The "Modern" View of Heart Failure
How Did We Get Here?

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The inauguration of a new journal provides a unique opportunity to look back on the way that we arrived at our present state of understanding. In the case of heart failure, it is possible to trace a remarkable history that, for Western medicine, extends back to clinical descriptions collected in works attributed to Hippocrates in ancient Greece. Since the fifth century BCE, physicians and scientists have approached this clinical syndrome in at least 9 different ways (Table). The increasing rapidity with which these views have changed illustrates how new knowledge has narrowed the gap between clinical medicine and basic science.[1]

The present article describes how our understanding of heart failure has evolved over the past 2500 years. Having been active in this area since the 1950s and having shared many reminiscences with my father, Louis N. Katz, who played an active role in academic cardiology between the 1920s and 1970s, I have included several personal insights about progress since the beginning of the 20th century.

Heart Failure as a Clinical Syndrome

Patients with what may have been heart failure are described in ancient Greek and Roman texts, but edema, anasarca, and dyspnea, the most common clinical manifestations mentioned in early writings, have other causes. Difficulties in evaluating these clinical descriptions are due partly to lack of pathophysiological understanding of disease, which was then viewed as an imbalance between opposing humors (Figure 1).

The Hippocratic corpus describes rales: "When the ear is held to the chest, and one listens for some time, it may be heard to seethe inside like the boiling of vinegar"[2] (*Diseases II, LXI*); also discussed are the succussion splash heard when patients with pleural effusions are shaken vigorously[3] (*Coan Prognostics*, 424) and a surprisingly modern way to drain this fluid through a hole drilled in a rib[2] (*Internal Afflictions XXIII*). However, there was no understanding about why fluid accumulated, as evidenced by the following explanation: "Should [phlegm coming from the brain] make its way to the heart, palpitation and difficulty breathing supervene . . . for when the phlegm descends cold to the lungs and heart, the blood is chilled . . . and the heart palpitates, so that under this compulsion difficulty of breathing and orthopnea result"[3] (*The Sacred Disease IX*).

The center of medical science shifted to Alexandria, in Egypt, during the third century BCE, where Herophilus and Erasistratus performed human dissection and physiological experiments. Although they recognized that the heart contracts and understood the function of the semilunar valves, the Alexandrian physiologists held that the arteries contain air and that blood flows from the right ventricle into the veins, so their efforts had no impact on understanding heart failure.

Galen, a Greek physician who lived in the Roman Empire during the second century CE, viewed the heart as the source of heat. Having read the work of the Alexandrians, Galen knew that ventricular volume decreases during systole and understood the function of the heart's valves, but failed to realize that the heart is a pump. Galen palpated the arterial pulse, a technique used for prognostication millennia earlier by the Egyptians,[4] but believed that the pulse is transmitted along the walls of the arteries rather than by blood flowing through their lumens[5] (*De Sang in art*, K733). He described what almost certainly represents atrial fibrillation when he noted "complete irregularity or unevenness [of the pulse], both in the single beat and in the succession of beats"[6] (*De locis affectis*, ii).

Galen's view that the heart's primary function is to distribute heat by an ebb and flow was to dominate Western thinking for more than 1500 years. Lack of understanding led physicians to recommend treatments for clinical manifestations such as dyspnea and dropsy that included the following: "Take scabwort and grind and squeeze its juice through a cloth, collect in an eggshell and temper with honeycomb; give the patient daily a full shell of the juice, do this for eleven days when the moon is waning because also man wanes in his abdomen."[7] We should resist the temptation to laugh at these nonphysiological treatments because we still make mistakes; it is only recently that inotropic therapy was recognized to do more harm than good in patients with heart failure (see below).

