The term “cardiomyopathy of overload” was coined by Arnold Katz in 1990. As he pointed out, it has been recognized since the time of Osler that in patients with chronic pressure or volume overload of the heart, a syndrome of progressive ventricular dysfunction can develop. Hypertrophy initially normalizes wall stress, but eventually ventricular dilation occurs, resulting in a secondary increase in wall stress because of ventricular remodeling and associated increase in the radius of curvature of the ventricle. This increase in wall stress is proposed to cause further deterioration of ventricular function by a progressive sequence of hypertrophy → decreased ventricular function → dilation → increased wall stress → hypertrophy → decreased ventricular function. This sequence of events may also account for the progressive nature of the ventricular enlargement and remodeling that can occur after loss of a significant component of functioning myocardium, or reduction in the number of myocytes as caused, for example, by myocardial infarction or myocarditis. Indeed, the well-recognized influence of depressed ventricular function and cardiac dilation on prognosis in patients with valvular disease, cardiomyopathy, and ischemic heart disease may in part be due to this process.

The potential causes of ventricular chamber dysfunction in patients with advanced hypertrophy were well summarized by Katz and include altered energetics, myocyte “drop out” caused by necrosis and/or apoptosis, alterations in the ventricular connective tissue matrix, and hypertrophy-induced changes in expression of myocyte genes and resulting alterations in myocyte protein constituents that lead to a decrease in myocyte function. Work from many laboratories has shown that hypertrophy in animals is associated with switch to a fetal pattern of gene expression including changes in actin and myosin isoforms, an increase in atrial natriuretic factor levels, a decrease in sarcoplasmic reticulum Ca\(^{2+}\) ATPase, and an increase in Na\(^+\)/Ca\(^{2+}\) exchanger expression. The latter two effects might be expected to alter Ca\(^{2+}\) homeostasis in the myocyte. Although it is recognized that molecular events associated with hypertrophy in animals may differ from those in humans, studies have shown that hypertrophy and failure in humans can be associated with similar changes in myocyte expression of genes and/or protein levels for the sarcoplasmic reticulum Ca\(^{2+}\) ATPase, the Na\(^+\)/Ca\(^{2+}\) exchanger, and contractile protein components of the myofilaments. Hypertrophy or sarcolemmal stress-induced decreases in the L-type Ca\(^{2+}\) current and/or in the cellular microdomains involved in coupling of the Ca\(^{2+}\) current to release of Ca\(^{2+}\) from the sarcoplasmic reticulum, as well as alteration of the cytoskeleton also may occur. The relative importance of these myocyte alterations is not clear, but they could obviously affect Ca\(^{2+}\) homeostasis, myofilament responsiveness, and internal myocyte load to cause the decreased myocyte contraction and relaxation and reduced Ca\(^{2+}\) transient that have been observed in initial studies of human myocytes from failing myocardium.

It is important to note that factors associated with the peripheral circulatory derangements occurring in chronic heart failure other than increased sarcolemmal stress and/or myocyte hypertrophy may also contribute to a progressive decrease in myocyte performance. These include long-term increased exposure to catecholamines, which can induce a myopathic effect and cause downregulation of the β-receptor, and increased circulating levels of cytokines such as tumor necrosis factor-α and other pro-inflammatory factors. Also, Kagaya et al have shown that treatment of rats with the ACE-inhibitor fosinopril improves depressed responsiveness of myocytes to [Ca\(^{2+}\)] transient that have been observed in initial studies of human myocytes from failing myocardium.

The existence and relative importance of factors causing load-dependent myocyte dysfunction have been investigated largely in animal models of hypertrophy and failure. The pathophysiology of failure in animals may differ significantly from that in humans. However, obtaining high-quality human myocytes for study has been technically challenging. Although some success has been achieved by dissociating human myocytes from biopsy specimens in general, arterial perfusion of ventricular tissue with collagenase is necessary to obtain myocytes of high enough quality to allow studies at physiologic temperature and contraction rates. In this issue, Dipla et al report a method for isolation of human ventricular myocytes suitable for such studies. They apply it to show that myocytes isolated from hearts with end-stage dilated failure caused by both ischemic and idiopathic dilated cardiomyopathy, in which a left ventricular assist device (LVAD) was used for an extended period of time to unload the ventricle, had significantly improved contraction, relaxation, and catecholamine responsiveness relative to myocytes isolated from the hearts of patients who did not undergo a period of ventricular unloading before heart transplantation. Preliminary data suggest this improvement in function reflects changes in calcium homeostasis.
This study is significant from several perspectives. In addition to establishing techniques that will facilitate the further study of the pathophysiology and pharmacology of failing human ventricular myocytes, it provides evidence to support the hypothesis that chronic dilation and failure of the human heart produces myocyte dysfunction, and importantly, that the processes involved are reversible. Whether the improvement in myocyte function produced by the LVAD is due to effects of a reduction in sarcolemmal stress and/or associated hypertrophy or to a decrease in myocyte exposure to depressant agents such as catecholamines and/or cytokines due to LVAD-induced improvement in the circulation will require further study. In addition, myocytes from nonfailing hearts will need to be examined with similar techniques to establish what is “normal” function and thus to gauge the extent of reversibility of depressed function. Development of a large-animal model of ventricular dilation and failure in which effects of ventricular unloading with an LVAD could be similarly investigated would be very helpful in this regard. If the improvement in myocyte function is due at least in part to the reduction in ventricular wall stress, the clinical implications are of considerable importance. It is possible that prolonged load reduction by medical, surgical, or assist device interventions in patients with dilated cardiomyopathy of many causes may cause sufficient improvement in myocyte function to allow reestablishment of cardiac compensation and thus avoid or retard the progressive deterioration that complicates the management of this disorder.

References


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William H. Barry

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