

HEART FAILURE: from Hippocrates and Harvey to molecular biology

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The understanding of heart failure has progressed in all but a linear fashion. The many false starts (due to failure to understand pathophysiology) led to therapeutic strategies that have subsequently been abandoned; these range from bloodletting—based on the belief that the heart is the source of the body's heat—to the use of inotropic drugs, which reflected a more recent view that the major problem in this syndrome is depressed contractility. The current focus on the beneficial and deleterious features of cardiac enlargement may be more durable because it has returned our attention to maladaptive hypertrophy, whose role in determining prognosis had been recognized during the 19th century, but which today is supported by new discoveries in cell signaling and molecular biology.

In attempting to construct a “tree” describing the history of heart failure, I have concluded that this tree of knowledge is, in fact, a bush. Although both have roots and branches, the middle structure is quite different; in a tree, a single trunk supports the entire structure, whereas in a bush, many stems link the branches to the roots. Because much of what was once widely believed to be true is now known to be incorrect, and much that we now view as correct emerged suddenly and unexpectedly, this structure exemplifies the *paradigm shifts* described by Thomas Kuhn.¹ The roots in heart failure research have always been nourished by the clinical syndrome, which by stimulating efforts to understand what is wrong with these patients, provided the nutrients for the many stems of pathophysiology and therapy. However, not all of these stems have remained viable; some disappeared completely, while others—including many that once seemed vibrant and strong—have withered. I wonder whether some of the stems that seem strong today will not suffer the latter fate.

HEART FAILURE AS A CLINICAL SYNDROME

Although humans have always suffered from heart failure, identification of this syndrome in early writ-

ings is difficult because the clinical findings, most of which are not diagnostic, were not understood in terms of pathophysiology.² Palpation of the pulse is noted in the Edwin Smith papyrus, written in Egypt some 5000 years ago,³ but it was Hippocrates and other Greek physicians of the 6th to 5th centuries BCE, who made the first solid efforts to organize their clinical observations. Their writings describe a few patients with what might be heart failure,⁴ but because the heart's function as a pump was not understood, it is difficult to relate signs and symptoms that suggest heart disease to this syndrome. Furthermore, most treatments were based on a physiology that viewed health as a balance between competing humors. The Hippocratic texts do include a few examples of what today can be viewed as rational therapy for the complications of heart failure. Most notable is drilling through a rib (to avoid eventual closure of a hole in soft tissue) to drain a pleural effusion that had been localized when the physician listened for a “succussion splash” while an assistant shook the patient.

Because blood spurting from a severed artery is hot, the heart came to be viewed as the source of heat. This misconception, promulgated by Galen—a 2nd-century Greek physician whose writings were to domi-

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nate medicine until the 17th century⁵—led to the widespread practice of bloodletting to treat fevers, and indeed most maladies. We now know, of course, that the adverse consequences of bleeding almost always exceed any benefit, which provides a classic example—indeed *the* classic example—of the harm caused by therapy that is based on an erroneous understanding of pathophysiology.

HEART FAILURE AS A HEMODYNAMIC SYNDROME

Virtually no progress could be made in treating heart failure until the heart was understood to pump blood. Credit for this discovery belongs to William Harvey, whose *De Motu Cordis*, published in 1628, marked the emergence of the most durable pathophysiological stem in the heart failure bush. That *De Motu Cordis* appeared at a time when others were beginning to describe key features of the circulation³ illustrates the general rule that discoveries occur when the time is propitious. Although lacking Harvey's physiological thoroughness, these earlier descriptions indicate that 17th-century physiologists had begun to realize that the heart is a pump and not a furnace.

