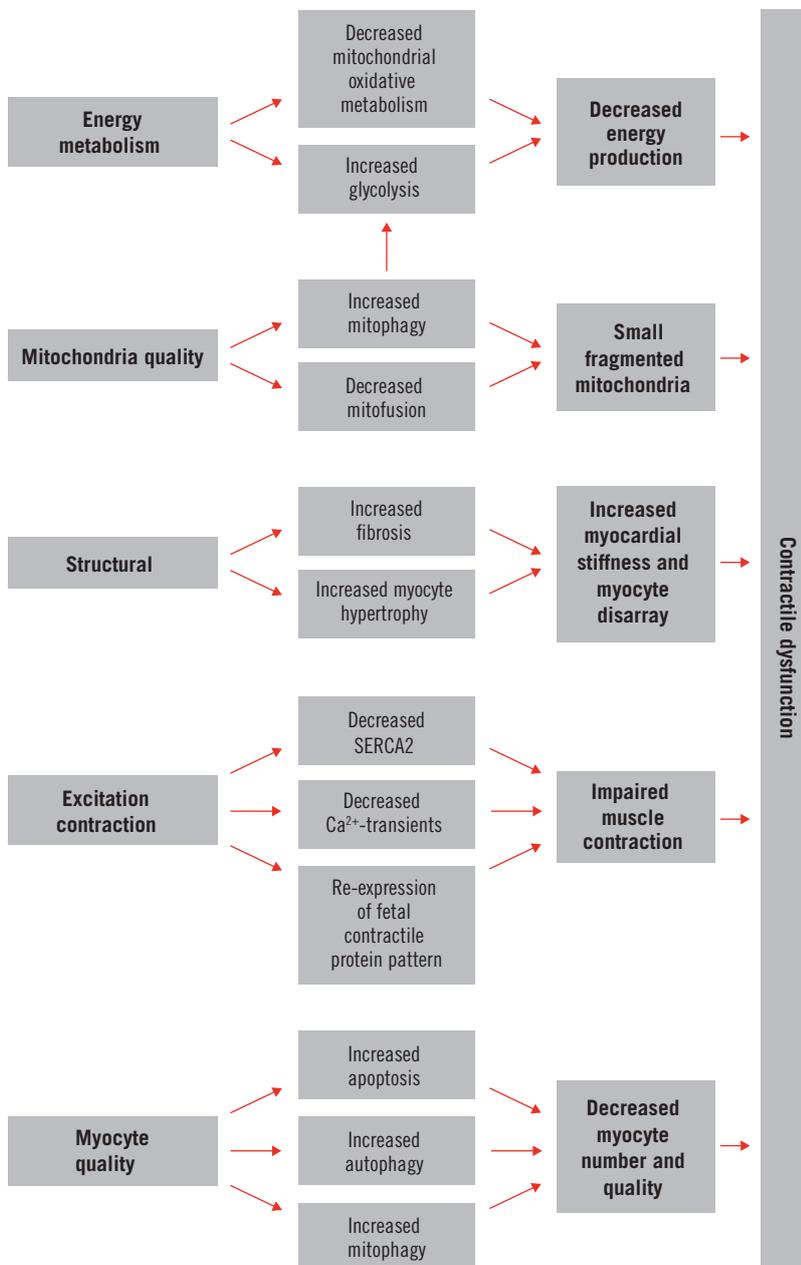
also be maladaptive and contribute to the severity of heart failure. As a result, many of the therapeutic approaches used, or being developed, to treat heart failure are aimed at preventing this adverse remodeling of the failing heart. The goal of this Refresher Corner article is to provide an overview of some of the metabolic and structural changes that occur in the failing heart.

### ***Metabolic remodeling in the failing heart***

Heart failure can result in a significant remodeling of cardiac energy metabolism. Some of this remodeling may be considered “adaptive” remodeling, whereas some may be considered “maladaptive.” A prominent metabolic change that occurs in the failing heart is a decrease in mitochondrial integrity and oxidative function.<sup>1-3</sup> Mitochondrial dysfunction can occur for a

number of reasons, including in response to increased reactive oxygen species production, decreased mitochondrial biogenesis, increased posttranslational modifications such as acetylation, and alterations in mitophagy, mitofusion, and mitofission.<sup>4,5</sup> Impaired mitochondrial function can lead to a decrease in mitochondrial fatty acid and glucose oxidation, which can then impair cardiac energy production.<sup>1-3</sup> Overall oxidative metabolism is impaired in heart failure; however, glucose oxidation is impaired to a greater extent than fatty acid oxidation.<sup>1</sup> The failing heart attempts to increase energy (adenosine triphosphate [ATP])

production independent of mitochondrial metabolism by increasing glucose uptake and glycolysis. The rise in glycolysis primarily occurs via insulin-independent processes, such as by upregulation of glucose transporter 1 (GLUT1), a glucose transporter that is not dependent on insulin. In fact, the failing heart actually becomes insulin resistant, showing a marked decrease in insulin-stimulated glucose metabolism, particularly glucose oxidation.<sup>6</sup> Despite the increase in glycolysis in the remodeled failing heart, only a small amount of ATP is produced compared with mitochondrial oxidative phosphorylation, resulting in



an energy-deficient state. In addition, since pyruvate from glycolysis cannot be adequately metabolized by the mitochondria, it is shunted toward lactate production, with the resultant by-product being an increased proton ( $H^+$ ) production.<sup>1</sup> This can have the negative effect of decreasing cardiac efficiency, which contributes to the energy-starved state of the failing heart.