Heart Failure as a Circulatory Disorder

In the early 16th century, physicians began to perform autopsies to identify causes of illness. Postmortem reports initially consisted of "two or three lines of symptomatology and four or five lines of gross autopsy findings".[8] There was no way to relate the clinical findings to heart disease until

Table. Changing Views of Heart Failure

1. A clinical syndrome
2. A circulatory disorder
3. Altered architecture of the heart
4. Abnormal hemodynamics
5. Disordered fluid balance
6. Biochemical abnormalities
7. Maladaptive hypertrophy
8. Genomics
9. Epigenetics

1628, when William Harvey (Figure 2) clearly described the circulation: "I am obliged to conclude that in animals the blood is driven round a circuit with an unceasing, circular sort of movement, that this is an activity or function of the heart which it carries out by virtue of its pulsation, and that in sum it constitutes the sole reason for the heart's pulsatile movement."[9]

Harvey's discovery provided a basis for understanding the hemodynamic abnormalities in heart failure. Forty years later, Richard Lower noted that ejection was impaired by compression of the heart in pericardial tamponade,[10] and in 1715, Raymond Vieussens published a remarkably clear description of the physiological basis for the signs and symptoms in a patient with mitral stenosis, then the most common cause of heart failure.[11]

Altered Architecture of the Heart

At the beginning of the 18th century, physicians began to focus on the abnormal structure of failing hearts. Giovanni Maria Lancisi, in a text published in 1745, noted that valvular regurgitation leads to ventricular dilatation but that the left ventricular cavity does not enlarge in aortic stenosis.[12] Lancisi also suggested that dilatation weakens the heart, a view that was confirmed and extended a century later by Nicolas

Corvisart[13] and John Bell,[14] both of whom observed that eccentric hypertrophy (dilatation) has a worse prognosis than concentric hypertrophy. Corvisart also noted that patients with heart failure can die in 2 ways: progressive heart failure, which "advances slowly, [until] life is insensibly extinguished," and sudden death, which can occur at any time in the course of this syndrome. René-Joseph-Hyacinthe Bertin, in 1833, concluded that dilatation "weaken[s] the contractile power of the muscular substance of that organ, in consequence of the distention to which it is subjected. The muscular fibers lose in strength what they acquire in extent." He noted the more benign course in patients with concentric hypertrophy, which is "in general, slow, tardy and *chronic* [and frequently] does not merit on its own account any thing more than a secondary consideration."[15] In the mid-19th century, Austin Flint suggested that concentric hypertrophy is "an important conservative provision, first, against over-accumulation of blood, and second, against the more serious form of enlargement, viz., dilatation."[16] The adverse prognostic effects of concentric hypertrophy become apparent during subsequent decades and in 1892 allowed William Osler to observe that hypertrophy, while initially adaptive, eventually becomes maladaptive.[17]

Distinctions between dilatation, with and without ventricular wall thickening, and hypertrophy, with and without reduction in cavity volume, were made (and confirmed at autopsy) in the 19th century, when there was no way to image the heart; Röntgen did not discover x-rays until 1895. Cavity size and wall thickness were evaluated at the bedside by palpation, percussion, and the characteristics of heart sounds and murmurs. Distinctions between various forms of cardiac enlargement continued into the 20th century, but the focus of efforts to understand the pathophysiology of heart failure returned to hemodynamics after 1918, when Ernest H. Starling described his "Law of the Heart."[18]
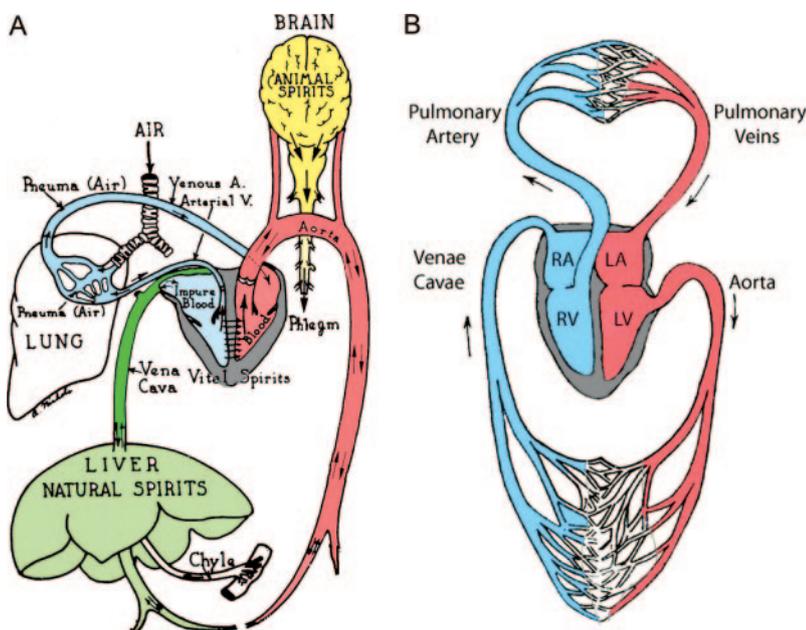

