Manipulating Cardiac Contractility in Heart Failure
Data From Mice and Men

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In the year 1990, cardiovascular disease surpassed infectious diseases as the leading cause of death worldwide, and by the year 2020 it is predicted to be the leading cause of all disability.1,2 In the United States, cardiovascular disease has been estimated to account for 44% of the nation’s mortality and is a leading cause of morbidity.3,4 Heart failure afflicts an estimated 5 million Americans, with ~400 000 new individuals diagnosed each year at an annual cost of more than $20 billion.4–6 The alarming reality behind these statistics is our current lack of an effective therapy to repair or otherwise reverse severe forms of cardiac dysfunction and pathological remodeling associated with heart failure. Typically, heart failure is the final culmination of protracted disease states precipitated by underlying hypertension, ischemic disease and atherosclerosis, valvular insufficiency, viral myocarditis, or mutations in genes encoding sarcomeric proteins.6 Given these diverse etiologies, it is not surprising that the final phenotypic manifestations of heart failure can also vary considerably, although dilated cardiomyopathy is the most common. This syndrome is characterized by a progressive loss in contractility and ejection fraction, ventricular chamber dilatation, ventricular wall thinning, increased peripheral vascular resistance, and dysregulated fluid homeostasis. The predominant therapeutic strategy used over the past two decades for treating such patients has been based in pharmacological manipulation of cardiac contractility.7–9 Initially, positive inotropic agents were used as a means of enhancing cardiac pump function aimed at alleviating congestive symptomology. However, use of positive inotropes is now indicated only as a means of acutely bridging patients in severe heart failure because these agents actually worsen prognosis in individuals with somewhat more stable heart failure.8 More recently, pharmacological blockade of β-adrenergic receptors has emerged as the favored treatment for individuals in heart failure. β-Adrenergic receptor antagonists initially function as negative inotropic agents on the cardiovascular system, thus partially reducing myocardial energy requirements and wall stress. However, this short-term negative inotropic effect benefits the myocardium, so that long-term treatment increases stroke volume, stroke work, pulmonary wedge pressure, and left ventricular ejection fraction.9–11 These beneficial hemodynamic alterations have also been associated with increased life span in many β-receptor antagonist trials performed to date.9–11 Collectively, such clinical results have suggested the general hypothesis that reduction in myocardial inotropy is desirable as a therapeutic strategy for the failing myocardium, where it can be tolerated. Despite the pervasive clinical picture that has emerged over the past decade, recent research in animal models of heart failure has suggested the potential benefits of selectively enhancing cardiac contractility as a means of treating heart failure. Indeed, data from mouse models have emerged over the past 5 years suggesting the potential therapeutic benefits of targeted enhancement in cardiac contractility as a way to prevent or reverse heart failure. Here we will examine the potential therapeutic ramifications of positively or negatively regulating cardiac inotropy in heart failure in light of new experimental paradigms generated in animal models and how this might relate to human applications. However, we will not attempt to review the vast clinical literature related to β-receptor antagonist trials but instead refer the reader to recent reviews that explored this subject in depth.9–11