### **Structural remodeling in the failing heart**

Heart failure is also associated with marked changes in structural remodeling. This can include increased cardiac fibrosis and increased cardiomyocyte hypertrophy (especially under conditions of pressure overload).<sup>7-9</sup> Although increased fibrosis and hypertrophy may initially be an adaptive response, excessive remodeling contributes to the severity of heart failure.

The cellular mechanisms involved in increased cardiac fibrosis in heart failure are numerous and are not yet fully defined. Cardiomyocytes, vascular cells, and fibroblasts are interconnected in the heart via a matrix of fibrillar collagen. In heart failure, collagen deposition increases due to alterations in collagen turnover (increased synthesis and decreased degradation) by myofibroblasts.<sup>8</sup> The

**Fig. 1** Metabolic and structural changes in the failing heart that contribute to contractile dysfunction.

**Abbreviation:** SERCA2, sarcoplasmic reticulum  $Ca^{2+}$ -ATPase.

increased deposition of collagen can be adaptive in the heart during compensatory concentric hypertrophy in order to create a stress-tolerant myocyte scaffold to enhance systolic force generation.<sup>8</sup> However, accumulation of interstitial and perivascular collagen fibers and disruption of the collagen network can contribute to left and right ventricular dysfunction and the development of heart failure.<sup>9</sup> Myocardial fibrosis alters the myocardial architecture, leading to myocyte disarray, as well as mechanical, electrical, and vascular dysfunction. The pathways that control collagen synthesis are complex and involve a number of cell types, including myocytes, myofibroblasts, and macrophage/leukocytes/mast cells, which secrete factors, cytokines, and hormones that trigger and maintain fibrosis. In addition, resistance of collagen to degradation by matrix metalloproteinases also occurs in heart failure, thus favoring matrix expansion.

When cardiac function is reduced in the failing heart, the heart typically remodels and myocyte hypertrophy occurs.<sup>10</sup> Although this hypertrophy may temporarily improve heart function and reduce ventricular wall stress, prolonged cardiac hypertrophy is a strong predictor of arrhythmias, sudden death, dilated cardiomyopathy, and heart failure.<sup>10</sup> Cardiac hypertrophy is initiated by a complex series of signal transduction pathways that are regulated in response to either neuroendocrine factors or mechanical wall tension or stretch-sensing pathways.<sup>11</sup> Neuroendocrine and cytokine hypertrophic signaling includes alterations in  $\beta$ -adrenergic signaling, angiotensin II signaling, aldosterone-receptor signaling, cytokine signaling, and natriuretic peptide signaling. These neuropeptides and cytokines act on multiple receptors and signal second messenger signaling pathways in the myocytes, inducing hypertrophic growth. Receptor and second messenger pathways include, but are not limited to,  $\beta$ -adrenergic receptor activation, angiotensin II receptor activation, natriuretic peptide receptor activation, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) receptor activation, G $_q$ -coupled receptor activation, protein kinase C  $\alpha$  (PKC) activation, mitogen-activated protein kinase (MAPK) kinase signaling pathway activation, increased calcium (Ca<sup>2+</sup>)/calmodulin-dependent kinase II signaling, phosphodiesterase 5 activation, nuclear histone deacetylase activation, and activation of many cardiac nuclear transcription factors that affect cardiovascular stress responsiveness (eg, nuclear factor of activated T-cells [NFAT], myocyte enhancer

factor-2 [MEF2], GATA binding protein 4 [GATA4]).<sup>11</sup> As these complex signaling pathways become better defined, they could provide new pharmacological targets to attenuate the hypertrophic response in heart failure.

### Remodeling of the contractile proteins and calcium handling

Contractile function of the heart is critically dependent on an efficient excitation-contraction coupling, with Ca<sup>2+</sup> being a key mediator of contractile protein function. In heart failure, there are marked defects in this excitation-contraction coupling, including defects in Ca<sup>2+</sup> handling by the cardiomyocytes. Whereas the sarcoplasmic reticulum (SR) ryanodine receptor (RYR) releases Ca<sup>2+</sup> in order to initiate contraction, the SR Ca<sup>2+</sup>-ATPase (SERCA2) is critical in sequestering cytoplasmic Ca<sup>2+</sup> into the SR to mediate muscle relaxation. In the failing heart, decreased expression and activity of SERCA2 and an increased Ca<sup>2+</sup> leak through RyR leads to decreased Ca<sup>2+</sup> transients that result in both reduced and slowed force generation, impaired muscle relaxation, increased potential for arrhythmogenesis, and increased Ca<sup>2+</sup> signaling of the hypertrophic pathway (which includes calcineurin activation).<sup>12</sup> These changes are also associated with upregulation of the sodium (Na<sup>+</sup>)/Ca<sup>2+</sup>-exchanger (NCX1), which is also associated with contractile dysfunction.<sup>13</sup>