Figure 1. Two views of the circulation. A, Galen's view. Pneuma derived from air (blue) reaches the heart from the lungs via the venous artery (pulmonary artery) and arterial vein (pulmonary veins). Natural spirits that enter the heart from the liver (green), along with vital spirits (heat) generated in the left ventricle, are distributed throughout the body by an ebb and flow in the arteries (red). Animal spirits transported from the brain through nerves as phlegm (yellow) contribute to formation of pleural effusions. B, The view after Harvey. Deoxygenated blood is depicted in blue, oxygenated blood in red. RA indicates right atrium; LA, left atrium; RV, right ventricle; and LV, left ventricle. Adapted from Major RH. *A History of Medicine*. Springfield, Ill: CC Thomas; 1954; and from Starling EH. *Principles of Human Physiology*. Philadelphia, Pa: Lea & Febiger; 1926.
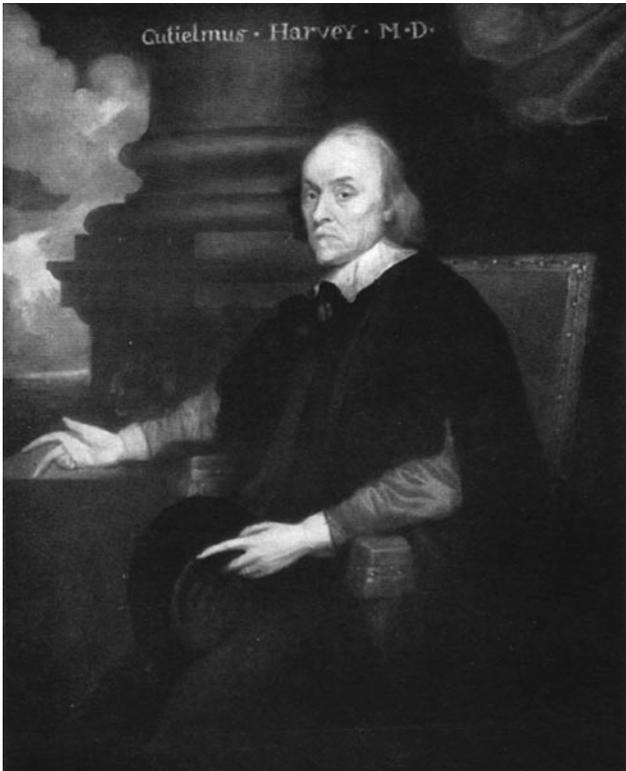
Figure 2. William Harvey. State portrait at the Royal College of Physicians, painted when Harvey was in his late 60s.

Abnormal Hemodynamics

Starling's demonstration that increasing end-diastolic volume enhances cardiac performance had an immediate impact on efforts to understand the pathophysiology of heart failure. Although many 19th-century physiologists knew that increasing diastolic volume leads to an increase in cardiac output,[19] most physicians had based their views of the effects of increased cavity size on the pathological evidence that dilatation is associated with a poor prognosis (see above). For this reason, Starling's demonstration that increased end-diastolic volume increases the heart's ability to do work was confusing because it seemed to contradict the 19th century view that dilatation weakens the heart. It was not until the end of the 20th century that the adverse long-term effects of pathological dilatation in diseased hearts were clearly distinguished from the beneficial short-term effects of physiological increases in cavity volume that underlie Starling's Law of the Heart (see below).

