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## **Is Depressed Myocyte Contractility Centrally Involved in Heart Failure?**

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This Review is part of a thematic series on **Unanswered Questions in Heart Failure**, which includes the following articles:

Is Depressed Myocyte Contractility Centrally Involved in Heart Failure?

What Causes Sudden Death in Heart Failure?

Is Abnormal Cell Growth and Hypertrophy the Cause of Heart Failure?

Does Energy Starvation Cause Heart Failure?

What Is the Role of Altered  $\beta$ -Adrenergic Signaling in Heart Failure?

What Mechanisms Underlie Diastolic Dysfunction in Heart Failure?

*Steven Houser, Guest Editor*

## Is Depressed Myocyte Contractility Centrally Involved in Heart Failure?

Steven R. Houser, Kenneth B. Margulies

**Abstract**—This review examines the evidence for and against the hypothesis that abnormalities in cardiac contractility initiate the heart failure syndrome and drive its progression. There is substantial evidence that the contractility of failing human hearts is depressed and that abnormalities of basal  $\text{Ca}^{2+}$  regulation and adrenergic regulation of  $\text{Ca}^{2+}$  signaling are responsible. The cellular and molecular defects that cause depressed myocyte contractility are not well established but seem to culminate in abnormal sarcoplasmic reticulum uptake, storage, and release. There are also strong links between  $\text{Ca}^{2+}$  regulation,  $\text{Ca}^{2+}$  signaling pathways, hypertrophy, and heart failure that need to be more clearly delineated. There is not substantial direct evidence for a causative role for depressed contractility in the initiation and progression of human heart failure, and some studies show that heart failure can occur without depressed myocyte contractility. Stronger support for a causal role for depressed contractility in the initiation of heart failure comes from animal studies where maintaining or improving contractility can prevent heart failure. Recent clinical studies in humans also support the idea that beneficial heart failure treatments, such as  $\beta$ -adrenergic antagonists, involve improved contractility. Current or previously used heart failure treatments that increase contractility, primarily by increasing cAMP, have generally increased mortality. Novel heart failure therapies that increase or maintain contractility or adrenergic signaling by selectively modulating specific molecules have produced promising results in animal experiments. How to reliably implement these potentially beneficial inotropic therapies in humans without introducing negative side effects is the major unanswered question in this field. (*Circ Res.* 2003;92:350-358.)

**Key Words:** heart failure ■  $\text{Ca}^{2+}$  regulation ■ contractility ■ hypertrophy ■ adrenergic regulation

Heart failure is a syndrome with many different well-described causes, including myocardial infarction, valve diseases, and hypertension.<sup>1</sup> Those processes that cause a heart which is initially able to compensate for disease-induced hemodynamic overload to decompensate and fail are not well understood. This article is the first in a review series that is designed to identify and discuss important unanswered questions in heart failure. The hope is that these questions

will stimulate thinking and research will lead to novel approaches to prevent, slow, or reverse the course of this syndrome.

Heart failure develops when the amount of blood pumped from the heart is inadequate to meet the metabolic demands of the body.<sup>2</sup> In its early stages, there is a reduction in exercise capacity, but as the syndrome progresses, the heart is eventually unable to pump a sufficient quantity of blood to

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meet the normal metabolic needs of the tissues, even at rest.<sup>1,3</sup> It is also well appreciated that treating heart failure patients with drugs (such as cardiac glycosides) that augment pump function by increasing the contractility of cardiac myocytes can improve hemodynamics and exercise tolerance.<sup>4</sup> These early observations led to the “hemodynamic hypothesis” that heart failure is primarily caused by defective cardiac myocyte contractility. The purpose of this review is to identify and discuss unanswered questions (listed below) related to this hypothesis.