In spite of its monumental importance, *De Motu Cordis* had little immediate impact on the understanding and treatment of heart failure. Although Harvey was an accomplished physician, he wrote surprisingly little about how his discovery might explain the signs and symptoms of heart failure. In fact, almost a century was to pass before the hemodynamic cause of this syndrome was elucidated.^{5,6} Post-mortem dissection of the human body, which provided the soil that nourished another durable stem of

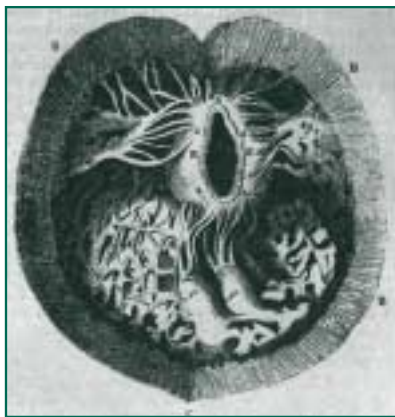


Figure 1. Vieussens' illustration of the stenotic mitral valve, viewed from below, illustrating the "fish mouth" appearance characteristic of rheumatic mitral stenosis.

Reproduced from reference 9: Major RH. *A History of Medicine*. Springfield, Ill: Charles C. Thomas. 1954. Courtesy of A. M. Katz.

the heart failure bush, became increasingly common during the 17th century. Autopsies allowed the clinical investigators of that time, after they had observed and recorded the clinical findings that preceded the death of a patient, to open the body in an attempt to learn what had caused the illness. In the century that followed *De Motu Cordis*, Lazare Rivière, James Hope, John Mayow, Richard Lower, Raymond Vieussens, and Giovanni Maria Lancisi began to relate the clinical features of heart failure to the abnormal hemodynamics.⁶⁻⁸ Assignment of priority among these and other 17th- and 18th-century authors is impossible because their case descriptions were generally compiled in books that were often published posthumously, frequently after the observations had circulated throughout Europe. The clearest early explanation of the hemodynamic abnormalities in heart failure is that of Vieussens, whose compassionate description of a patient whose death was caused by mitral stenosis is followed by a detailed discussion of the autopsy findings that includes a drawing of the stenotic mitral valve (*Figure 1*)⁹ and a remarkably mod-

ern explanation of the pathophysiology. Unfortunately, recognition of the hemodynamic basis for the signs and symptoms of heart failure was to have almost no impact on treatment for almost 300 years.

An exception to the generalization that understanding of pathophysiology is essential to treating disease occurred in 1785, when William Withering learned of an herbalist in Shropshire who was dispensing a remedy that was effective in treating dropsy. Using his knowledge of botany (which until the late 19th century was included in the medical curriculum), he concluded that the active ingredient is the leaf of *Digitalis purpurea*, the purple foxglove. Withering, of course, had no way of knowing how digitalis helped his patients, most of whom probably had rheumatic mitral stenosis complicated by atrial fibrillation; the ability of cardiac glycosides to slow the heart in this condition may have been the basis for his observation that digitalis "has a power over the motion of the heart, to a degree yet unobserved in any other medicine." Others thought that the benefits of this drug were due to a diuretic effect mediated by the kidneys, later to its inotropic effect, and most recently to its sympatholytic and vagomimetic effects—but this gets us ahead of our story.

HEART FAILURE AS A CONSEQUENCE OF ARCHITECTURAL ABNORMALITIES IN THE HEART

Emphasis on postmortem examination drew attention to changes in the size and shape of the failing heart,⁸ and led 18th- and 19th-century authorities to recognize two forms of hypertrophy, which today are generally called concentric and eccentric hypertrophy. Credit for this



distinction is generally assigned to Jean Nicolas Corvisart, a French clinician-pathologist who noted that the former, which he called “active hypertrophy,” has a better prognosis than “passive hypertrophy,” which came to be called *dilatation*. Concentric hypertrophy, or more simply *hypertrophy*, was for a time believed to be an adaptive response that helps the heart avoid the dire prognosis associated with dilatation. By the end of the 19th century, however, it had become clear that hypertrophy, like dilatation, is an imperfect adaptive response. This led William Osler, in 1892, to describe three phases in the response to overload (*Table I*).^{10,11} The first, *development* of hypertrophy, alleviates symptoms, because, as the heart enlarges, it becomes better able to handle the increased load; this led to the second phase of *full compensation*, when symptoms improve further. The adaptive response ends in a third, maladaptive, phase of hypertrophy, which Osler called *broken compensation*, where degeneration and weakening of the heart muscle worsen symptoms and cause the death of the patient.