Starling's 1918 article added to confusion about the pathophysiology of heart failure in another way because, for more than 60 years, it was commonly taught that failing hearts operate on the descending limb of the Starling curve, where increasing chamber volume decreases the heart's ability to eject (Figure 3). This incorrect view overlooked Starling's observation that when dilatation exceeds "the optimum length of the muscle fiber and the muscle has to contract at such a mechanical disadvantage . . . the heart fails altogether."[18] It was not until 1965, when I pointed out that the heart cannot achieve a steady state on the descending limb of the Starling curve,[21] that this erroneous view began to disappear. How-

ever, this fallacy continued to represent "a pervasive and powerful misconception" that, as recently as the 1980s, was believed by a majority of medical students at a prominent United States medical school.[22]

Hemodynamic abnormalities were of enormous importance in heart failure during the first half of the 20th century, when almost three fourths of patients hospitalized for heart disease in England had structural abnormalities (51% rheumatic, 11% bacterial endocarditis, 9% cardiovascular syphilis, and 2% congenital).[23] In the United States at the same time, rheumatic valvular disease accounted for 60% to 80% of adult heart disease.[24–26] Today, in developed countries, rheumatic heart disease has become a rarity, which makes it difficult to appreciate the impact of this cause of heart failure, which had been a scourge since antiquity.

The prevalence of structural heart disease highlighted the importance of the work of Starling, Carl J. Wiggers, and other physiologists who studied the hemodynamics of valvular and congenital abnormalities. However, hemodynamics had little impact on patient care except for use of rotating tourniquets and venesection to treat acute pulmonary edema. My father, who graduated from medical school in 1921 after having worked with Wiggers, told me that during his internship little could be done for most cardiac patients except to try to determine what was wrong, after which the treating physicians would wait until the patient died to see who was correct; because dad did not find this at all satisfying, he returned to research. Sir George Pickering, in an even more telling anecdote that documents how little impact hemodynamics had on patient care in the 1930s, wrote that while an intern to one of London's best cardiologists who "was not acquainted with the message contained in the veins of the neck," he was asked to transfuse a patient with mitral stenosis and severe anemia who had markedly distended jugular veins.[27] It struck Pickering as odd to transfuse a patient who "presented a sign indicating the desirability of venesection," but he did as he was told and was "scarcely surprised" when the patient developed acute pulmonary edema and died as a result of the transfusion.
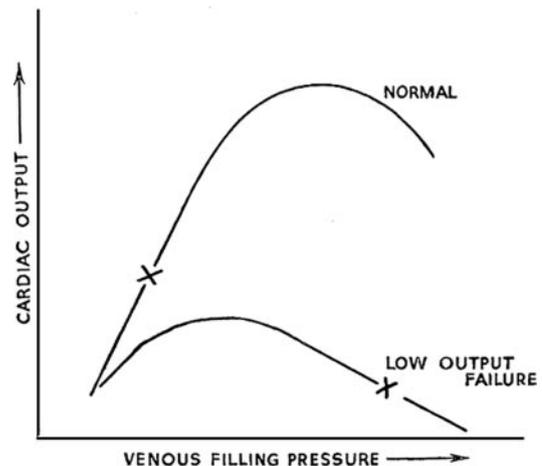

Figure 3. Diagram illustrating the failing heart operating on the descending limb of the Starling curve. Adapted from McMichael.[20]

It was not until the early 1940s that introduction of cardiac catheterization by André Cournand and Dickinson W. Richards brought more than a half century of hemodynamic research to the bedside.[28] I vividly remember my father, after returning from a meeting in the 1940s, saying "This is it!" By this, he meant that having learned of Cournand's and Richards' work, he knew that cardiac catheterization had brought the lifetime he had spent in basic research into clinical medicine.