### Is Myocyte Contractility Abnormal in Heart Failure?

Poor pump function of the heart does not have to be the result of fundamental defects in myocyte contractile properties. The traditional hemodynamic hypothesis is that diseases that increase the hemodynamic burden of the heart ultimately cause heart failure by inducing defects in myocyte contractility.<sup>1</sup> It is important for us to point out that other factors (changes in cardiac structure (dilatation),<sup>5,6</sup> cell death (apoptosis),<sup>7</sup> altered vascular structure and reactivity,<sup>1</sup> abnormal energy utilization, and neurohormonal disturbances<sup>8–10</sup> also contribute to the progression of heart failure, at least under certain conditions. All of these processes are likely to contribute to the poor pump performance of the failing human heart and may do so independent of defective myocyte contractility.<sup>5–10</sup>

The idea that myocyte contractility is depressed in the failing heart is supported by most,<sup>2,11–14</sup> but not all,<sup>15</sup> studies. Importantly, it is now clear that myocyte contractility must be evaluated over a broad range of conditions (varying muscle length, loading conditions, beating frequency,  $[Ca^{2+}]$ , and [sympathetic amines]) because contractile properties (such as peak isometric force in isolated muscle strips) can be similar in normal and failing muscles under basal conditions, whereas their responses to inotropic stimuli (rate,  $[Ca^{2+}]$ , increased preload, and catecholamines) are very different.<sup>11–14</sup> The force-generating capabilities of ventricular muscle strips from normal and failing human hearts are similar at low inotropic state (slow pacing rates, low  $[Ca^{2+}]$ , no catecholamines).<sup>11,12</sup> However, as the beating rate increases, the rate and magnitude of developed force increase in normal muscles but developed force decreases or remains unchanged in failing muscles.<sup>16–18</sup> Therefore, rate-related contractile reserve is absent or significantly reduced in failing human myocardium. Likewise, the ability of adrenergic agonists to increase the contractility of the failing heart is significantly blunted.<sup>19</sup> These studies show that at least in the end-stage failing human heart, basal contractility is well preserved but “contractility reserve” (the ability to increase contractility with heart rate or sympathetic stimulation) is severely depressed. These fundamental changes in muscle performance and regulation can explain the poor pump function, reduced exercise capacity, and tachycardia intolerance of the failing human heart.<sup>20,21</sup>

### What Is the Role of Abnormal Adrenergic Regulation of Contractility in Heart Failure?

A characteristic feature of the failing human heart is blunted adrenergic effects on myocyte contractility.<sup>10,22–24</sup> In the

normal human heart, activation of the sympathetic nervous system is the primary mechanism to increase myocyte contractility when demand for cardiac output increases (exercise, fight-or-flight response).<sup>2,10</sup> The cellular basis of adrenergic-mediated increases in contractility are well known and involve binding of adrenergic amines to  $\beta$ -adrenergic receptors and the subsequent activation of adenylate cyclase, increased production of cAMP, activation of protein kinase A (PKA), PKA binding to A-kinase anchoring proteins (AKAPs),<sup>25,26</sup> and phosphorylation of  $Ca^{2+}$  regulatory proteins such as phospholamban (PLB), L-type  $Ca^{2+}$  channels, the  $Ca^{2+}$  release channel (ryanodine receptor; RYR), and troponin.<sup>19,27,28</sup> Activation of the  $\beta$ -adrenergic signaling pathway causes an increase in  $Ca^{2+}$  influx, an increase in  $Ca^{2+}$  transport rate, and storage by the sarcoplasmic reticulum (SR), and a decrease in the  $Ca^{2+}$  binding affinity of troponin. These changes cause an increase in the amplitude of the systolic  $Ca^{2+}$  transient and a decrease in its duration. The net effect is an increase in the rate and magnitude of force (pressure) generation and an increase in the rate of relaxation.<sup>29</sup>