One of the more remarkable observations made during the 19th century was that obstruction of left ventricular ejection, for example, in aortic stenosis, causes concentric hypertrophy, whereas regurgitant lesions like aortic insufficiency cause the heart to dilate. In modern terms, these observations suggest that increased *afterload* and increased *preload* initiate different phenotypes of hypertrophy by activating different proliferative signaling pathways (see below). Unfortunately, until the end of the 20th century, these and other features of the architectural stem provided few clues regarding treatment; aside from “pushing” digitalis, which sometimes killed the patient, little could be done to alle-

viate the suffering caused when increasingly frequent and more severe episodes of pulmonary edema heralded the approach of a cruel death.

HEART FAILURE AS A HEMODYNAMIC SYNDROME (AGAIN)

The hemodynamic abnormalities in heart failure, while understood by a few highly trained physicians, were largely ignored until 1915, when Ernest Starling presented his Linacre Lecture on the “Law of the Heart.” Although the role of diastolic volume in determining cardiac output was known to physiologists during the latter half of the 19th century,¹² most physicians based their views regarding the consequence of increased cavity size on the pathological finding that dilation is associated with a poor outcome.

Starling’s prestige was such that, within a decade after his lecture, dilation had come to be viewed as a beneficial short-term hemodynamic response, rather than a deleterious long-term architectural response. This focus on hemodynamics was also stimulated by Carl Wiggers’ research on valvular heart disease, which after World War II was to provide the foundation for modern cardiac surgery.

The renewed interest in hemodynamics had little impact on patient care, except for the use of rotating tourniquets, and sometimes venesection (a rare example where Galen’s therapy was appropriate), to treat acute pulmonary edema. My father, Louis Katz, who graduated from Medical School in 1921 after having worked as a student with Wiggers, told me that during his in-

THREE PHASES IN THE HEART’S RESPONSE TO HEMODYNAMIC OVERLOAD

Phase 1: Osler: *Development*; Meerson: *Transient breakdown*.

Clinical: Symptomatic left ventricular dysfunction after mild overload acute left ventricular failure and cardiogenic shock after severe overload.

Pathophysiology: Left ventricular dilatation, pulmonary congestion, low cardiac output, early hypertrophy.

Phase 2: Osler: *Full compensation*; Meerson: *Stable hyperfunction*.

Clinical: Class I-II heart failure.

Pathophysiology: Improved symptoms, resolved pulmonary congestion, increased cardiac output, established myocardial hypertrophy.

Phase 3: Osler: *Broken compensation*; Meerson: *Progressive cardiosclerosis*.

Clinical: Class III-IV heart failure.

Pathophysiology: Worsening congestion, hemodynamic deterioration, continued hypertrophy with progressive ventricular dilatation, myocardial cell death, fibrosis.

Based on data from reference 10: Osler W. The Principles and Practice of Medicine. New York, NY: Appleton; 1892.

and on data from reference 11: Meerson FZ. On the mechanism of compensatory hyperfunction and insufficiency of the heart. Cor Vasa. 1961;3:161-177.

Table I.

ternship he could do little for most cardiac patients except to try to determine what was wrong, after which he would wait until the patient died to see if he was correct—as he did not find this at all satisfying, he returned to research. An even more telling anecdote was published by Sir George Pickering:

...very few clinicians knew [anything] of the venous pressure. I remember vividly being an intern in 1930 to one of the best physicians whom it was my privilege to know, whose specialty was heart disease, and who was not acquainted with the message contained in the veins of the neck. This struck me most forcibly when I was asked to transfuse a patient with mitral stenosis and severe anemia, whose jugular veins were intensely distended... It struck me at the time as very odd that a patient who presented a sign indicating the desirability of venesection should be transfused. I was thus, in a way, scarcely surprised when the patient developed acute pulmonary edema as a result of transfusion and died.¹³