Significant changes also occur in the contractile proteins during the development of heart failure. Myosin is a key motor molecule that generates force by cyclic interactions with actin and tropomyosin, and it consists of two myosin heavy chains (MHC) and two regulatory light chains (MLC). In the failing heart, there is a transition from a fast  $\alpha$ -isoform of MHC to a slow  $\beta$ -isoform, resulting in a decrease in contractile velocity.<sup>14,15</sup> Heart failure also induces changes in contractile regulatory proteins. The troponin complex consists of a Ca<sup>2+</sup>-binding protein, troponin C (TnC); an inhibitory protein, troponin I (TnI); and a tropomyosin-binding protein, troponin T (TnT). In the failing heart, TnT shifts to a more fetal isoform (TnT4), which has the potential to impact cardiac contractility. Although shifts in TnI to a more fetal isoform have also been demonstrated in rodent hearts, a similar switch has not been observed in the human heart.<sup>16</sup> Changes in structural proteins, such as titin, can also occur in the

failing heart. In particular, titin, a very large sarcomeric protein important in the elastic recoil of the cardiomyocyte, can switch toward a more fetal isoform, which can lead to increased ventricular stiffness.<sup>17</sup>

### Apoptosis, autophagy, mitophagy, and mitofusion in the failing heart

There are a number of processes in the heart that aim to maintain quality control of the cardiomyocyte. This includes: (i) apoptosis, or programmed cell death, which is a normal physiological process that eliminates DNA-damaged or unwanted cells; (ii) autophagy, a cellular degradation process in which cytoplasmic constituents are recycled by lysosomal enzymes for reuse; (iii) mitophagy, a process where damaged mitochondria undergo selective degradation; (iv) mitofission, a process where mitochondrial fragmentation occurs; and (v) mitofusion, a process where mitochondria fuse to form larger mitochondria. In the failing heart, all of these pathways are adversely altered.

Apoptosis has been extensively studied in the failing heart; in this condition, numerous markers of apoptosis and enzymes identified in the apoptotic pathways have been shown to be upregulated.<sup>17</sup> Although controversial, it is generally believed that excessive apoptosis in the failing heart augments contractile dysfunction and decreases cardiomyocyte numbers in the heart.<sup>18</sup> Autophagy is also upregulated in response to stresses such as heart failure.<sup>19,20</sup> As a result, both apoptosis and autophagy are increased in the failing heart. Although increased autophagy may be an attempt to degrade protein aggregates and defective organelles as part of a protective homeostatic mechanism to maintain cell survival, excessive autophagy may contribute to the pathology of heart failure. It is not clear as to whether autophagy is a sign of failed cardiomyocyte repair or a suicide pathway for failing cardiomyocytes. Mitophagy, which is the selective degradation of mitochondria by autophagy is also accelerated in the failing heart. This may initially be adaptive, serving to remove defective mitochondria following damage or stress. Defective mitochondria may, in part, arise from the increased production of mitochondrial reactive oxygen species that occurs in the failing heart.<sup>21</sup> However, emerging studies suggest that excessive autophagy may also contribute to the severity of heart failure, due to an

excessive loss of mitochondria in the failing heart.<sup>5,20</sup>

Considerable recent interest has focused on the role of mitofission and mitofusion in the control of mitochondrial quality.<sup>5</sup> Mitochondrial fission leads to mitochondrial fragmentation, whereas mitochondrial fusion results in the formation of enlarged mitochondria and in the fusion of damaged mitochondria with healthy organelles. Growing evidence suggests that fusion/fission factors in cardiomyocytes are critical in mitochondrial quality control and cell death. As such, impairment of these pathways can result in cardiomyocyte dysfunction and death, contributing to heart failure. Heart failure can result in small and fragmented mitochondria associated with an increase in the proteins involved in the mitofission pathway.<sup>22</sup> In contrast, mitofusion decreases in heart failure, and the ratio of mitofusion proteins to mitofission proteins decreases.<sup>23</sup> This increase in the rate of mitofission compared with mitofusion may explain the small fragmented mitochondria seen in the failing heart.

### Summary

Dramatic metabolic and structural changes occur in the failing heart. This includes impaired mitochondrial function and oxidative metabolism, which results in an increased reliance of the heart on glycolysis as a source of energy. Increased fibrosis and cardiac hypertrophy are also two common structural changes seen in the failing heart. In addition, remodeling of Ca<sup>2+</sup>-handling and contractile proteins also occurs in heart failure. Accelerated apoptosis, autophagy, mitochondrial reactive oxygen species production, mitophagy, and mitofission also occur in heart failure. Combined, these metabolic and structural changes contribute to the severity of this condition. Thus, targeting these pathways has potential as a therapy to lessen the severity of contractile dysfunction in heart failure. ■

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