The factors leading to abnormal adrenergic signaling in heart failure are well studied and understood. The poor pump performance of the failing heart produces a reflex-mediated, sustained increase in sympathetic activity to maintain blood pressure.<sup>2</sup> It is the persistence of the increased adrenergic activity that induces significant changes in  $\beta$ -adrenergic signaling.<sup>22,24</sup> In the failing human heart, reduced  $\beta_1$  receptor density and uncoupling of  $\beta_2$  receptors from downstream effector molecules reduce the consequences of sympathetic amines on  $Ca^{2+}$  regulatory target proteins<sup>23,24</sup> and thereby limit inotropic responsiveness. Beyond the level of reduced cAMP production, adrenergic signaling abnormalities in the failing heart also include defects in the AKAPs that help target cAMP to effector proteins.<sup>30</sup> Together, these changes reduce the ability of the failing heart to increase contractility in proportion to hemodynamic demands. What is still not known and remains an important unanswered question is whether adrenergic signaling abnormalities are an adaptive response to prevent overstimulation of the pathway or a maladaptive change that depresses contractility reserve and initiates decompensation and drives heart failure progression.

### Is Abnormal $Ca^{2+}$ Handling the Cause of Depressed Myocyte Contractility in Heart Failure?

There is substantial evidence supporting a role for changes in myocyte  $Ca^{2+}$  regulation as a central feature in the altered contractility of the failing heart.<sup>11,13</sup> Decreased peak systolic  $Ca^{2+}$  with prolongation of the duration of the  $Ca^{2+}$  transient can explain the systolic defects such as reduced force-generating capacity and slower rates of force decay that characterize the failing heart.<sup>12,16,31–33</sup> Slower rates of SR  $Ca^{2+}$  uptake and changes in the multiple determinants of  $Ca^{2+}$  efflux via the  $Na^+$ - $Ca^{2+}$  exchanger (including increased intracellular  $Na^+$ <sup>17,34</sup> and changes in action potential shape and duration<sup>12,35</sup>) produce rate-dependent elevation in diastolic  $Ca^{2+}$  and thus explain certain diastolic defects in the failing heart.<sup>33,36</sup>

In spite of significant research, the molecular basis of abnormal  $\text{Ca}^{2+}$  regulation in the failing human heart is still an unanswered question. Alterations in the abundance and/or activity of numerous  $\text{Ca}^{2+}$  regulatory proteins including the SR  $\text{Ca}^{2+}$  ATPase (SERCA),<sup>11</sup> L-type  $\text{Ca}^{2+}$  channels (LTCCs),<sup>37,38</sup> the ryanodine receptor,<sup>39,40</sup> the  $\text{Na}^+$ - $\text{Ca}^{2+}$  exchanger,<sup>11,41–43</sup> and the  $\text{Na}^+$ , $\text{K}^+$ -ATPase<sup>44</sup> have all been associated with abnormal  $\text{Ca}^{2+}$  regulation in heart failure. However, the functional consequences of each of these abnormalities in the initiation and progression of heart failure are largely unresolved.

SR function appears to be abnormal in the failing human heart.<sup>11,45</sup> Slow net  $\text{Ca}^{2+}$  uptake by the SR would cause the slow decay of the  $\text{Ca}^{2+}$  transient and the reduced SR  $\text{Ca}^{2+}$  storage and release that are found in failing myocytes.<sup>16,32,46</sup> An important unanswered question is the molecular basis for abnormal SR  $\text{Ca}^{2+}$  uptake and release. A reduction in the abundance or activity of SERCA could explain the observed abnormalities in SR function.<sup>11,14</sup> However, SERCA abundance (or  $\text{Ca}^{2+}$  uptake rate) can be normal in failing hearts with depressed contractility,<sup>13,47,48</sup> suggesting critical abnormalities in the function of other molecules that regulate SR function. Decreases in PLB phosphorylation in the failing human heart<sup>11</sup> could disrupt normal SR function or could exacerbate the effect of decreased SERCA abundance. There is also evidence that an increase in  $\text{Ca}^{2+}$  efflux, caused by increased NCX activity,<sup>36,41,42,49</sup> could reduce SR  $\text{Ca}^{2+}$  loading and SR  $\text{Ca}^{2+}$  release.