Another decade was to pass before hemodynamic knowledge was of practical importance.[29] The story began when treatment of cardiac injury during World War II demonstrated the feasibility of operating on human hearts. Their wartime experience led Charles Bailey and Dwight Harken in the United States and Russell Brock in Great Britain to develop operations to open the narrowed valve in patients with rheumatic mitral stenosis. Harken told how thoracic surgeons overcame the fear of operating on the heart, once thought to be impossibly dangerous, when they began to remove shrapnel from the hearts of wounded soldiers. He described how he cited this experience to defend animal experimentation, then under attack by antivivisectionists. At a trial, he testified that the first patients on whose hearts he had operated all died, after which he was able to operate on dozens without a death. He concluded by stating that his initial patients had been dogs; the rest were American soldiers.

Development of open heart surgery and prosthetic valves, which began in the 1960s, allowed cardiac surgeons to palliate many forms of structural heart disease, both rheumatic and congenital. However, these advances did not solve the challenges posed by heart failure because ischemic heart disease and dilated cardiomyopathies were emerging as the major causes of systolic heart failure, and systemic arterial hypertension and reduced aortic compliance led to an epidemic of diastolic heart failure in today's aging population.

Disordered Fluid Balance

Little progress was made in the management of patients with dropsy (anasarca), a common manifestation of heart failure, until the 20th century. Although fluid retention had been proposed as a cause of dropsy as early as the 16th century, there had been no safe way to get rid of the excess salt and water. The diuretic effect of inorganic mercurials was well known, but their low toxic/therapeutic ratio meant that they usually did more harm than good. The major breakthrough occurred in 1920, when Saxl and Heilig gave an organic mercurial to kill the spirochetes in a patient with syphilitic aortic valve disease complicated by heart failure and observed a massive diuresis.[30] However, the value of these drugs is limited because these compounds have to be administered parentally and lose their efficacy when given more than 2 to 3 times each week, which means that organic mercurials are of little benefit in end-stage heart failure. Efforts to develop more powerful, orally active diuretics became so intense that for a time the focus in heart failure research shifted to the kidneys. When I was a medical student applying for internship in 1956, I attended a grand rounds on heart failure at my first-choice hospital. As a budding cardiologist, I was so nonplussed to find that the entire discussion dealt with fluid retention and the kidneys that, unable to restrain myself, I asked whether the heart had anything to do with heart failure. Not surprisingly, I interned at my second choice. I take some consolation that thiazides, loop diuretics, and more recently ultrafiltration, although able to alleviate fluid retention in virtually every patient, cannot cure heart failure.

Biochemical Abnormalities

Beginning in the 1950s, 3 areas of biochemistry came to have a major impact on cardiology. The initial focus was on energetics, which had influenced thinking in muscle physiology since the beginning of the 19th century. The second began to unfold in the 1960s, when elucidation of the mechanisms responsible for muscle contraction, relaxation, and excitation–contraction coupling helped in understanding how hearts failed and initiated a search for new inotropic drugs that were initially viewed as able to cure, or at least significantly palliate, this syndrome. At the same time, rapid advances in the third area, the biochemical basis for the neurohumoral response to reduced cardiac output, led to the first major advances in treating this syndrome since the introduction of effective diuretics.

Energy Starvation

Thermodynamics was among the first of the sciences to be applied to muscle physiology (electricity was another) when it was realized that during contraction, muscles liberate energy as both work and heat. Helmholtz, who described the first law of thermodynamics, published records of heat production by muscle in 1848; according to A.V. Hill, "[Helmholtz's] early work on muscle heat production . . . lighted a flame which . . . burnt brightly in Germany till the end of the [19th] Century."[31] My father was burned by this flame in 1925 when, as a fellow working with Hill in London, he tried to measure heat production by the heart. His efforts failed because cardiac muscle liberates much less heat than skeletal muscle, in amounts too small to be quantified with the thermopiles available at that time.