HEART FAILURE AS A DISORDER OF THE KIDNEYS

The discovery of the diuretic effect of organic mercurials had an enormous impact on the treatment of heart failure. Although fluid retention had been proposed as a cause of dropsy in the 16th century, there was no safe way to get rid of it. The diuretic effect of inorganic mercurials was well known, but their toxic/therapeutic ratio is so low that they usually did more harm than good. All this changed in 1920, when Paul Saxl and R. Heilig injected an organic mercurial to kill the spirochetes in a patient with syphilitic heart disease and, to their surprise, observed a massive diuresis¹⁴ that was subsequently found to be caused by inhibition of sodium resorption by

the renal tubules. However, because these drugs cease to be effective when given more than 2 to 3 times each week, they are of little benefit in severely ill patients. The search for powerful diuretics that could be given orally shifted the focus of heart failure research to renal physiology, and ended successfully in the late 1950s and early 1960s with the discovery first of the thiazides, and then of loop diuretics. This solid and durable stem of the heart failure bush illustrates how a chance discovery, along with an understanding of pathophysiology, came to alleviate human suffering.

The attention paid to the kidneys had an impact on my own training when, as an intern applicant in 1956, I attended a Medical Grand Rounds on heart failure at a prominent New York hospital that I had selected to be my first choice. After listening to an hour-long discussion dealing only with the kidneys, I could not resist asking: “Does the heart have anything to do with heart failure?” Not surprisingly, I went on to intern at my second choice in Boston.

ENERGETICS OF HEART FAILURE

Between the 1930s and 1950s, most experimental studies of heart failure used animal models whose hemodynamics resembled those seen clinically, but where the pathophysiology was entirely different. These included deteriorating heart-lung preparations, where the heart fails largely because particulates in the perfusates occluded the coronary microcirculation, and a model of acute right heart dilatation created by constricting the pulmonary artery and avulsing the tricuspid valve. While useful in studying the renal response, these models have little relevance to clinical heart failure. It is not surprising that these studies

led to the erroneous view that energetics in the failing heart are normal; a conclusion that was reinforced by data that for technical reasons were flawed, suggesting that heart failure is caused by a change in the molecular weight of cardiac myosin.¹⁵ The erroneous view that energy-starvation does not play an important role in heart failure was one reason that many failed to predict the detrimental effects of inotropic therapy and the potential benefits of β -adrenergic blockers (see below).

CARDIAC CATHETERIZATION AND CARDIAC SURGERY

Cardiac catheterization, which in the late 1940s brought more than a half century of basic research to the bedside, provided the accurate clinical diagnoses needed for cardiac surgery and so helped revolutionize the treatment of rheumatic and congenital heart disease—then the most common causes of heart failure. These advances, which are described elsewhere in this issue, are mentioned here because they are among the clearest examples of how basic science research improves clinical therapy.¹⁶

HEART FAILURE AS IMPAIRED MYOCARDIAL CONTRACTILITY

Between the 1920s and the 1960s, students were commonly taught that the failing heart operates on the descending limb of the Starling curve. This is surprising because Starling had made it clear in his Linacre Lecture that the heart cannot achieve a steady state when increasing chamber volume decreases its ability to eject. This confusion ended in 1955, when Stanley Sarnoff demonstrated that the heart can operate on different Starling curves,



shifting to a “lower” curve when contractility is depressed (*Figure 2*).¹⁷ This discovery came at a time when rapid progress in muscle biochemistry had shown that calcium delivery to the cytosol and its binding to troponin, a regulatory protein in the myofilaments, are major deter-

minants of myocardial contractility.¹⁸ Together, these discoveries shifted the focus of heart failure research to the depressed contractility. Efforts to apply this new knowledge to patients were hampered by difficulties in defining myocardial contractility and the fact that, although most investigators had some idea as to what contractility was, no one knew how to measure it. Research in this field during the 1960s and 1970s was based on concepts developed by A. V. Hill, whose classic work on the frog sartorius—where curves relating muscle load to shortening velocity are hyperbolic—had dominated skeletal muscle physiology for almost half a century. However, efforts to measure V_{max} , the maximal shortening velocity of a muscle contracting with zero load,