An unphysiologically high rate of  $\text{Ca}^{2+}$  leak from the SR, caused by an abnormally high phosphorylation state of the  $\text{Ca}^{2+}$  release channel (RyR),<sup>39,40,50,51</sup> could also reduce SR  $\text{Ca}^{2+}$  content and release and net SR  $\text{Ca}^{2+}$  uptake rate. The RyR channel is usually closed during diastole, and this allows the  $\text{Ca}^{2+}$  transported into the SR by SERCA to accumulate in the junctional SR<sup>52</sup> until activation by the L-type  $\text{Ca}^{2+}$  current causes SR  $\text{Ca}^{2+}$  release.<sup>53</sup> Recent studies suggest that RyR phosphorylation is increased in human heart failure and that this “hyperphosphorylation” increases the RyR open probability to cause a persistent leak of  $\text{Ca}^{2+}$  from the SR.<sup>39,40,50,51</sup> Whether this controversial<sup>54,55</sup> defect is present in failing human hearts is an important unanswered question because a persistent SR  $\text{Ca}^{2+}$  leak would reduce the ability of the SR to store  $\text{Ca}^{2+}$  and could explain many of the systolic and diastolic abnormalities of the failing heart.

There is also evidence for a reduction in the density and an increased level of phosphorylation of the L-type  $\text{Ca}^{2+}$  channels<sup>38</sup> and a reduction in T-tubule density in heart failure.<sup>37</sup> These abnormalities would reduce both the magnitude and homogeneity of SR  $\text{Ca}^{2+}$  release and should contribute to depressed myocyte contractility.

The studies discussed above show that the abundance, localization, and phosphorylation state of critical  $\text{Ca}^{2+}$  regulatory proteins can be abnormal in failing myocytes. Important unanswered questions are which of these abnormalities are routinely present in human heart failure, what are their causes, and how can they be corrected. We will argue below that the abundance and phosphorylation state of these  $\text{Ca}^{2+}$  regulatory proteins are targets for novel inotropic therapy in the failing human heart. This idea is supported by those

observations suggesting that the beneficial effects of  $\beta$ -blockers on cardiac performance<sup>56,57</sup> and survival<sup>58</sup> may result from improving cardiac contractility and that this effect may occur by correcting abnormalities and imbalances of  $\text{Ca}^{2+}$  regulatory protein abundance, phosphorylation, and function.<sup>57,59</sup>

### **Do Contractile Proteins Contribute to Depressed Contractility in Heart Failure?**

The abundance, isoform type,<sup>60–62</sup> and phosphorylation of thin- and thick-filament contractile proteins are significant determinants of the contractile properties of the heart. Abnormalities in the structure<sup>63</sup> and function<sup>64</sup> of these molecules are likely to be involved in depressed contractility in heart failure.<sup>62,65–67</sup> However, the specific role(s) of changes in myosin isoforms<sup>60,68,69</sup> and alterations in thin-filament isoforms and their phosphorylation<sup>66,70,71</sup> state in the initiation of heart failure and its progression<sup>66</sup> are not well known and are important unanswered questions for the future.

### **Is Abnormal Myocyte Contractility a Cause of or an Effect of Heart Failure?**

Studies with a longitudinal design, where contractility can be measured at critical times during the progression from normal or compensated hypertrophic states to heart failure, are required to test this question. These are not easily performed in humans.<sup>59</sup> Therefore, most of the evidence for or against a causative role for depressed contractility in the transition to heart failure or in heart failure progression comes from experiments in small animal models.<sup>72</sup> Studies using an aortic constriction model in rats and mice<sup>73,74</sup> strongly support the hypothesis that depressed contractility induces the transition from compensated hypertrophy to heart failure and that the depressed contractility is caused by abnormal  $\text{Ca}^{2+}$  regulation. Similar results have been observed in some larger animal models and in humans.<sup>75–77</sup>