The efficiency of failing hearts became a major issue in the 1920s and 1930s, when most basic investigations used the mammalian heart–lung preparations pioneered by Starling. In 1927, Starling and Maurice Visscher reported that mechanical efficiency (work per unit of oxygen consumption) decreased in failing heart–lung preparations,[32] but a decade later my father's group found parallel decreases in work and oxygen consumption when these preparations deteriorated.[33] In the 1950s, Robert E. Olson's conclusion that the underlying problem was impaired energy consumption by the contractile machinery[34] suggested that failing hearts are not energy starved. However, these experimental studies were flawed because heart–lung preparations deteriorate when particulates in the perfusates occlude the coronary microcirculation, and Olson's model of heart failure, which was created by pulmonary stenosis and tricuspid insufficiency, had little pathophysiological resemblance to most clinical heart failure. More recently, analytical tools like nuclear magnetic resonance spectroscopy have shown conclusively that adenosine triphosphate (ATP) and phosphocreatine levels are signifi-

cantly reduced in overloaded and failing hearts,[35,36] which made it clear that energy starvation plays an important role in heart failure.

Depressed Contractility

The dominance of changing end-diastolic volume in regulating the work of the heart ended quite suddenly in 1955, when Stanley Sarnoff described "families of Starling curves."[37] His demonstration that the heart could shift from one Starling curve to another, which meant that cardiac work is not determined solely by end-diastolic volume, clarified the role of myocardial contractility as a major regulator of cardiac performance. Characterization of this regulatory mechanism in patients was hampered by difficulties in defining myocardial contractility and the fact that, although most investigators had some idea of what contractility was, no one knew how to measure it.[38] Much of the research on this subject during the 1960s and 1970s had been based on the work of A.V. Hill, whose classic studies of muscle mechanics in tetanized frog sartorius muscle dominated muscle physiology for almost a half century. However, efforts to measure maximal shortening velocity (V_{max}), which in the 1970s was viewed as the "gold standard" in quantifying contractility, in mammalian myocardium overlooked complications that arose because the heart pumps, rather than hops, and because it is not possible to tetanize cardiac muscle.[39] After almost 2 decades of heated controversy, it became clear that myocardial contractility cannot be precisely quantified in patients.[40] Despite these theoretical limitations, Eugene Braunwald's group was able to show convincingly in the late 1960s that contractility is reduced in patients with chronic heart failure.[41]

Emphasis on myocardial contractility occurred at a time of rapid progress by muscle biochemists, who by the mid-1960s had shown that calcium delivery to the cytosol and its binding to troponin, a regulatory protein in the myofilaments, are major determinants of contractility.[42] These discoveries provided clues to mechanisms that depress contractility in failing hearts and stimulated efforts to develop inotropic drugs more powerful than digitalis, the benefits of which in heart failure were then viewed as resulting from increased contractility. The widely held belief that powerful inotropic agents would benefit patients with failing hearts was reinforced by observations that β-agonists, which increase cellular cyclic adenosine monophosphate levels, cause short-term hemodynamic improvement in heart failure.

Evidence that failing hearts are energy starved (see above), along with the known adverse effects of increased intracellular calcium,[43] led some to believe that the energy cost of the inotropic and chronotropic responses to cyclic adenosine monophosphate could harm patients with chronic heart failure[44] and that reducing energy expenditure with β-blockers might benefit these patients.[45] This provoked a sharp controversy that ended when clinical trials showed that long-term inotropic therapy with β-agonists and phosphodiesterase inhibitors does more harm than good[46,47] and that β-blockers, despite their negative inotropic effects, prolong survival, reduce hospitalizations, and improve well-being in these patients.[48] Additional evidence that heart failure is not simply a hemodynamic disorder came when cardiac glycosides,

despite their inotropic effect, were found not to improve survival in patients with heart failure and sinus rhythm.[49] However, as noted below, the mechanisms responsible for the adverse effects of inotropes and beneficial effects of β-blockers turned out to be far more complex than changes in energy balance.