Cardiac β-Adrenergic Signaling Apparatus Controls Contractility

The cardiac β-adrenergic signaling network is highly specialized in the myocardium as a direct regulator of contractility through changes in intrinsic inotropy and chronotropy (heart rate). Norepinephrine- and epinephrine-mediated stimulation of β-receptors is the primary mechanism whereby cardiac output is increased in humans, whereas mice show less dynamic range in cardiac output alterations after adrenergic stimulation.12,13 The following 3 β-adrenergic receptor subtypes have been identified: β1, β2, and β3, with β1 and β2 receiving the most interest as mainstay regulators of cardiac performance, whereas the functional role of β3 is largely unknown. The cardiac β1-adrenergic receptor is primarily coupled to the stimulatory G protein (Gαs) within the sarcolemma, which itself couples to adenyl cyclase, resulting in cAMP production (Figure 1). The cardiac β2-adrenergic receptor is coupled
both to Gαi and to the inhibitory G protein (Gαi), which functions, in part, to diminish adenylyl cyclase activity and subsequent cAMP levels (Figure 1). The β-receptor-dependent activation of guanylyl cyclase constitutes ~70% to 80% of the total β-receptor population on normal adult cardiac myocytes, so that catecholamine stimulation primarily leads to an increase in cAMP.13 However, the cardiomyopathic heart exhibits a downregulation of β-receptor so that the ratio of β1 to β2 is closer to 50:50, ultimately increasing Gαi signaling and diminishing cAMP-mediated responses.13 With respect to regulation of myocyte contractility, β-receptor–mediated activation of Gαs can also directly couple to the voltage-dependent L-type calcium channel in the sarcolemma, enhancing calcium influx.14,15 Once generated, cAMP plays a preeminent role in regulating myocyte contractility through the direct activation of the cAMP-dependent protein kinase A (PKA). PKA in turn directly phosphorylates the L-type calcium channel, the ryanodine receptor, and phospholamban, which together coordinate significant increases in calcium inotropy.16 (Figure 1). Phospholamban is a negative regulator of the sarco(endoplasmic reticulum Ca(2+)-ATPase 2 (SERCA2) within the sarcoplasmic reticulum (SR). PKA-mediated phosphorylation of phospholamban at Ser16 causes its dissociation from SERCA2, permitting maximal calcium ATPase activity and maximal SR loading, which in turn generates larger action potentials during systole.16 cAMP-dependent PKA activation further augments the contractile response by directly phosphorylating the type-1 protein phosphatase (PP1) inhibitor-1 protein, thus reducing PP1 activity that normally functions to remove the phosphate at Ser16 in phospholamban16 (Figure 1). Finally, PKA-dependent phosphorylation of contractile proteins such as troponin I and myosin binding protein C also enhances the relaxation cycling of myofilaments17 (Figure 1). Thus, β-adrenergic receptors mediate acute contractile alterations through only a handful of downstream “nodal” regulatory proteins in the heart. Manipulating the expression or activity of these nodal regulatory proteins profoundly influences the contractile function of the heart and its propensity toward cardiomyopathy after injury, as discussed below.

**Regulation of β-Adrenergic Receptor Signaling**

Chronic stimulation of β-adrenergic receptors, as typifies the failing myocardium, leads to receptor desensitization through uncoupling of downstream signaling effectors. β-Adrenergic receptor desensitization has been deemed an adaptive response that potentially benefits the myocardium by limiting energy utilization and secondary ventricular remodeling and myocyte death associated with sustained reactive signaling.10 A number of molecular feedback effectors have been defined in the failing myocardium that tend to limit the long-term activation of β-adrenergic receptors, thus reducing signaling and contractile drive. A primary means of uncoupling β-adrenergic receptors is through the activity of G-protein coupled receptor kinases (GRKs).18 The most important of these is GRK2 (βARK1), which directly phosphorylates occupied β-adrenergic receptors on cardiac myocytes leading to their internalization and degradation in concert with the activity of β-arrestin18 (Figure 1). The failing myocardium is also characterized by an upregulation in βARK1 expression and activity.19,20 Overexpression of βARK1 in the mouse heart led to receptor desensitization and reduced contractility, whereas expression of a peptide inhibitor of the GRKs (βARKct) enhanced basal and β-receptor–stimulated contractility.21 Another “compensatory” alteration in β-receptor action is mediated through Gαi upregulation, which in conjunction with the relative increase in the β2/β1 ratio leads to less adenylcyclase coupling and subsequent cAMP generation.22 In summary, reductions in β-adrenergic receptor coupling, increasing the β2/β1 ratio, and increasing Gαi expression likely serve as important adaptations that buffer the long-term effects associated with catecholamine drive that characterizes the failing heart.