Studies in transgenic mouse models of heart failure show that abnormalities of *in vivo* cardiac function are closely associated with the evolution of the heart failure phenotype, particularly in those animals expressing mutated forms of contractile proteins that cause hypertrophic cardiomyopathies in humans.<sup>62,67</sup> Unfortunately, the role of the acquisition of depressed myocyte contractility as a pivotal factor in the transition to heart failure has not been well addressed<sup>78</sup> in most of these studies. Although reduced cardiac function has been shown with echocardiography, a specific role for depressed myocyte contractility versus changes in other determinants of *in vivo* function (sympathetic activity, altered ventricular geometry, and/or myocyte death) has not been well established.<sup>79–81</sup> In those mouse studies that have specifically evaluated myocyte contractility, experiments have usually been performed after heart failure has occurred and thus do not address the issue of cause and effect. Along these lines, a recent study showed that mice with genetically induced reductions in SERCA expression have modest abnormalities in myocyte contractility.<sup>82,83</sup> It will be interesting to see whether these animals are more prone to heart failure after hemodynamic stress.

Strong evidence supporting a pivotal role for  $\text{Ca}^{2+}$  regulation and altered cardiac contractility in the initiation and progression of heart failure comes from studies in which the evolution of heart failure (in animal models) was slowed,<sup>84,85</sup> reversed,<sup>78,86,87</sup> or prevented<sup>88</sup> by treatments (genetic or drugs) that modify contractility or alter  $\text{Ca}^{2+}$ -dependent (calcineurin<sup>89</sup>) signaling pathways. These experiments support an association between the transition to heart failure and the development of  $\text{Ca}^{2+}$ -dependent contractility defects and show proof of concept that abnormalities of contractility ( $\text{Ca}^{2+}$  regulation or myofibrillar mutations) can cause heart failure.<sup>90</sup> However, these studies do not prove that contractility defects are an important cause or necessary feature of heart failure progression in common forms (such as after myocardial infarction) of this syndrome in humans. It is anticipated that answers to these unanswered questions will be obtained soon because techniques to induce controllable defects in cardiac myocyte contractility are now available. Conditional transgenesis in mice would be one approach that should provide important new data.<sup>91</sup> However, because the regulation of contractility is so fundamentally different in large and small animals,<sup>12,92</sup> techniques to induce controllable defects in cardiac contractility in larger animals are also needed. Gene transfer techniques should be useful in this regard.<sup>85,86,88,93,94</sup>

Importantly, there are studies in animal models that show that heart failure can develop in the absence of depressed  $\text{Ca}^{2+}$  regulation and with normal or even increased basal myocyte contractility. Myocytes from transgenic mice with heart failure (MLP-KO,<sup>95</sup> overexpression of an activated calcineurin<sup>96</sup>) have increased rather than depressed  $\text{Ca}^{2+}$  transients at a time when pump function is depressed. We suggest that  $\text{Ca}^{2+}$  transients and contractility are increased in these animals in response to a primary genetically induced defect (MLP deficiency or constitutive activation of calcineurin), but that this compensatory response is not sufficient to prevent the development of heart failure. Related observations in failing human myocardium also suggest that heart failure is not always associated with abnormal contractility. For example, in heart failure from acute mitral regurgitation or acute myocardial infarction, pump failure is clearly present, but the function of viable myocytes is almost surely intact or supranormal.<sup>97</sup> By analogy, in progressive pressure overload, it may well be that myocytes with normal or supranormal contractility cannot overcome a truly excessive demand leading to failure at the organ level (perhaps due to an inadequate degree of hypertrophy) with no contractility defect at the cellular level. Indeed, some studies in cells and muscle strips from severely failing hearts obtained at the time of cardiac transplantation have failed to observe marked abnormalities in  $\text{Ca}^{2+}$  regulation and cardiac contractility, at least under basal conditions.<sup>11,12</sup> Further evidence supporting the possibility that reduced contractility is an effect, rather than a cause, of heart failure comes from clinical trials showing delayed improvements in cardiac contractility in some patients after pharmacological interventions (eg, vasodilators or  $\beta$ -adrenergic antagonists)<sup>98–101</sup> that are not positive inotropic and may even depress cardiac function initially.<sup>101</sup>

