

# Reversing subcellular remodelling in the rescue of depressed contractility

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Systolic heart failure with reduced ejection fraction has long been regarded as a heart with an irreversible depression in myocardial contractility. Improvements in ventricular function with recovery of contractility, however, have occurred during a period of cardiac unloading provided by a continuous-flow left ventricular assist device. The authors briefly review subcellular remodelling involved in the appearance of depressed cardiomyocyte

Contractility is the property of cardiac muscle that determines myocyte shortening independent of muscle length before shortening (preload determined) and the load muscle encounters during shortening (afterload determined) (1). For the heart, it has been divided into intrinsic and manifest components (2): intrinsic contractility – a function of cardiomyocyte contractile protein composition and its handling of calcium as it shuttles between intracellular domains; and manifest contractility – determined by substances released within the heart (eg, from adrenergic nerve endings or its myocytes and nonmyocyte cells) or circulating hormones (eg, catecholamines, angiotensin II) and their cognate receptor binding.

Contractility is often expressed as a global measure of the work performed by the myocardium. For example, ejection fraction (EF), or stroke volume displaced from a given end-diastolic volume, is a frequently used index of contractility. Systolic heart failure is suggested when EF falls below the range established for normal hearts. Fallen EF is presumed to imply an irreversibly failing heart – one that would not likely recover over time with or without pharmacological support. However, the recent experience with continuous-flow left ventricular-assist devices (CF-LVAD) suggests otherwise. Following a period of device-induced unloading, depressed EF has improved and remained stable in some patients to enable device removal (destination therapy) (3-5).

The present mini-review addresses subcellular remodelling and its potential for reversal in the rescue of depressed contractility. Dr Naranjan S Dhalla (Winnipeg, Manitoba) and coworkers have contributed substantively to our understanding of subcellular remodelling and its potential for prevention and recovery (vide infra).

## SUBCELLULAR REMODELLING

Contractility is largely a function of subcellular events occurring within cardiomyocytes (6). Studies conducted by Lompre et al (7) and reported in 1979 would draw attention to the dynamic shift between fast (alpha [ $\alpha$ ]) and slow (beta [ $\beta$ ]) myosin heavy chain (MHC) composition when the heart hypertrophied in response to a pressure overload or with hypothyroidism, and that was reflected in a reduced speed and extent of ventricular shortening. Alpert and Mulieri (8) would draw attention to how these responses were, in fact, myothermic adaptations (work performed and heat lost/energy consumed). Gustafson et

work. Redox-sensitive deiodinase 3 (Dio3) is held responsible for a reduction of intracellular thyroid hormone signalling with the re-expression of a fetal gene program that includes slow  $\beta$ -myosin heavy chain. The attendant reduction in contractile work is an adaptation that preserves myocyte efficiency (work/energy consumed) and viability. Neutralizing oxidative stress and Dio3 is integral to the reversal of subcellular remodelling and rescue of depressed contractility.

**Key Words:** *Fetal gene program; Heart failure; Myocardial contractility; Myocyte efficiency; Thyroid hormone signalling*

al (9) would further identify the important role of intracellular thyroid hormone signalling in regulating the ratio of  $\alpha$ -MHC/ $\beta$ -MHC.

The studies conducted by Dhalla et al (10) would reveal the plastic behaviour of subcellular elements that appear in the hypertrophied heart. This included the dynamic nature of the biochemical composition and molecular structure of myocytes based on changes in cardiac gene expression, including shifts between  $\alpha$ - and  $\beta$ -MHC isoforms and downregulation of sarcoplasmic reticulum  $\text{Ca}^{2+}$  ATPase (SERCA2a) in response to diverse stressor states. Ventricular function was determined by events involving these contractile proteins and handling of  $\text{Ca}^{2+}$  and their potential for preventing or reversing such remodelling by pharmacological agents interfering with neurohormonal activation (11-17). The term 'subcellular remodelling' would be coined to identify iterations in intracellular responses that followed acute myocardial infarction, ischemia/reperfusion injury, chemical-induced diabetes, and hypo- or hyperthyroidism. In each of these stressor states, the  $\beta$ -MHC response, or slow phenotype, was upregulated along with a re-expression of the atrial (ANP) and brain (BNP) family of natriuretic peptides, while the fast  $\alpha$ -MHC isoform along with SERCA2a were downregulated. This myocyte dedifferentiation would recapitulate the fetal gene program with a reduction in the speed and extent of contractile work. Consequent depressed indexes of contractility would suggest the myocardium was failing. However, when viewed in terms of myocyte work performed relative to energy consumed, the heart had adapted to preserve its efficiency and myocyte viability.