![Diagram of β-adrenergic signaling pathways that directly regulate myocardial contractility and cardiac output.](image-url)
Enhancement of β-Receptor Signaling Benefits Select Animal Models of Heart Failure

In contrast to the adaptive, myocardial sparing hypothesis proposed for β-adrenergic receptor desensitization, more recent data in genetically modified mouse models have suggested some unique twists. For example, β-adrenergic receptor overexpression in the mouse heart by transgenesis has suggested functional divergence between β₁ and β₂ receptors. As discussed above, β₁-adrenergic receptors are primarily coupled to Gαs-adenyl cyclase, whereas β₂-adrenergic receptors are also coupled to Gαi. Moreover, Gαi preferentially interacts with the phosphorylated form of the β₂-adrenergic receptor, suggesting that desensitization is of lesser consequence for this subtype compared with β₁-adrenergic receptor. β₁-Adrenergic receptors also show unique localization within caveolar subdomains of the sarcolemma in contrast to the localization of β₂-adrenergic receptors. β₂-Adrenergic receptors can also perform a number of unexpected signaling events such as modulation of sodium/hydrogen exchanger, coupling with phosphatidylinositol 3′-kinase (PI3K), and indirect coupling to phospholipase A₂ (PLA₂).26

Given the functional divergence between β₁- and β₂-adrenergic receptors discussed above, it is not surprising that transgene-mediated overexpression of each receptor subtype in the mouse heart produced different phenotypes. Transgenic mice with 60-fold overexpression of the β₂-adrenergic receptor showed enhanced cardiac contractility without significant pathological consequences. However, 350-fold overexpression of the β₂-adrenergic receptor produced substantial pathology in the heart, likely as a result of excessive signaling. By comparison, relatively low levels of β₂-adrenergic receptor overexpression (5- to 30-fold) produced significant ventricular pathology, similar to 350-fold β₂-adrenergic receptor overexpressors. These results further underscore the functional differences between β₁- and β₂-adrenergic receptors, suggesting that one might have more of a pathological role in a failing heart. Indeed, we have observed that low expressing β₁-adrenergic receptor transgenic mice can actually rescue a model of cardiomyopathy due to Gαq overexpression. The mild hypercontractile phenotype associated with β₂-adrenergic receptor overexpression was likely the causative aspect of the rescue in ventricular function and secondary hypertrophy in Gαq mice. These results suggested that a mild or defined stimulation in cardiac contractility is potentially of benefit to the diseased myocardium. Similarly, enhanced cardiac contractility that characterizes the βARKct transgene rescued hypertrophic and dilated cardiomyopathy in 3 separate genetic mouse models of heart failure.31 Once again, the βARKct transgene is a peptide inhibitor of GRK2 that would otherwise directly desensitize β-adrenergic receptors and blunt contractile responsiveness. In the first study, cardiomyopathy associated with targeted disruption of the muscle lim protein (MLP) was rescued with the βARKct transgene, presumably as a result of maintenance/augmentation of cardiac contractility.31 In a second study, the βARKct transgene enhanced ventricular function and overall survival in a mouse model of lethal cardiomyopathy due to calsequestrin overexpression.32 Finally, Freeman et al transgenic mice with a model of hypertrophic cardiomyopathy, resulting in a reduction in cardiac disease manifestation. White et al have extended these mouse-based observations in a meaningful way through acute administration of an adenovirus encoding the βARKct minigene in a rabbit model of myocardial infarction–induced heart failure.34 Notably, adenovirus-mediated gene therapy improved the loss of cardiac function after myocardial infarction and delayed the onset of failure.34 Collectively, these various studies have extended the hypothesis that augmentation in cardiac contractility by maintaining β-receptor action can prevent secondary hypertrophy, fibrotic remodeling, and the molecular alterations associated with a primary disease-causing stimulus. These observations also suggest that augmentation in β-receptor activity is not necessarily of pathological consequence, in contrast to the known effects associated with enhanced catecholamine levels. This discordance could be explained if either catecholamines or the βARKct minigene have β-receptor–independent effects on the heart (either direct or indirect; eg, vascular effects). For example, GRK2 negatively regulates the activity of a number of G-protein–coupled receptors, and hence would be affected by βARKct expression, potentially contributing to its beneficial profile during heart failure.