Our interpretation of the studies summarized above is that depressed myocyte contractility is usually sufficient but is not always necessary to induce heart failure. The demonstration that depressed myocyte contractility can be either a cause or an effect of heart failure raises the very real prospect that progression of the heart failure syndrome is a reciprocating pathological dynamic. For example, some adaptations to increased demand, including cardiac dilation and vasoconstriction, may drive contractile defects, and contractile defects in turn may induce pathological adaptations, irrespective of which came first. We conclude that whether abnormal contractility plays a causative role in the initiation or progression of human heart failure is still an important unanswered question.

### Is Contractility a Good Target for Heart Failure Therapy?

An underlying theme of heart failure research is that if we could define the cellular and molecular defects that initiate heart failure or drive its progression, we could fix them and thereby improve the course of the disease. This general approach has led to the development of inotropic drugs for improving the pump performance of the failing heart. A large number of clinical trials with various inotropic drugs have been conducted over the past 10 years.<sup>102</sup> We will not review these trials here but will simply state that most available data from properly powered studies indicate that inotropic therapy increases rather than decreases mortality.<sup>102</sup> The exception is cardiac glycosides, relatively weak inotropes that improve symptoms but neither increase nor decrease mortality among patients with more advanced degrees of congestive heart failure.<sup>103,104</sup>

Somewhat more encouraging results concerning the desirability of increasing contractility come from studies of animal models, which are prone to developing heart failure.<sup>72</sup> Studies in rats have shown that adenovirus-mediated transfer of SERCA (which should increase contractility by increasing SR  $\text{Ca}^{2+}$  uptake) reduces the contractile dysfunction that develops after pressure overload<sup>88,105</sup> and during aging.<sup>85</sup> Genetically engineered mice that overexpress SERCA also were protected from the damaging effects of aortic constriction.<sup>106</sup> Studies in mice show that when animals with genetically induced increases in contractility are bred with others that normally develop heart failure,<sup>107</sup> cardiac function can be “rescued.” When the MLP-KO mouse, which normally develops heart failure,<sup>107</sup> is crossed with either the hypercontractile PLB-KO<sup>108</sup> or a mouse expressing a protein that prevents adrenergic signaling defects by reducing the activity of  $\beta$ -adrenergic receptor kinase ( $\beta$ ARK-ct),<sup>109</sup> heart failure does not develop. Other examples of this type of genetic “rescue” have been reported.<sup>110</sup> A related recent study<sup>111</sup> on this topic showed that a persistently phosphorylated form of PLB (to increase contractility by stimulating the activity of SERCA) introduced via gene transfer prevented heart failure in a cardiomyopathic hamster. These studies show that improving contractility by increasing the abundance<sup>112</sup> or activity<sup>28</sup> of specific  $\text{Ca}^{2+}$  regulatory proteins or by improving adrenergic signaling<sup>113,114</sup> can prevent or delay the develop-

ment of heart failure, suggesting that successful heart failure prevention requires maintenance of contractility.