in cardiac patients failed to take into account the fact that the heart pumps, rather than hops, and, more importantly, that hyperbolic force-velocity curves cannot be measured in the heart because cardiac muscle cannot be tetanized.¹⁹ The latter, which meant that active state could

pectoris in patients with ischemic heart disease, which in developed countries was emerging as the major cause of cardiovascular death. At the same time, more precise diagnostic tools were identifying an increasing number of patients in whom heart failure is caused by a cardiomyopathy. For these reasons, heart failure came to be viewed as a hemodynamic disorder caused when depressed left ventricular contractility reduces the ability of the diseased heart to eject. This view, along with recognition of the harm caused by increased afterload, one of the body's responses to low cardiac output, provided the rationale for two new stems in the heart failure bush—afterload reduction and inotropic therapy.

The short-term benefits of afterload reduction, which by unloading the failing heart causes obvious hemodynamic improvement, led Jay Cohn to organize VHeFT I (Veterans Administration Heart Failure Trial I), a long-term clinical trial that examined the effects of several vasodilators on long-term prognosis. This randomized double-blind trial, published in 1986, was the first of the large heart failure trials that now represent the “gold standard” in evaluating therapy. The major findings were that a long-acting nitrate in combination with hydralazine prolongs survival, whereas prazosin, an α -adrenergic blocker, has no benefit (*Figure 3A, next page*).²¹ This pioneering study, which also highlighted the poor prognosis in heart failure, led to additional trials that sought to document a survival benefit for other vasodilators. However, the results were generally disappointing because, in spite of the ability of all vasodilators to cause short-term hemodynamic improvement, most worsen long-term prognosis. A major exception was CONSENSUS (COoperative North

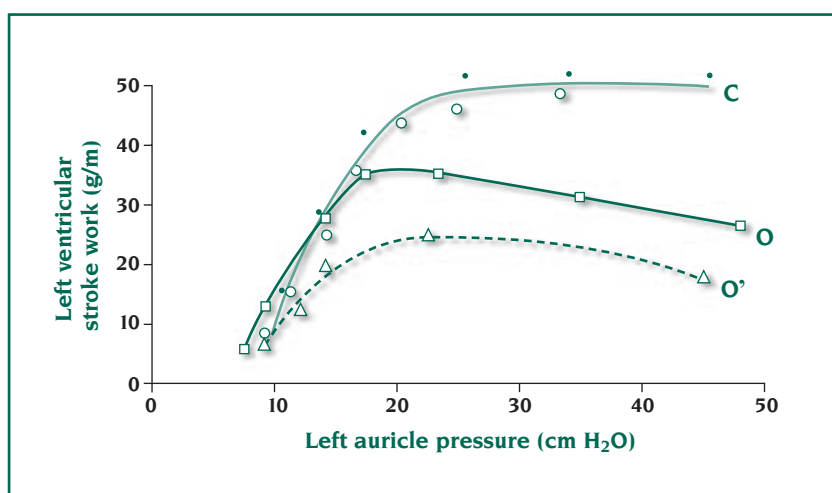


Figure 2. Effects of reduced coronary flow on left ventricular stroke work in an anesthetized dog; C: control; O: mild restriction of coronary flow; O': moderate restriction of coronary flow.

Modified from reference 17: Case, RB, Berglund E, Sarnoff SJ. Ventricular function. II. Quantitative relationship between coronary flow and ventricular function with observations on unilateral failure. *Circ Res.* 1954;2:319-325. Copyright © 1954, Lippincott Williams & Wilkins.

not be stabilized, made it impossible to determine V_{max} , which many viewed as the gold standard in quantifying contractility. After almost two decades of heated controversy,²⁰ it became clear that myocardial contractility cannot be measured accurately in patients.