Enhanced β-Receptor Signaling Is Not of Universal Benefit in Mice

In contrast to the data discussed above, other studies have suggested that the degree to which contractility is augmented, and the severity of the cardiomyopathy itself, can influence the ability of augmented β-adrenergic receptor activity to rescue disease. For example, the βARKct transgene did not significantly rescue a more severe model of heart failure due to transgene-mediated overexpression of a dominant-negative CREB protein.36 Consistent with these results, increased contractility associated with mild β₂-adrenergic receptor overexpression actually enhanced myocardial injury in mice after ischemia-reperfusion injury.37 Moreover, β₂-adrenergic receptor transgenic mice showed greater functional deterioration, left ventricular hypertrophy, and death rates after 9 weeks of aortic stenosis.38 By comparison, overexpression of the Gαs protein in the heart by transgenesis enhanced catecholamine-induced inotropy and chronotropy but eventually led to cellular necrosis, fibrosis, and hypertrophy.39 Moreover, Gαs transgenic mice eventually succumbed to lethal cardiomyopathy later in life, suggesting that chronic enhancement in sympathetic drive through this signaling effector is deleterious.40 Collectively, these results have suggested that enhanced contractile function might not benefit the mouse heart under all conditions or in response to all stimuli, in opposition to the hypothesis discussed in the paragraph above. However, as will be discussed later in this review, mice lacking the SERCA2 inhibitory protein
phospholamban have sustained maximal contractility at rest, which is tolerated throughout the life of the animal without deleterious consequences if left “unstressed.”

This simple result indicates that the state of maximal contractility itself does not induce cardiac dysfunction in a mouse heart. It is likely that enhancing cardiac contractility through Gs or β-adrenergic receptors may be more pathological given the simultaneous activation of deleterious signal transduction cascades that secondarily promote myocyte death and/or remodeling of the ventricles, so that interpretation of effect based exclusively on contractility alterations is problematic. However, a caveat here is the beneficial effects associated with the βARKct minigene. Another consideration, discussed in detail below, is that most studies supporting the benefits of augmented contractility in heart failure have relied on the mouse. Contractility in the mouse is more exclusively regulated by SR calcium release dynamics compared with the human myocardium, suggesting that each might respond differently to sustained inotropy and secondary defects in calcium handling that characterizes a failing heart.41,42 For example, a putative phospholamban-null polymorphism in the human is actually detrimental to survival43 (see section below).

Examination of the effects of β-adrenergic blockers has further fueled the controversy regarding the benefits or detriments of augmenting cardiac contractility. Whereas β-adrenergic receptor antagonists function in the short term to reduce myocardial inotropy, chronotropy, and energy utilization, they eventually augment cardiac function long-term when administered for cardiomyopathy and heart failure. For example, augmentation in contractility due to βARKct overexpression partially rescued cardiomyopathy in calsequestrin-overexpressing transgenic mice, which was rescued even further by administration of the β-adrenergic receptor antagonist metoprolol.44 Indeed, the cardiomyopathy and reduction in ventricular function that characterizes the Gs transgenic mouse was prevented by chronic treatment with the β-adrenergic receptor antagonist propranolol.45

