SPECIAL FEATURE

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Depressed Myocardial Contractility: Can It Be Rescued?

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ABSTRACT

Current dogma suggests patients with advanced systolic heart failure have an irreversible depression in myocardial contractility. Recent experience with improved ventricular function during continuous flow ventricular assist devices used as destination therapy would suggest otherwise. Herein, cellular and molecular signaling involved in reversing depressed myocardial contractility would be addressed. This includes cardiomyocyte thyroid hormone signaling responsible for the reexpression of fetal gene program that preserves cell efficiency (work and energy consumed) and the rescue of an endogenous population of atrophic myocytes bordering on microdomains of fibrosis to improve contractile mass.

Key Indexing Terms: Heart failure; Myocardial contractility; Thyroid hormone signaling; Fetal gene program; Rescue atrophic myocytes. **[Am J Med Sci 2016;▮(▮):▮▮▮–▮▮▮.]**

INTRODUCTION

Heretofore, patients with advanced systolic heart failure have been viewed as having an irreversible depression of myocardial contractility presenting as markedly reduced ejection fraction (EF) and absent contractile reserve to dobutamine, a β_1 adrenergic receptor agonist. Recent experience with continuous flow assist devices, used as destination therapy (vis-à-vis as a bridge to cardiac transplantation), challenges this dogma. In some of these patients, EF has improved and the dimensions of their enlarged left ventricular chamber have declined after a period of cardiocirculatory support to suggest a rescue of contractility and which persisted to allow device removal and patient recovery.[1-3] Patients with spontaneous recovery in EF, absent circulatory assist, have also been identified as a distinct clinical phenotype.[4,5] Whether this response represents true recovery from heart failure vs. remission of ventricular function despite ongoing oxidative stress, neurohormonal activation, and myocyte necrosis with continued adverse clinical events is uncertain. This brief review addresses the cellular and molecular signaling upon which depressed contractility could be rescued, including reversal of oxidative stress and neurohormonal activation, together with revised cardiomyocyte thyroid hormonal signaling and the expression of the fetal gene program it regulates. In addition, the prospect is raised of improving contractile mass through the rescue of an endogenous population of atrophic myocytes found bordering on microdomains of fibrosis.

MYOCARDIAL CONTRACTILITY DEFINED

In elegant studies, conducted by Sonnenblick[6] some 50 years ago using isolated strips of cardiac muscle, contractility was identified as that property where the velocity and extent of shortening are independent of (a) preload determined muscle length before shortening and (b) the load encountered during shortening, or afterload. An increment or decline in contractility were respectively termed positive and negative inotropic responses.

In 1968, Harrison and Reeves[7] advanced the concept of cardiac muscle contractility to the intact myocardium with its: (i) a contractile assembly of myofibers each consisting of cardiomyocytes aligned in series with one another—forming a syncytium of cells—and whose synchronized contraction is facilitated by intercellular signaling; and (ii) adrenergic nerve endings whose release of stored catecholamines and their cognate β_1 adrenergic receptor-ligand binding can alter contractility. As they envisaged it, contractility had 2 components: *intrinsic contractility*, encompassed the maximal force generated from a given myofiber length as determined by cardiomyocyte α and β myosin contractile protein composition, together with the availability and handling of intracellular $[Ca^{2+}]_i$; and superimposed upon which was *manifest contractility*, governed by locally released or circulating substances (*vide infra*).

Over the years, various indices have been used to assess and quantify contractility. Early on, a theoretical model of cardiac muscle consisting of a contractile element aligned in series and in parallel with elastic elements was used to calculate the maximum velocity of contractile element shortening extrapolated to zero afterload.[6] For the intact heart, the peak rise in developed left ventricular pressure with respect to time during the isovolumic contraction period, before ejection, was monitored.[8] Later on, the end-systolic stress-length relation was used and where stress is the force exerted per cross-sectional area of myocardium with systolic force a product of instantaneous systolic pressure and chamber radius.[9] Echocardiographic-derived load-independent end-systolic indices of contractility were used in the assessment of cardiac transplantation and to

monitor the progressive nature of hypertensive heart disease.[10,11] In assuming the left ventricle to be a truncated ellipse, calculated meridional and circumferential systolic wall stresses were employed in the comparison of ventricular function between hearts of different size and shape.[12] Today, speckle tracking echocardiography is used to derive longitudinal and circumferential strains and strain rates in the assessment of contractility.[13]

DEPRESSED CONTRACTILITY

Intrinsic contractility can decline acutely. Such occurs with the necrotic and apoptotic loss of cardiomyocytes attendant with myocardial infarction. A fall in manifest contractility can also appear acutely mediated by the synergistic action of negative inotropic proinflammatory cytokines (e.g., TNF-1, IL-1β, and IL-6) released by cardiomyocytes via the redox-sensitive p38 mitogen-activated protein kinase/c-Jun N-terminal kinases/nuclear factor κB pathway in response to burn trauma or sepsis.[14] The autocrine action of these myocardial depressant factors appears within hours of the acute stressor state and can last for days; gradual recovery generally follows. Negative inotropic responses may also be elicited by cytokines emanating from outside the heart, such as when the gut's large immune system is activated.[15]