VASODILATOR AND INOTROPIC THERAPY

At the end of the 1970s, in spite of the successful development of oral diuretics and use of digitalis, patients with heart failure continued to suffer and die. However, the causes of this syndrome were changing; rheumatic fever was disappearing; and most patients with valvular and congenital heart disease were improved by the cardiac surgeon, who could also alleviate angina

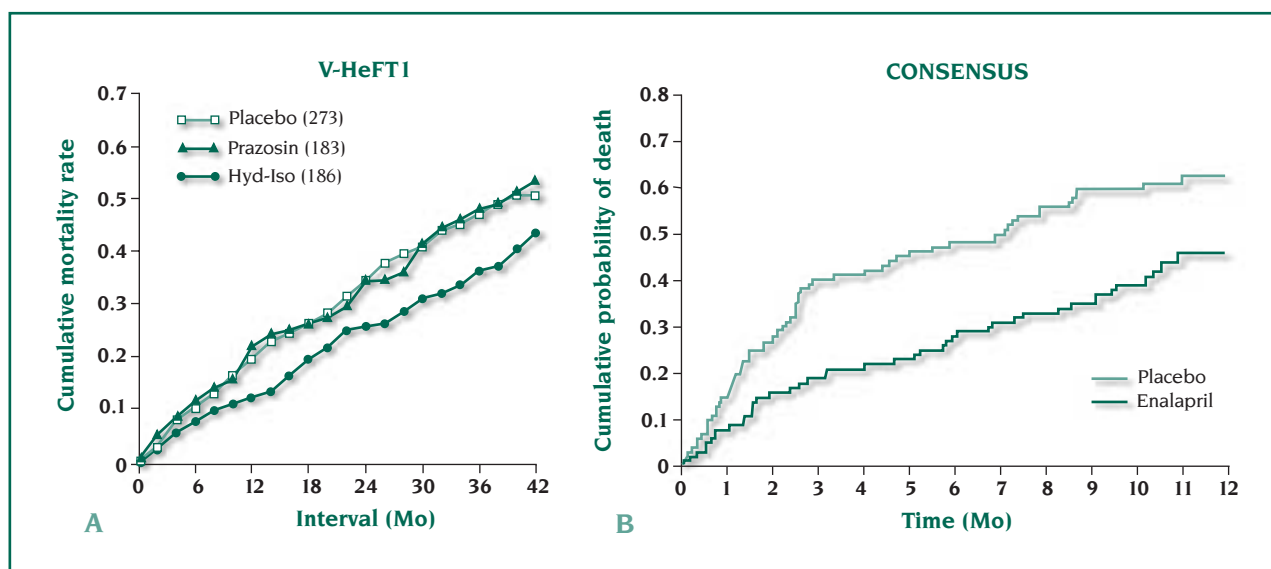


Figure 3. Clinical trials showing effects of vasodilators on mortality in heart failure.

A. Effects of isosorbide dinitrate in combination with hydralazine (Hyd-Iso) and of prazosin in V-HeFTI (Veterans Administration Heart Failure Trial I). Modified from reference 21: Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration cooperative study (V-HeFT). *N Engl J Med.* 1986;314:1547-1552. Copyright © 1986, Massachusetts Medical Society.

B. Effect of enalapril showing a highly significant benefit in severe heart failure in CONSENSUS (COoperative North Scandinavian ENalapril Survival Study). Reproduced from reference 22: CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study. *N Engl J Med.* 1987;316:1429-1434. Copyright © 1987, Massachusetts Medical Society.

Scandinavian ENalapril SURvival Study), which, by documenting a remarkable benefit in patients given an angiotensin II converting-enzyme (ACE) inhibitor (Figure 3B),²² opened a new area of research.