The Neurohumoral Response

The third major advance in understanding the biochemical abnormalities in failing hearts began with recognition of the importance of the neurohumoral response.[50,51] Peter Harris, in 1983, provided a clear explanation of the adverse role played by the body's responses to lowered cardiac output, the most important of which are vasoconstriction, salt and water retention, and adrenergic stimulation.[50] Harris pointed out that these responses, which had evolved to maintain cardiac output during exercise and support the circulation when cardiac output falls after hemorrhage, become harmful when they are sustained and therefore are deleterious in chronic heart failure.

The ability of reduced afterload to increase both cardiac efficiency[52] and cardiac output[53] provided a rationale for the introduction of vasodilators to treat heart failure.[54] The likelihood that these drugs would benefit patients with chronic heart failure was further supported by short-term benefits of afterload reduction, which include increased ejection, decreased ventricular diastolic pressure, and improved cardiac energetics. These considerations stimulated Jay N. Cohn and others to organize the Vasodilator Heart Failure Trial (VHeFT) I to examine the effects of vasodilators on long-term prognosis in these patients.[55] This randomized double-blind trial, which was the first of the large heart failure trials that now represent the gold standard in evaluating therapy, showed that despite short-term hemodynamic improvement, afterload reduction does not always prolong survival. Although there was a trend toward improved survival after administration of a combination of isosorbide dinitrate and hydralazine, the α_1-adrenergic blocker prazosin had no long-term benefit. More surprising were the results of subsequent trials that showed that many other vasodilators, although of short-term benefit, worsen long-term prognosis.[56] A major exception was Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) I, which documented a dramatic benefit of angiotensin II–converting enzyme (ACE) inhibitors.[57] The implications of CONSENSUS I became apparent when the results of this trial were first presented in 1986 at a meeting in Oslo, Norway, when a member of the audience implied that these results could not be true because, to paraphrase, "No other vasodilator has this marked effect on survival." The question, which I attempted to answer by suggesting that ACE inhibitors could have effects other than vasodilatation, overlooked the fact that, unbeknownst to most in the audience, investigators had begun to explore the possibility that angiotensin II is not only a vasodilator but also a regulator of proliferative signaling (see below).

Maladaptive Hypertrophy

The aforementioned advances in hemodynamics and biochemistry relegated studies of the architecture of the failing

heart to the background throughout most of the 20th century; however, the earlier work on cardiac hypertrophy had not been entirely forgotten. Felix Meerson, who in the 1950s was the first to use modern methods in studying the hypertrophic response to overload in animals,[58] observed, as had Osler more than 50 years earlier,[17] that overload-induced hypertrophy is both beneficial and deleterious. Meerson's experiments resurrected interest in cardiac enlargement, which had held center stage during most of the 19th century (see above). Subsequent studies showed that left ventricular hypertrophy initially normalizes wall stress in patients with compensated aortic stenosis[59–61] and therefore made it clear that deterioration of hypertrophied hearts is not simply a consequence of sustained overload. A critical clue to the mechanisms responsible for the survival benefits of ACE inhibitors was published in 1985 when Janis Pfeffer, Mark Pfeffer, and Eugene Braunwald found that these drugs slow the progressive cavity enlargement, which they called *remodeling*, that follows experimental myocardial infarction[62] (Figure 4). The possibility that progression in heart failure is caused by maladaptive features of the hypertrophic response led me to suggest that overload-induced hypertrophy represents a cardiomyopathy that contributes to the poor prognosis with heart failure[63] and that the benefits of ACE inhibitors occur when these drugs block maladaptive effects of angiotensin II on transcriptional signaling.[64]