Other Considerations Surrounding Manipulation of β-Receptor Signaling

On the surface, β-receptor antagonists might appear to benefit the failing myocardium through a reduction in sympathetic drive (contractility). However, β-adrenergic receptor antagonists only show a negative inotropic effect on cardiovascular performance in the short term, whereas long-term these inhibitors improve systolic function and lead to reverse remodeling of the ventricles.10 Such data actually support the hypothesis that enhanced contractility might benefit the prognosis associated with heart failure. In other words, β-adrenergic receptor antagonists might impart their benefit by partially reversing desensitization and hence improving contractility through increasing β-receptor responsiveness within defined parameters. However, it could also be argued that the initial negative inotropic phase associated with β-blocker therapy partially unloads the myocardium for a period, which secondarily promotes reverse remodeling and benefits systolic performance, much like the known effects associated with left ventricular assist devices,46 or angiotensin-converting enzyme (ACE) inhibitors.

It should also be considered that primary alterations in contractility might not be the only significant mechanism whereby manipulation of β-receptors can benefit a failing myocardium. It is also likely that β-blockers enhance ventricular performance and survival by reducing the secondary signaling effects associated with enhanced sympathetic drive, although the associated long-term enhancement in contractility could also be a primary benefit. Indeed, genetically modified mice lacking the ability to produce epinephrine and norepinephrine showed a blunted hypertrophic response and reduced functional decompensation after long-term aortic banding.47,48 These same mice showed a reduction in the activation of downstream signaling pathways such as mitogen-activated protein kinase, but no significant alteration in contractility.47,48 These results also support the perspective that β-adrenergic receptors play a dichotomous role in the heart, whereby their ability to augment ventricular performance long-term is of benefit, yet their recruitment of secondary reactive signaling pathways is of detriment.

**SERCA2 and Phospholamban Function as Nodal Regulators of Cardiac Contractility**

Given that β-adrenergic receptors regulate more than simply contractility in cardiac myocytes, manipulating their function may not be the simplest way of assessing the hypothesis that enhanced contractile performance protects the myocardium from failure-associated insults. However, manipulating the expression or activity of select downstream β-adrenergic effectors in the heart could impart a more defined and unitary biological response. With respect to contractility, one of the most relevant biological effectors of β-adrenergic receptors is the negative regulator of SERCA1, phospholamban. Once again, phosphorylation of phospholamban by PKA leads to disassociation of the inhibitory complex and greater SERCA2 activity, thus generating greater SR calcium loads and subsequent transients.16,41 Given these relationships, a manipulation of SERCA2 or phospholamban should impart a more unitary effect on myocardial contractility without impacting other signaling pathways, as can occur through β-adrenergic receptors. That SERCA2 and phospholamban are relevant targets for genetic dissection of the contractility hypothesis is further supported by the observation that failing human hearts often have reduced SERCA2 ATPase activity with a corresponding blunting and prolongation of the calcium transient.16,41

Perhaps the most meaningful observation related to SERCA2 function and myocardial contractility was made by Luo et al49 nearly 10 years ago when they reported that phospholamban gene–targeted mice were characterized by maximal myocardial contractility at baseline and hence were unresponsive to further augmentation with β-adrenergic receptor agonists. This result suggested that the most significant contractile effect associated with β-adrenergic receptor stimulation is mediated through
phospholamban and its ability to alter SERCA2 function. Gratifyingly, the antithetic experiment provided the opposite result; overexpression of phospholamban itself diminished cardiac contractility through greater inhibition of SERCA2 function.16 Similarly, increasing SERCA2a protein expression in the mouse heart enhanced SR calcium loading, the calcium transient, and contractility.50,51 Unlike β-adrenergic receptor overexpression, unrestrained contractility mediated by phospholamban gene disruption or SERCA2 overexpression did not produce cardiac pathology.16,41 These results establish the critical principle that simply enhancing myocardial contractility is not intrinsically harmful to the (mouse) heart.