Efforts during the 1970s and 1980s to develop new inotropic agents were aided by further clarification of the role of calcium in contraction, excitation-contraction coupling, and relaxation, and by the discovery that cyclic AMP mediates the positive inotropic response to sympathetic stimulation. The widely held belief that increasing contractility would benefit patients with heart failure was reinforced by observations that norepinephrine and other β -agonists, which increase cellular cyclic AMP levels, cause short-term hemodynamic improvement in patients with *acute* heart failure. However, evidence that the failing heart is energy-starved led a minority to believe that the energy cost of the

inotropic and chronotropic responses to cyclic AMP could harm patients with *chronic* heart failure. This provoked a sharp controversy that ended when several clinical trials showed that long-term inotropic therapy with β -agonists and phosphodiesterase inhibitors does more harm than good. At the same time, a long-awaited clinical trial showed that cardiac glycosides, which had come to be viewed as inotropes, do not improve survival in patients with heart failure who remain in sinus rhythm.

REMODELING, ACE INHIBITORS, AND MOLECULAR BIOLOGY

A new era of heart failure research began in 1985, when a landmark paper by Janis Pfeffer, Mark Pfeffer, and Eugene Braunwald²³ showed that it is possible to inhibit deterioration of the failing heart. The key observation was that an ACE inhib-

itor slows the progressive dilatation that follows experimental myocardial infarction (Figure 4).²³ To describe the cavity enlargement, which the investigators viewed as “a compensatory remodeling (dilation) of the left ventricle [that allows] preservation of forward output at any filling pressure,” they chose the term *remodeling*, which highlights the beneficial short-term hemodynamic response to dilatation described by Starling, rather than the deleterious long-term architectural effect noted in the 19th century.

The clinical importance of this discovery became apparent the following year when, at a meeting held in Oslo, Norway, the results of CONSENSUS I were announced. This trial documented a survival benefit of an ACE inhibitor that was so striking (Figure 3B)²² that a member of the audience stood up and said that these results could not be true because, to paraphrase, “No other



vasodilator has this marked effect on survival.” This led me to suggest that the improved prognosis might not be due to the vasodilator effect of the inhibiting angiotensin II production, but instead to a different response not known at that time. Clearly, no one at the Oslo meeting was aware that research had already begun that was to show that angiotensin II also stimulates proliferative responses.²⁴

HEART FAILURE AS A CONSEQUENCE OF ARCHITECTURAL ABNORMALITIES IN THE HEART (AGAIN)

Although advances in hemodynamics during the 20th century had relegated studies of the architecture of the failing heart to the background, the earlier work had not been entirely forgotten. Felix Meerson, who in the 1950s was the first to use

sufficiency normalizes wall stress.¹⁴ This finding, which made it clear that deterioration of the hypertrophied heart is not due simply to continued overload, highlighted the importance of *maladaptive* hypertrophy as a cause for the poor prognosis in patients with chronic heart failure.²⁶ It remained simply to figure out how hypertrophy can be both adaptive and maladaptive, and at the same time, in the same patient!

PROLIFERATIVE SIGNALING AND SURVIVAL IN HEART FAILURE

The first clue that overload changes the molecular composition of the heart had come in 1962, when Norman Alpert and Michael Gordon reported a reduction in the ATPase activity of myofibrils isolated from failing human hearts. This study heralded a still growing body of knowledge that has characterized molecular changes in the failing heart, such as reversion to the fetal phenotype, and is now describing the proliferative signaling pathways that initiate adaptive and maladaptive hypertrophy.²⁷⁻³³

At the same time that the molecular mechanisms responsible for deterioration of the failing heart were coming into focus, progress continued in efforts to prolong survival in patients with heart failure. Virtually all large clinical trials in heart failure enrolled patients with a low ejection fraction, often called *systolic heart failure*, where progressive dilatation is a major consequence of maladaptive hypertrophy. The most remarkable finding was the beneficial effect of β -blockers, which because of their negative inotropic effect had been almost universally viewed a decade earlier as contraindicated in these patients. As had happened before, the extent of the benefit was unexpected and, for