These new animal studies should be interpreted cautiously because the “treatments” were usually given before heart failure was established. Therefore, an important question is whether these same approaches would be successful if they were initiated after the heart failure phenotype was established. It is also important to point out that crossbreeding heart failure and hypercontractile animals did not always rescue heart failure phenotypes. When  $\beta$ ARK-ct mice, which has rescued other mouse heart failure models,<sup>113,115</sup> were crossed with a CREB-KO heart failure<sup>116</sup> mouse, contractility and adrenergic signaling defects were largely eliminated but heart failure still developed.<sup>117</sup> These findings show that in mice (and perhaps in humans) not all forms of heart failure can be prevented by increasing contractility or by improving adrenergic signaling.<sup>114</sup> Moreover, in some circumstances, overstimulation of the adrenergic signaling can cause or exacerbate the heart failure.<sup>114,118,119</sup>

Despite these caveats, our interpretation of the composite body of animal “rescue” studies is that increasing or maintaining contractility at critical times before or just after injurious cardiac stimuli can delay or eliminate heart failure. The applicability of these approaches to humans is an important unanswered question because inotropic interventions have rarely, if ever, been examined in the setting of presymptomatic cardiac dysfunction.

### **Does Overstimulation of Ca<sup>2+</sup>-Mediated Hypertrophic Signaling Cause Heart Failure?**

A link between Ca<sup>2+</sup> regulation and cardiac hypertrophy has been clearly established.<sup>90</sup> Activation of the Ca<sup>2+</sup>-dependent phosphatase, calcineurin, can induce hypertrophy, and overstimulation of this pathway can lead to heart failure.<sup>86,89,120–122</sup> These studies suggest that the same increases in cytosolic Ca<sup>2+</sup> required to maintain cardiac function during hemodynamic overload also cause hypertrophic growth via activation of calcineurin. We hypothesize that persistent or uncontrolled stimulation of this pathway leads to heart failure. Along these lines, a transgenic mouse with cardiac-specific overexpression of the L-type Ca<sup>2+</sup> channel and unregulated increases in Ca<sup>2+</sup> influx develops adrenergic signaling abnormalities, apoptosis, and cardiac dysfunction.<sup>123,124</sup> The observation that Ca<sup>2+</sup> channel blockers prevent development of a hypertrophic cardiomyopathy and dysregulated Ca<sup>2+</sup> signaling in mice with mutant sarcomeric proteins<sup>78</sup> further supports these ideas. These animal studies show that heart failure treatments that increase or maintain Ca<sup>2+</sup> regulation can have either beneficial or detrimental effects on heart failure progression. We suggest that this is a quantitative issue with those treatments that restore inotropic reserve without producing damaging effects associated with Ca<sup>2+</sup> overload and will produce the most favorable outcomes.

### **Does It Matter How Contractility Is Preserved in Heart Failure?**

One explanation for the increased mortality caused by inotropic drugs is that although they increase contractility they overstimulate signaling cascades (such as the cAMP or Ca<sup>2+</sup>-calcineurin pathways) that are already chronically acti-

vated.<sup>119,124</sup> We hypothesize that these treatments cause negative side effects, such as apoptosis, which further depress cardiac function and exacerbate heart failure, or cause arrhythmias that induce sudden death. This hypothesis predicts that approaches that increase inotropy without increasing cAMP or without persistently increasing Ca<sup>2+</sup> may produce beneficial effects associated with increased contractility without the detrimental effects associated with overstimulated adrenergic<sup>118,119</sup> and nonadrenergic<sup>89</sup> signaling cascades. Indeed, improving contractility should decrease activation of adrenergic signaling cascades by improving hemodynamics and thereby reducing sympathetic activation. In this context, studies in mouse heart failure models show that not all “treatments” that increase contractility were equally effective. Those that overstimulated adrenergic signaling worsened heart failure.<sup>118,119</sup> Selectively increasing Ca<sup>2+</sup> transients without activating cAMP improved function<sup>88,93,108</sup> but did not always reduce hypertrophy.<sup>125</sup> Normalizing adrenergic signaling with  $\beta$ ARK-ct can restore contractility, reduce hypertrophy, and reduce the risk of heart failure.<sup>114</sup> These results show that, at least in rodents, the magnitude and nature of the mechanism used to increase contractility influence the effectiveness of the therapy. We hypothesize those new therapies that increase “contractility reserve” will slow the progression of or reverse the heart failure syndrome. As a note of caution, the fact that recently developed molecular approaches that restore contractility reserve such as  $\beta$ ARK-ct are beneficial in some<sup>113</sup> but not all<sup>117</sup> heart failure animal studies shows that the application of these therapies in humans (with heterogeneous heart failure etiologies) will be challenging.