A more gradual depression in intrinsic contractility accompanies myocyte hypertrophy, which appears with chronic pressure overload (e.g., aortic stenosis or arterial hypertension). Concordant with incremental protein synthesis attendant with hypertrophy are energy-sparing responses accounting for a decline in the rate and extent of myocyte force development. Termed myocyte dedifferentiation, these responses consist of a shift in myosin isoform composition to preserve cell efficiency (contractile work relative to oxygen consumption) (vide infra).[16,17] Oncostatin, a cytokine of the IL-6 family, is a mediator of myocyte dedifferentiation.[18] These protective myocyte transformations occur based on intracellular signaling which links mitochondrial and nuclear responses with cytosolic events.[19] Included here is the fetal gene phenotype consisting of the reexpression of slow β-myosin heavy chain (MHC) and atrial natriuretic peptide (ANP) coupled to the downregulation of the fast α-MHC and sarcoplasmic reticulum Ca^{2+} ATPase (SERCA)2a involved in Ca^{2+} homeostasis integral to myocyte contraction. Positive inotropic β_1 and β_2 adrenergic receptors are downregulated whereas negative inotropic β_3 receptors are upregulated. Collectively, myocyte energetics are conserved.[20]

Some have considered these responses as physiologic metabolic adaptations (Figure 1). When persistent, however, they can be pathophysiologic particularly when hypertrophied, β-MHC dominant myocytes are confronted with a pressure overload. Termed an afterload mismatch, it can be invoked experimentally with the placement of a constrictive aortic band or clinically with the graded

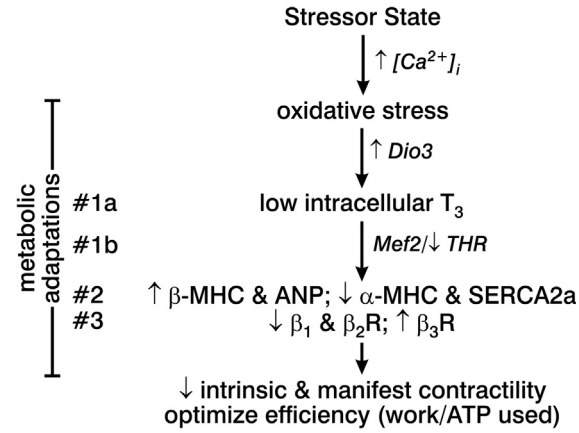

FIGURE 1. A prospective pathophysiologic scenario which overviews hyperadrenergic stressor state-induced events leading to cardiomyocyte intracellular $[Ca^{2+}]_i$ overload and oxidative stress, upregulated deiodinase (Dio)3 activity with resultant low intracellular T_3 signaling, and subsequent dedifferentiation. Ensuing metabolic adaptations (#1-3) with fetal gene reexpression includes β-MHC and ANP coupled to downregulated α-MHC and SERCA2a, together with β_1 and β_2 adrenergic receptors (R), whereas β_3R is upregulated. These collective adaptations eventuate in depressed intrinsic and manifest myocardial contractility with reduced contractile work relative to energy expenditure that serve to optimize myocyte efficiency.

infusion of vasopressor doses of angiotensin II.[21] The ensuing reduction in left ventricular shortening leads to chamber enlargement and what can ultimately be interpreted as a dilated cardiomyopathy. This notwithstanding, these myocyte responses are reversible and stand in sharp contrast to the irreversible structural remodeling of the infarcted heart with the loss of necrotic cardiomyocytes and their replacement by scar tissue. There also exists the potential to rescue contractility by augmenting contractile mass through the recruitment of an endogenous population of viable, atrophied myocytes, ensnared by stiff collagen fibrils at sites of fibrosis (vide infra).[22,23]

THYROID HORMONE SIGNALING AND METABOLIC ADAPTATIONS

Intracellular thyroid hormone (TH) signaling regulates myocyte expression of contractile proteins: high TH favors fast α-MHC whereas low TH promotes slow β-MHC.[24] Thyroxine (T_4) is deiodinated into biologically active triiodothyronine (T_3) by deiodinase (Dio)2 found in liver and kidneys. A reduction in Dio2 activity, as occurs with oxidative stress of acute stressor states, creates a systemic low T_3 state referred to as the sick euthyroid syndrome.[25] Cardiomyocytes have little or no Dio2, and therefore are spared intracellular T_3 formation with its adverse incremental demand on oxygen consumption.

Dio3 is a deiodinase that converts both T_4 and T_3 into inactive metabolites. Dio3 is present in cardiomyocytes. It is activated by oxidative stress via the p38 MAPK pathway.[26] Dio3 protects myocytes from T_3 and thereby preserves their