It is increasingly recognized that pathological cardiac remodeling, including myocardial hypertrophy and chamber dilation, is a process that promotes progression of myocardial dysfunction and adverse clinical sequelae among patients with dilated cardiomyopathies, regardless of the pathogenesis. Accordingly, the goals of delaying progression or inducing regression of pathological cardiac hypertrophy and dilation, so-called “reverse remodeling,” have emerged as important therapeutic targets in the treatment of dilated cardiomyopathies.

In recent years, some of the most dramatic examples of reverse remodeling have been observed after application of devices that reduce global or regional left ventricular loading conditions. Perhaps most striking have been the myocardial adaptations after placement of a left ventricular assist device (LVAD) in patients with medically refractory heart failure awaiting heart transplantation. In these settings, studies from multiple laboratories have demonstrated that LVAD support induces regression of many of the typical abnormalities of the failing myocardium including pathological hypertrophy,1,2 action potential prolongation,3 impaired contractility and contractile reserve,4–6 extracellular matrix abnormalities,7 and expression of genes normally associated with fetal development.8 Such studies support the hypothesis that the progression and persistence of many of the myocardial abnormalities observed in dilated failing hearts, regardless of pathogenesis, are a direct or indirect consequence of increased myocardial wall stress. Because LVADs are only used among patients with the most severe degrees of myocardial failure, studies of LVAD-supported hearts also suggest that the potential for myocardial reverse remodeling is retained across a wide spectrum of disease severity.

Indeed, recent applications of other devices, most notably multisite ventricular pacing and passive cardiac support devices, have demonstrated the potential to induce regression of pathological hypertrophy and improvements in myocardial contractile performance by altering regional and global myocardial wall stress in hearts with less severe degrees of dysfunction. For example, in a large trial of multisite ventricular pacing to improve regional synchronization of LV contraction among patients with a reduced left ventricular ejection fraction (LVEF), there were 27% and 26% decreases in LV end-diastolic and end-systolic volumes, respectively, and a 12% decrease in LV mass over a 6-month period.9 Similarly, in a small study of a passive cardiac support device (CSD), LV end-diastolic dimension decreased by 11% and LVEF increased from 22±2% to 33±5% at 6 months after the device had been placed in patients with New York Heart Association class II and III symptoms of heart failure.10 While the rate, magnitude, and consistency of reverse remodeling with multisite pacing and CSDs are less than observed with LVAD support, these therapies can be applied in less advanced cases of heart failure and with lower procedural risk. However, because these devices do not necessitate any removal of myocardial tissue suitable for in vitro studies, these clinical investigations permit only limited insights into the mechanisms of device-induced adaptations of the failing heart.

In this issue of Circulation Research, Sabbah and colleagues11 report the results of studies examining the cellular and molecular mechanisms of altered myocardial structure and function induced by a CSD. This study used a well-established canine model of progressive dilated cardiomyopathy produced by sequential intracoronary injections of polystyrene microspheres to induce a loss of viable myocardium throughout the left ventricle. A key feature of this model is the progressive dilation and dysfunction that occurs during the 3 months after the last embolization procedure. In this setting, dogs with equivalent degrees of initial dilation and dysfunction were assigned to receive either no intervention or the Acorn CSD device beginning 2 weeks after the last microsphere embolization.

Consistent with previous studies of this CSD, Sabbah et al11 observed reductions in end-systolic and end-diastolic volume and improvements in LV ejection fraction while controls experienced progressive cardiac dilation with reductions in LV ejection fraction. To provide new insights into the mechanisms through which adverse cardiac remodeling was blocked/reversed, these investigators performed morphological, functional, and molecular analyses of isolated cardiac myocytes and tissues from the myopathic hearts with and without the CSD and compared findings to normal controls. The CSD induced virtually complete prevention/reversal of pathological cellular remodeling, including decreases in cell length, width, and cross-sectional area. In contrast, the CSD induced only a partial improvement in myocyte contractility, rates of shortening and relengthening, and Ca2+ uptake kinetics in isolated sarcoplasmic reticulum membrane vesicles. In molecular analyses, several “stretch-response proteins” (p21ras, c-fos, and p38 mitogen-activated protein kinase) and pathological shifts in α- and β-myosin heavy chain abundances were normalized in the myopathic hearts receiving the CSD, but the abundance of two key Ca2+ regulatory hormones, SERCA2a and phospholamban, were...
not affected. Finally, there was marked augmentation of phospholamban phosphorylation (to levels even greater than in normal controls) in the hearts receiving the CSD.