A further cardioprotective adaptation operative during hyperadrenergic stressor states is the downregulation of positive inotropic  $\beta_1$  and  $\beta_2$  adrenergic receptors, while negative inotropic  $\beta_3$  receptors are upregulated to offset catecholamine excess (18).

Collectively, these protective myocyte transformations occur based on intracellular signalling, which links mitochondrial and nuclear responses with cytosolic events to conserve myocyte energetics.

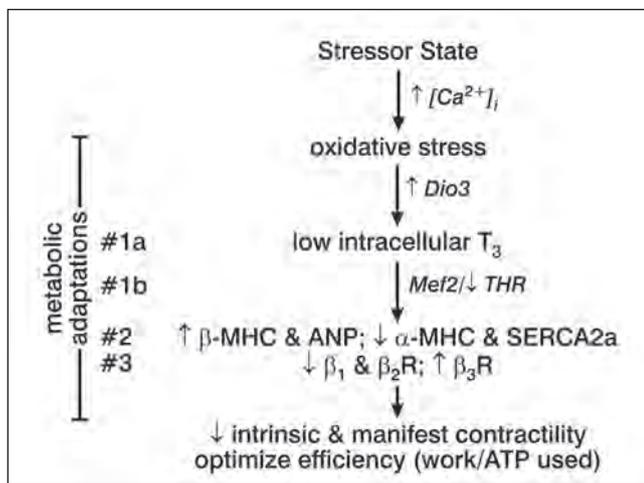
Some have argued the subcellular remodelling that accompanies hypertrophy with reduced contractile work is pathological and increases the risk for heart failure and, accordingly, suggest hypertrophy should be prevented (19-22). The fetal gene program and reduced contractile work of the hypertrophied heart is not equipped to accommodate acute increments in ventricular pressure work imposed by the placement of a constrictive aortic band or infusion of angiotensin II in pressor dosage.

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**Figure 1** A pathophysiological scenario that overviews a common pathophysiological stressor state leading to cardiomyocyte intracellular  $[Ca^{2+}]_i$  overload and oxidative stress with subsequent upregulated deiodinase (Dio)3 activity and resultant subcellular remodelling. This includes low intracellular T3 signalling and cell dedifferentiation with recapitulation of the fetal gene phenotype. Ensuing adaptations (#1 – #3) accompany fetal gene re-expression, including  $\beta$  myosin heavy chain ( $\beta$ -MHC) and atrial natriuretic peptide (ANP) coupled to downregulated  $\alpha$  MHC and SERCA2a, together with  $\beta_1$  and  $\beta_2$  adrenergic and thyroid hormone (TH) receptors (R), while  $\beta_3R$  are upregulated. Collectively, these adaptations eventuate in depressed intrinsic and manifest myocardial contractility with reduced contractile work relative to energy expenditure to optimize myocyte efficiency (see text). Reproduced with permission from Weber KT. Depressed myocardial contractility. Can it be rescued? *Am J Med Sci* 2016 (In press)

The resultant afterload mismatch (23) with reduced shortening and ventricular dilation are cited as further evidence of pathological hypertrophy.

Myocyte hypertrophy and subcellular remodelling, however, are reversible following ventricular unloading such as occurs with the replacement of a stenotic aortic valve (24,25) or constrictive aortic band (26-28), CF-LVAD support (3-5) or with antihypertensive agents (29). Depressed contractility is reversible and, therefore, can be rescued.

### DEIODINASE 3 AND INTRACELLULAR THYROID HORMONE SIGNALLING

Intracellular thyroid hormone (TH) signalling regulates myocyte expression of contractile proteins: high TH favours fast  $\alpha$ -MHC as dominates the normal heart or with hyperthyroidism, while low TH promotes slow  $\beta$ -MHC of the hypertrophied heart or in hypothyroidism (8). Circulating thyroxine (T4) is deiodinated into biologically active triiodothyronine (T3) by deiodinase (Dio)2. A reduction in Dio2 activity, as occurs with the oxidative stress of acute stressor states, creates a low circulating T3 systemic state referred to as the 'sick euthyroid syndrome' (30). Cardiomyocytes, however, have little or no Dio2 and, therefore, are spared intracellular T3 formation with its potential adverse demand on energy consumption.

Deiodinase (Dio3), a deiodinase that converts both T4 and T3 into inactive metabolites, is similarly activated by oxidative stress (31). Dio3 is present in cardiomyocytes, where it protects these cells from incremental T3 and preserves their efficiency; it is considered metabolic adaptation (#1a in Figure 1). Dio3 expression and activity are increased in the hypertrophied ventricle associated with pressure overload and which follows infarction or induction of diabetes (32-34). Low intracellular T3 regulates the re-expression of the fetal gene program in favour of slow  $\beta$ -MHC and downregulated SERCA2a. Low-dose T3 replacement or forced myocyte expression of Dio2 activity will prevent myocyte re-differentiation and decline in contractility (34-36).