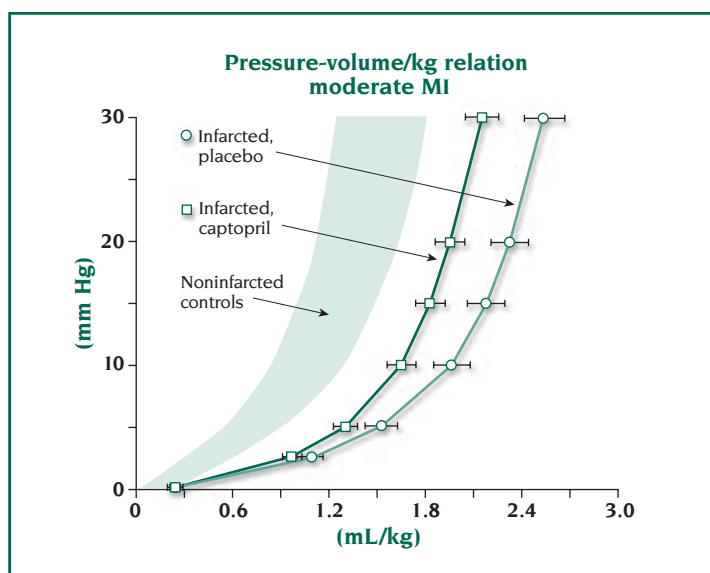


Figure 4. Effect of captopril on diastolic pressure-volume relationships in rats following myocardial infarction (MI). Left ventricular diastolic volumes (abscissa) and pressures (ordinate) after 3 months are shown for noninfarcted control rats (shaded area, mean ± 2 SD), infarcted hearts of untreated rats (O), and infarcted hearts of rats treated with captopril (\square). The difference between the latter is significant ($P < 0.05$).

Modified from reference 23: Pfeffer JM, Pfeffer MA, Braunwald E. Influence of chronic captopril therapy on the infarcted left ventricle of the rat. *Circ Res.* 1985;57:84-95. Copyright ©, 1985 Lippincott Williams & Wilkins.

The context for both these experimental and clinical findings came into focus at a second meeting, held in Boston in 1987, which made it clear to all who attended that molecular biology had arrived on the scene.²⁵ This new discipline, which describes how altered gene expression regulates cardiovascular function, is revolutionizing the way we view heart failure, and promises to improve our ability to treat this syndrome (see below).

modern methods to study overload-induced myocardial deterioration in animal models, described three phases that are similar to those proposed by Osler in 1892 (Table I).^{10,11} In the 1960s and 1970s, after cardiology rediscovered the Law of Laplace (which although known to 19th-century physiologists, had been forgotten since the 1920s), at least 3 groups found that the initial *adaptive* hypertrophic response in patients with aortic stenosis and in-

those who did not believe that the failing heart is energy-starved, counterintuitive. Another remarkable finding was that spironolactone, a potassium-sparing diuretic that had been used for decades, also improves prognosis.

It is probably significant that the drugs that prolong survival in systolic heart failure also inhibit remodeling; these include nitrates, ACE inhibitors, angiotensin II receptor blockers, β -blockers, and aldosterone antagonists. Furthermore, cardiac resynchronizing therapy (CRT) and left ventricular assist devices (LVADs), which also improve prognosis, reverse many features of maladaptive hypertrophy, including reversion to the fetal phenotype and remodeling. Although a rigorous assessment of the impact of these new therapeutic approaches on survival has not been carried out, comparisons of heart failure trials in the 1980s and early 1990s with those reported in the past few years suggest that life expectancy has been doubled.

CONCLUSION

The emergence of the new stem of molecular biology clearly represents a major addition to the heart failure bush, but much remains to be done. Perhaps the most important challenge today is how to manage the growing population of patients, mostly elderly, who have heart failure with low ejection fraction (so-called *diastolic heart failure*). I suspect that the drugs that have been shown to improve prognosis in systolic heart failure will not have the same benefit in diastolic heart failure because in the latter progressive dilatation does not, by definition, contribute to the clinical deterioration. Answers to this and other important questions will probably depend on the emergence of

additional stems in the heart failure bush. Although these new stems will be rooted in the clinical syndrome, history tells us that they are likely to emerge from unexpected places on the growing bush of basic knowledge.

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See also:

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