New heart failure therapies could be targeted to an underlying molecular defect that is causing reduced contractility, such as the use of  $\beta$ ARK-ct to prevent or reverse  $\beta$ -adrenergic signaling defects. This approach can prevent the development of heart failure in some mouse models<sup>113</sup> but has also been shown to be beneficial after myocardial infarction in larger animals.<sup>126</sup> This is one example of a targeted new potential therapy that challenges an existing concept (down-regulation of adrenergic signaling in congestive heart failure is protective) and is clearly worthy of additional study. Another example of a therapy directed at a defective process is the use of gene therapy to correct Ca<sup>2+</sup> transient abnormalities in heart failure.<sup>85,88,93,94,111</sup> Whether these approaches will lead to beneficial therapies in humans is an important unanswered question.

Interestingly, the alternative approach (therapy not targeted at the defective molecule) has also been successful. Many of the studies in which therapies have been introduced into animals that develop heart failure via crossbreeding<sup>108</sup> show that the therapeutic molecular intervention need not be targeted to the primary molecular defect to be effective. The use of Ca<sup>2+</sup> channel blockers to eliminate depressed cardiac function in mice with mutated contractile proteins that usually led to heart failure is a recent example.<sup>78</sup> Also, recent clinical studies showing improved myocyte contractility after left ventricular assist device (LVAD) for refractory heart failure,<sup>127,128</sup> strongly support the contention that therapeutic interventions need not target defective processes for contrac-

tility to improve. Another intriguing aspect of the observed myocyte recovery after LVAD support is that many different types of molecular defects show improvements after this nonspecific intervention. This observation supports the view that many of the defects observed in end-stage failing hearts are interrelated either as adaptations, counterregulatory processes, or epiphenomena that tend to respond in a parallel fashion during changes in the severity of disease. A corollary of this hypothesis is that a targeted intervention that induces substantial improvement in the contractile state of the myocardium without undesirable side effects may reverse many of the pathological features of the failing heart.

In terms of pharmacological therapy, one of the most interesting developments in the past decade are the clinical trials showing that  $\beta$ -adrenergic antagonists, which have short-term negative inotropic effects, produce beneficial effects on cardiac remodeling, contractility, and patient survival.<sup>58,100,129,130</sup> The efficacy of drugs with direct negative inotropic effects when given to patients or animals<sup>78</sup> with depressed contractility shows the complexity of the heart failure syndrome and may even support the contention that depressed contractility is an effect rather than a cause of heart failure. How  $\beta$ -blockers produce their beneficial effects in heart failure patients is an important unanswered question in heart failure research. How  $\beta$ ARK-ct,<sup>113</sup> PLB,<sup>108</sup>  $\text{Ca}^{2+}$  channel blockers,<sup>78</sup> and calcineurin inhibitors<sup>120</sup> produce their beneficial effects in animal models and whether these approaches will be broadly applicable to more complex scenarios in humans are likewise important unanswered questions for the future.

In summary, despite decades of research, it is clear that many fundamental pathophysiological and therapeutic questions related to the role of contractility defects in the evolution of heart failure are still unanswered. Nevertheless, more than ever, novel tools to answer important unresolved are now available. Therefore, basic studies can be performed to evaluate the efficacy of therapies that enhance or depress cardiac contractility by specifically modulating the abundance or activities of  $\text{Ca}^{2+}$  regulatory and signaling proteins. These new studies are likely to provide answers to the unresolved questions related to the role of depressed and enhanced cardiac contractility in the initiation and progression of heart failure. At the same time, additional mechanistic clues and ultimate validation of new therapeutic approaches will only come from studies in patients with cardiac dysfunction and heart failure.

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