Manipulation of SERCA2-Phospholamban
Alters Heart Failure in Animal Models

More recently, investigators have used SERCA2 or phospholamban genetically altered mouse models to address the benefits or detriments of augmenting contractility in a “failing” heart. An important observation was made by Minamisawa et al52 when they crossed phospholamban gene–targeted mice with the MLP mouse model of dilated cardiomyopathy. Increasing SERCA2 function by phospholamban gene deletion in the MLP-null background prevented ventricular dysfunction, fibrosis, and long-term heart failure. Phospholamban gene ablation also prevented the manifestation of cardiac hypertrophy and ventricular dysfunction that characterizes calsequestrin-overexpressing transgenic mice.53 Similarly, intracoronary gene delivery of a recombinant adeno-associated virus gene expressing a dominant-negative phospholamban mutant (that gives greater SERCA2 activity) rescued heart failure in a cardiomyopathic hamster model.54 Enhanced contractility associated with SERCA2 overexpression was also reported to benefit heart failure and secondary remodeling and/or hypertrophy. For example, overexpression of SERCA2 by transgenesis was protective against diabetic cardiomyopathy as well as cardiac dysfunction induced by chronic pressure overload.55,56 Similarly, del Monte et al57,58 showed that increased phospholamban protein expression, or expression of an antisense phospholamban RNA, each improved contractile function of failing human ventricular myocytes in vitro. Moreover, adenovirus-mediated overexpression of SERCA2 in a pressure-overload rat model of heart failure produced a rescue in depressed cardiac function, myocardial energetics, and survival.59,60 Collectively, each of the studies discussed above suggests that enhanced myocardial contractility mediated through alterations in calcium handling affords benefit to the failing myocardium in rodents. Indeed, expression of inhibitory forms of phospholamban can even induce heart failure in an otherwise normal setting, presumably as a result of diminished myocardial contractility that invokes a secondary increase in catecholamine drive and reactive signaling.61,62 Importantly, Schmitt et al62 recently identified a human family containing a dominant-negative type of mutation in phospholamban that promoted dilated cardiomyopathy, presumably by diminishing contractility or the ability to enhance contractility after β-adrenergic stimulation.

The studies discussed in the preceding paragraph paint a fairly uniform picture that augmentation of cardiac contractility through SERCA2-phospholamban is of significant benefit to the failing myocardium and, hence, survival. However, as is often the case in biology, the story is more complex than initially supposed. For example, we were the first to report that increased cardiac contractility associated with phospholamban gene disruption provided no benefit whatsoever to dilated cardiomyopathy in tropomodulin-overexpressing transgenic (TOT) mice.63 Hearts from tropomodulin transgenic mice showed the same degree of chamber dilation and increased heart weights with or without phospholamban gene ablation (Figure 2). Phospholamban gene targeting also failed to rescue the secondary hypertrophic response observed in a mouse model of cardiomyopathy generated by Freeman et al,33 although systolic dysfunction was rescued. More recently, Song et al64 crossed the phospholamban-null mutation with either a Gαq-transgenic mouse model of cardiomyopathy or with a myosin binding protein C–mutant model (MyBP-Cmut), neither of which showed a rescue in whole-organ performance or secondary hypertrophy. Provocatively, Haghighi et al65 identified 2 human families with presumed null-like polymorphisms in phospholamban. Heterozygotes for this polymorphism showed cardiac hypertrophy, whereas 2 homozygous individuals showed dilated cardiomyopathy and failure requiring transplantation at 16 and 27 years of age. Although it has yet to be formally proven that this polymorphism functions as a true null allele, no phospholamban protein was present in homozygous individuals.