Intracellular TH receptor (THR) is physically bound to myocyte enhancing factor (Mef)2 (37); their functional interaction activates  $\beta$ -MHC expression as adaptation (#1b in Figure 1). Forced expression of one of its isoforms (Mef2 a, c or d), together with aortic banding, reduces contractile work and leads to a dilated cardiomyopathy (38-40). THR binding is downregulated in the failing heart (41). Collectively, reduced T3 and THR binding favour  $\beta$ -MHC re-expression with reduced contractile work.

During hyperadrenergic stressor states, catecholamine-driven  $Ca^{2+}$  entry via L type  $Ca^{2+}$  channels is enhanced leading to cytosolic  $[Ca^{2+}]_i$  and mitochondrial  $[Ca^{2+}]_m$  overload in cardiomyocytes (42,43). The ensuing induction of oxidative stress by these organelles leads to myocyte activation of Dio3 to cause low intracellular T3 – a cardiac tissue-specific hypothyroid state that favours adaptation #2 in Figure 1. Concurrent store-operated  $Ca^{2+}$  channel entry with  $Ca^{2+}$  overload and oxidative stress occurs in response to other circulating hormones (eg, angiotensin II) and too may be contributory. Dhalla, et al (44) suggested intracellular  $Ca^{2+}$  overload and oxidative stress represent a common pathophysiological scenario operative in diverse stressor states.

An additional cardioprotective adaptation during hyperadrenergic states is the concordant downregulation of positive inotropic  $\beta_1$  and  $\beta_2$  adrenergic receptors, which account for the reduction in contractile reserve to dobutamine, a  $\beta_1$  agonist (18). Manifest contractility and contractile reserve are further reduced by the upregulation of negative inotropic  $\beta_3$  receptors presented as adaptation #3 in Figure 1 (45).

Collectively, this subcellular remodelling has the potential to be reversed and contractility to be rescued.

### REVERSING SUBCELLULAR REMODELLING

The rescue of depressed contractility draws on reversing molecular signalling and attendant pathophysiological responses. CF-LVAD-induced optimal unloading of the failing heart has, as its objective, the reduction of left ventricular pressure and volume work and, thereby, the regression of hypertrophy and chamber dilation (3-5). A proportional reduction in ventricular mass and chamber volume must be obtained (normal mass/volume ratio 1.3) to avoid increments in systolic wall stress with impaired shortening (46). Reverse remodelling at the organ level includes a regression of fibrosis with its multiple adverse effects on myocardial structure and function (47,48). Reductions in plasma and tissue natriuretic peptides – biomarkers of chamber distention and myocyte dedifferentiation (49) – also occur. Improvements in contractility and myocardial functional recovery with CF-LVAD support have been found in younger patients with nonischemic cardiomyopathy (3-5) and patients with a shorter duration of heart failure (50-52). In addition, recovery in EF has correlated with morphological findings that include smaller myocytes and less fibrosis at the time of device implantation (53,54). Prolonged LVAD unloading and/or body immobilization with bed rest, on the other hand, must be avoided because each favours cardiomyocyte and muscle atrophy, where fetal gene re-expression can be expected (55,56). This finding is accentuated by data that found left ventricular function to already have improved as early as 30 days with the greatest degree of functional recovery within six months of LVAD implantation (4).

A reversal of systemic oxidative stress is essential to recovery and rescue of contractility (57,58). This includes its role in the regulation of Dio2 and Dio3 deiodinases, with respective low T3 at systemic and cardiomyocyte levels. Enhancing endogenous antioxidant defenses can be used to attenuate redox stress (59-61). Pharmacological blockade of effector hormones of the activated renin-angiotensin-aldosterone and adrenergic nervous systems must also be addressed.

### SUMMARY

Based on subcellular remodelling and myocyte adaptations, indexes of contractility will be reduced in the failing heart. Dedifferentiation of hypertrophied myocytes driven by low intracellular T3 signalling with re-expression of slow  $\beta$ -MHC coupled to downregulation of  $\alpha$ -MHC

and SERCA2a is integral to these adaptations; so too is the concordant downregulation of  $\beta_1$  and  $\beta_2$  adrenergic and TH receptors with upregulation of negative inotropic  $\beta_3$  receptors. These adaptations are invoked to preserve myocyte efficiency and, thereby, viability. Attendant reductions in subcellular remodelling with depressed indexes of myocardial contractility, however, can be rescued by antioxidants and a period

of ventricular unloading, whose optimal duration will likely need to be determined for each patient.

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