As with studies of LVAD-supported human myocardium, this type of multilevel observational analysis cannot necessarily prove a causal role for any particular mechanism. Moreover, because the cellular and molecular phenotype of the model was not defined at the specific time the CSD was placed, the relative balance of delayed progression and reverse remodeling cannot be determined. Nevertheless, this study provides several important clues concerning mechanisms of prevention and/or reversal of myocardial remodeling with CSDs. First, the molecular data provide strong support for the hypothesis that the CSD does not simply restrain expansion by physical means but clearly blocks the stretch-responsive signaling pathways that trigger and transduce many aspects of the remodeling process. The parallel normalization of stretch-responsive proteins, myocyte morphology, and myosin heavy chain isoforms abundance suggests a functional linkage during regression/prevention of remodeling that is consistent with previous studies from more reductionist model systems and previous work in LVAD-supported human myocardium. The fact that the CSD neither constrains the ventricles under basal conditions nor prevents preload-dependent increases in contractility, yet effectively blocks the activation of stretch-mediated signaling pathways and downstream effects, suggests that persistent increases in transmural wall stress are necessary to induce myocardial remodeling.

In addition, the dissociation between stretch-response proteins and the abundance of Ca$^{2+}$ regulatory proteins in the CSD-treated animals is also of interest. In many, but not all, previous studies of pathologically remodeled human and animal hearts, parallel alterations in the abundance of calcium regulatory proteins and so-called “fetal genes” have been reported. However, the dissociation observed in CSD-treated animals strongly supports the hypothesis that stretch-responsive signaling pathways are not predominant in governing the abundance of calcium regulatory proteins. Rather, other factors such as neurohumoral stimulation and/or paracrine effects mediated by the extracellular matrix may be responsible for persistent reductions in SERCA2a abundance independent of stretch-responsive signaling pathways.

Cardiomyopathic dogs without the CSD were found to have significantly reduced phospholamban phosphorylation despite a likely increase in circulating catecholamines accompanying their heart failure syndrome. This is consistent with the uncoupling of $\beta$-adrenergic receptor stimulation and adrenergic responsiveness characteristic of heart failure. In contrast, the CSD-treated animals demonstrated supranormal degrees of phospholamban phosphorylation that could well be contributing to the increases in the rates of shortening, relengthening, and Ca$^{2+}$ uptake observed in these animals. The more difficult, and thus-far unaddressed, question is how does the CSD affect adrenergic-dependent phospholamban phosphorylation. Of relevance, previous studies showing improved adrenergic responsiveness with CSD in this model failed to observe alterations in $\beta$-adrenergic receptor density or binding affinity. Sabbah et al suggest a possible contribution of decreases in protein phosphatase (PP1) activity after CSD. While this has not been experimentally verified, increases in PP1 activity have been observed in this and other models of cardiomyopathy and have been linked to reductions in adrenergic responsiveness. Even if CSD therapy decreases PP1 activity, the mechanism for this effect remains uncertain, yet might provide an important link between transmural wall stress and alterations in myocardial function including calcium handling.

Whatever the mechanism for the linkage between the CSD and phospholamban phosphorylation, the studies by Sabbah et al demonstrate that posttranslational protein modifications and their determinants will likely be as pivotal in mediating reverse remodeling as they are in regulating normal myocardial function. These studies also underscore the importance of continuing mechanistic inquiries even after new therapeutic devices have been “translated” into clinical settings. Quite often, the most interesting and important questions will arise during the clinical applications of new devices, yet ethical, practical, and commercial constraints will limit the scope of the research that can be performed through patient-based research. In such circumstances, as with the studies by Sabbah et al, carefully executed studies using relevant animal models of acquired cardiac disease will be invaluable for developing and exploring new hypotheses.

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