Editorial

Regression of Left Ventricular Hypertrophy
New Hope for Dying Hearts
Arnold M. Katz, MD

Only a decade ago, end-stage heart failure was viewed as an irreversible condition for which therapy could offer only transient symptomatic relief. This led to a sense of hopelessness that resembled the prevailing attitude toward coronary occlusive disease 50 years ago, when atherosclerosis was thought to be an inevitable feature of natural aging. In the case of heart failure, as recently as the mid-1980s it was believed that little could be done to improve the natural history in patients with advanced chronic heart failure and a severely dilated ventricle. Yet within a few years, work from unexpected directions demonstrated that the progressive deterioration of the failing heart can be slowed and prognosis improved.

The first class of drugs shown in large clinical trials to improve prognosis in these patients was vasodilators. Because unloading the failing heart has an obvious energy-sparing effect and because virtually all vasodilators alleviate symptoms over the short term, it came as a surprise that not all of these drugs improve prognosis and that some accelerate deterioration of the failing heart and shorten survival. Equally counterintuitive was the finding that positive inotropic agents, which, like vasodilators initially improve symptoms, also increase mortality. Perhaps the most surprising finding of the clinical trials in heart failure was that long-term administration of β-adrenergic receptor blockers, although they initially worsen symptoms, reduce long-term morbidity and improve survival. Taken together, these clinical findings have led to a paradigm shift in our understanding of heart failure, one that by highlighting long-term mortality as a major problem has redefined the challenge in managing these patients. Today, it is clear that we can do more than simply relieve symptoms; we must also improve long-term survival. This, in turn, requires that we identify the causes of the poor prognosis in our growing population with left ventricular dysfunction.

An association between cardiac enlargement and shortened survival was identified by the great clinician-pathologists of the 18th and 19th centuries, who recognized that different patterns of cardiac hypertrophy have different prognostic implications (for review see Reference 12). In 1745, Giovanni Maria Lancisi in Italy distinguished between dilatation of the cavities of the heart and thickening of its walls, a distinction that was correlated with clinical outcome by Jean Nicolas Corvisart in France, who noted in 1801 that hypertrophy (“active aneurism”) strengthens the heart, whereas dilatation (“passive aneurism”) decreases the energy of cardiac contraction. By the middle of the 19th century, Austin Flint in the United States and James Hope in England had noted the rapid downhill course in patients with ventricular dilatation. In the latter third of the last century, Leopold Schroetter in Germany and Constantin Paul in France postulated that hypertrophy, although it provides an adaptive response that increases the ability of an overloaded heart to pump blood, is also maladaptive, because cardiac enlargement appeared to shorten survival. These views were elegantly summarized by William Osler in Canada, who in 1892 noted that the hypertrophic response of the failing heart, while initially compensatory, is followed by progressive worsening of symptoms that ends with the death of the patient. Osler called this “broken compensation,” which he stated is due to “degeneration and weakening of the heart muscle.”

Our modern understanding of the importance of maladaptive hypertrophy (Osler’s “broken compensation”) began in the early 1960s, when Felix Meerson demonstrated that aortic banding in experimental animals shortened survival and caused premature myocardial cell death, a process that can be viewed as a “cardiomyopathy of overload.” More recently, progressive dilatation of the failing heart, now called “remodeling,” was again recognized as playing an important role in determining the poor prognosis in heart failure (for review see Reference 16). The 18th and 19th century distinction between concentric hypertrophy (active aneurism) and dilatation (passive aneurism) was given new meaning by the finding that dilatation is due largely to cell elongation, whereas concentric hypertrophy results from cell thickening. A molecular basis for these different growth responses was provided by the demonstration that cell elongation and cell thickening in isolated cardiac myocytes are mediated by different signal transduction pathways. Because neither of these changes in phenotype is accompanied by a change in sarcomere length, myocyte thickening can be attributed to addition of new sarcomeres in parallel, whereas elongation occurs when the new sarcomeres are added at the ends of the fibers. These studies indicate that cardiac myocyte thickening and elongation, and thus concentric hypertrophy and dilatation, are mediated by different growth responses that generate different phenotypes. These fundamental observations make it likely that inhibition of the signal transduction pathways that lead to the addition of sarcomeres in series can slow, and perhaps reverse, the maladaptive growth response that causes progressive dilatation (remodeling) of the failing heart.

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(Circulation. 1998;98:623-624.)
Reversal of abnormal cell elongation in the failing human left ventricle is documented in this issue of Circulation by Zafeiridis et al,19 who used a left ventricular assist device (LVAD) to reduce left ventricular preload and afterload for an average of 75 days. In the 6 patients for whom echocardiographic data were obtained before and after unloading, left ventricular mass decreased almost 45% and left ventricular end-diastolic diameter decreased by >25%. The most interesting of these findings is that unloading the failing left ventricle reduced both myocyte length and width by ≈20%. These findings, which confirm other recent reports of the benefit of “resting” the failing heart (see Reference 19 for review), document the reversibility of a major cause of maladaptive hypertrophy. This study also provides an excellent model for future research, in both animals and humans, that could identify what is and what is not reversible in dilated (remodeled) hearts. This model may also prove useful in identifying means to block signal transduction pathways that, by causing sarcomeres to be added in series, lead to cell elongation in failing hearts.

Demonstration that cardiac myocyte elongation can be reversed (“reverse remodeling”) adds to a growing optimism regarding the possibility of alleviating at least some of the maladaptive features of myocardial hypertrophy. Use of the LVAD to achieve this benefit, however, raises a number of practical issues. The first, and perhaps the most important clinically, is whether a short course of therapy that reverses maladaptive changes in cardiac myocyte phenotype can provide significant and sustained clinical improvement. This question could not be addressed by Zafeiridis et al19 because, by design, the LVAD was a “bridge” to transplant. Much therefore remains to be learned regarding the durability of this morphological improvement and whether the benefits of reversion to a more normal cell size provide useful long-term palliation in end-stage heart failure. If LVAD therapy does lead to a useful and sustained remission in end-stage heart failure, we will need to learn whether this invasive approach has a role in less severely ill patients.

The overarching question raised by the findings of Zafeiridis et al19 extends beyond the ability of a surgically implanted device to “rest” the failing heart (see Reference 19 for review), document the reversibility of a major cause of maladaptive hypertrophy. This study also has implications for future research, in both animals and humans, that could identify what is and what is not reversible in dilated (remodeled) hearts. This model may also prove useful in identifying means to block signal transduction pathways that, by causing sarcomeres to be added in series, lead to cell elongation in failing hearts.

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Circulation. 1998;98:623-624
doi: 10.1161/01.CIR.98.7.623
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/98/7/623

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