Clinical Versus Experimental Heart Failure:
A Mouse Is Not a Man

In attempting to extrapolate findings in “heart failure” from mouse models to the human condition, it is useful to consider the profound differences between the two. Most mouse heart failure models described as having defects in myocardial contractility are dilated cardiomyopathies with impaired systolic function, and the measures of functional improvement have (with the exception of mortality effects) largely been performed at an early stage of heart failure.
that is not typically seen in clinical practice, the stage of asymptomatic left ventricular dysfunction. A major cause of “heart failure” in the aging human population, but not in mouse models, is so-called “diastolic heart failure,” in which left ventricular systolic function and contractility are normal. Finally, a number of nonsurgical mouse models of heart failure utilize a genetic “lesion” (transgene or gene-targeting event) without a natural analogue in typical human disease. In addressing the potential therapeutic efficacy of modulating contractility in human heart failure, as has been suggested in certain mouse models, it is well to consider that the inciting event and disease manifestation in the human are typically multifactorial and polygenic in etiology. Moreover, the mouse and human differ for a number of more obvious reasons such as overall size, lifespan, circulatory physiology, and pharmacological response heterogeneity. Despite each of these concerns, mouse models of heart failure represent a mainstay in the arsenal of researchers in identifying novel therapeutic strategies given the ease and relative speed of performing genetic manipulations and the general conservation of broader anatomic and physiological parameters. However, we must be cautious so as not to overextrapolate data obtained in mouse models and to guard against occasional claims of having created a “human-like heart” without due diligence or phylogenetic scale-up.

**Inotropic Therapy in Human Heart Failure**

There is a strong and obvious rationale for inotropic therapy in heart failure. At the whole-organ level, the hallmark of dilated cardiomyopathy is diminished systolic ventricular function. At the cellular level, most studies have shown diminished cardiomyocyte contractility in heart failure. Indeed, at the biochemical level, abnormalities of β-adrenergic receptor signaling and SR calcium cycling appear to be the critical lesions. Clearly, then, therapy should be targeted at increasing cardiomyocyte and ventricular contractility by augmenting the β-adrenergic/SERCA axis. Because catecholamines are relatively ineffective in heart failure as a result of receptor downregulation and desensitization, phosphodiesterase inhibitors were used to directly increase cAMP levels and therefore enhance calcium cycling. Although preliminary results suggested that low-dose therapy could reduce mortality in heart failure, the large-scale randomized Vesnarinone trial (VEST), a phosphodiesterase inhibitor with additional antiarrhythmic therapy, was prematurely terminated as a result of increased mortality at the original low dose (60 mg) and at an even lower dose (30 mg). Indeed, despite the compelling mechanistic rationale for inotropic therapy in heart failure, most outpatient trials have demonstrated adverse outcomes, typically increased mortality (reviewed in Reference 69). The accumulated clinical data surrounding inotrope use were recently reviewed in depth. The mortality associations with positive inotropes are put into greater perspective when one considers the overwhelming survival benefit of negative inotropic therapies such as β-adrenergic receptor blockade.

**Inotropy Versus Unloading: Wherein Lies the Benefit?**

Parenteral therapy with inotropes (as opposed to “inotropic therapy”) has had a role in short-term treatment for acutely decompensated heart failure or as a longer-term “bridge-to-transplant.” Accumulated data suggest that intermittent infusion therapy can provide symptomatic improvement, although possibly at the cost of increased arrhythmic risk. It is interesting to note that 2 agents widely used in this manner, the β1-selective adrenergic agonist dobutamine and the phosphodiesterase inhibitor milrinone, have systemic and renal vasodilating properties that are probably essential to their beneficial effects, as they unload the failing heart.

A recent addition to the therapeutic armamentarium for infusion therapy is B-type natriuretic peptide (BNP, nesiritide). An endogenous cardiac-secreted peptide, BNP levels increase in heart failure, and increased BNP correlates with mortality and morbidity in heart failure. Whereas BNP levels have been used as an experimental and clinical diagnostic marker, nesiritide, an identical synthetic peptide, was recently approved for use in acute heart failure decompensation. Like dobutamine and milrinone, nesiritide is a powerful peripheral vasodilator and increases renal blood flow. However, unlike the above agents, there is no direct inotropic effect. Thus, clinical benefit accrues purely from reductions in cardiac afterload afforded by systemic vasodilation and diminished cardiac preload that is a consequence of a diuretic and natriuretic effect. Accordingly, a comparison of dobutamine, a potent inotrope with vasodilating properties, with nesiritide, a vasodilator without inotropic actions, could help address the relative benefits of enhancing cardiac contractility versus improving global systolic function through optimization of loading conditions. Two such studies exist. First, Colucci et al compared the hemodynamic and therapeutic effects of nesiritide with a variety of other vasoactive agents (chosen by the investigator). Because more than half of the patients in this comparison trial were treated with dobutamine, it was possible to determine that the efficacy of both agents to improve heart failure symptoms was similar. Additional data are provided by the PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy) Study, which was a head-to-head comparison of the arrhythmic effects of dobutamine and nesiritide. Ventricular tachycardia occurred in 13% of dobutamine patients, compared with 6% of those treated with nesiritide, in whom ventricular ectopic beats actually decreased. Together, these studies indicate that a noninotrope with the same vasoactive properties as an inotrope is equally efficacious and less toxic.

**Novel Approaches**

There is no doubt that optimizing cardiac loading though pharmacological (see above) or mechanical means enhances cardiac function and provides symptomatic relief in heart failure. Likewise, it is widely recognized that limiting or reversing ventricular remodeling can improve car-
diac function and prolong life in this lethal syndrome (the relevant data on β-adrenergic blockers and ACE inhibitors have been reviewed extensively elsewhere). In contrast, inotropic therapies have failed to provide a mortality or morbidity benefit. The overall conclusion would seem to be that ventricular function is more important than ventricular contractility. Yet the two are inextricably related, and if it were possible to enhance contractility without further injuring the heart, then it is reasonable to assume that this would provide clinical benefit. An example is provided by digoxin, which is a mild inotrope that directly enhances cardiac calcium cycling, and which provides symptomatic benefit in heart failure without apparent deleterious effects.

A new approach for increasing cardiac contractility while avoiding the major limitations of agents that increase intracellular cAMP is through the use of so-called “calcium-sensitizing” agents such as levosimendan and toborinone. Levosimendan, available in Europe, enhances contractility primarily by binding to troponin C and increasing myofilament sensitivity to calcium. Importantly, there is no impairment of myocardial relaxation, and there may be a positive lusitropic effect. Additional effects of levosimendan include vasodilation, likely mediated via activation of potassium–dependent ATP channels, and (at high concentrations) inhibition of phosphodiesterase. In patients with functional class III or IV heart failure, levosimendan increased left ventricular stroke volume and cardiac output, decreased left ventricular filling pressures, and only modestly increased heart rate. There was no proarrhythmic effect, and some reports have even suggested that intermittent infusions of this calcium-sensitizing agent may provide a survival benefit in severe acute heart failure. These tantalizing results suggest that positive inotropic agents are not necessarily detrimental in ventricular contractility. The most apparent deleterious effects.

More importantly, it appears as though humans lacking phospholamban actually develop cardiomyopathy, and heart failure, in direct contrast to the mouse. The most straightforward interpretation of all the results discussed herein is simply that too much or too little contractility is bad for the heart. However, this adage does not necessarily mean that acute inotropic therapies directed at SERCA or phospholamban are to be disregarded. Indeed, certain types or stages of heart failure might significantly benefit from a therapeutic that enhances contractility through alterations in SERCA2-phospholamban, or from a calcium-sensitizing agent as discussed above. However, such strategies may prove effective for only a subclass of patients or only in combination with existing strategies/therapeutics that positively affect ventricular remodeling. The provocative data that continue to derive from genetic mouse models, although necessarily viewed with appropriate caution, will undoubtedly continue to challenge our perspectives on human heart failure and suggest new therapeutic avenues.

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_Circulation_. 2004;109:150-158
doi: 10.1161/01.CIR.000011581.15521.F5
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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