An early suggestion that the composition of the failing heart is not normal was published in the 1950s, when Olson and Dorothy Piatnek reported that the molecular weight of myosins isolated from failing hearts had doubled.[34] However, "heart failure myosin" turned out to be the result of a technical error. In 1962, Norman R. Alpert and Michael S. Gordon reported that ATPase activity is reduced in myofibrils isolated from failing human hearts[65]; J.Y. Hoh et al subsequently found that these differences are due to expression of different myosin isoforms.[66] James Scheuer and colleagues demonstrated that molecular changes in failing hearts include not only decreased energy turnover by the contractile proteins but also slower calcium transport by the sarcoplasmic reticulum,[67] and Seigo Izumo, Bernardo Nadal-Ginard, and others found that increased expression of the low ATPase β-myosin heavy chain isoform in failing hearts is part of a pattern of isoform shifts that are part of a reversion to the fetal phenotype.[68,69] Scheuer's finding that opposite changes occur in training-induced physiological hypertrophy (the "athlete's heart"), in which increased expression of the high ATPase α-myosin heavy chain isoform increases ATPase activity and contractility,[70] confirmed my earlier suggestion that changes in molecular composition participate in the long-term regulation of cardiac function.[71] Molecular changes are now known to cause additional problems in heart failure; for example, depolarizing currents that accompany calcium efflux via the sodium–calcium exchanger appear to be a major cause of arrhythmias and sudden death,[72] whereas inhibition of progressive dilatation (remodeling) contributes to the beneficial effects of β-blockers[73] as well as ACE inhibitors.

Genomics

A new approach to understanding the mechanisms responsible for the progressive deterioration of failing heart came into
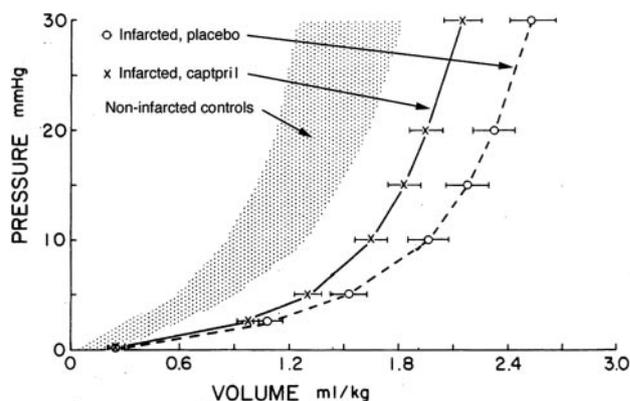

Figure 4. Effect of the ACE inhibitor captopril on left ventricular diastolic pressure-volume relationships after myocardial infarction. Diastolic volumes and pressures are shown for noninfarcted control rats (shaded area, mean±2 SD), infarcted hearts of untreated rats (o), and infarcted hearts of rats treated with captopril (x). Data derived from Pfeffer et al.[62]

focus in 1987, when molecular biology moved to center stage in cardiology.[74] Three years later, in 1990, the Seidman laboratory reported the first molecular cause of a familial cardiomyopathy, a missense mutation in the cardiac β-myosin heavy chain gene.[75] This discovery identified one of a growing number of mutations involving additional proteins that cause both hypertrophic and dilated cardiomyopathies.[76,77] The possibility of modifying the signal pathways controlled by these mutations raises the possibility that transcriptional therapy can be developed to help some of these patients.[78] Similarly, efforts to modify signaling pathways that could allow activation of adaptive cardiac myocyte growth and inhibition of maladaptive hypertrophy are under way[79–81] (Figure 5). One can expect that the pages of *Circulation: Heart Failure* will soon contain promising reports based on these and other discoveries in cardiac genomics.

Epigenetics

A newly discovered type of regulation, referred to as *epigenetics*,[82] has recently been identified as operating in heart failure. Epigenetic regulation differs from the more familiar genomic mechanisms, the primary targets of which include transcription factors that interact with DNA and alternative splicing that allows synthesis of different protein isoforms by rearranging the information encoded in the exons of genomic DNA. Epigenetic mechanisms modify later steps in proliferative signaling pathways, including methylation of cytosine in genomic DNA, histone acetylation, and inhibition of RNA translation by small RNA sequences, called *microRNAs*. Cytosine methylation has been implicated in some familial cardiomyopathies,[83,84] and histone acetylation can modify overload-induced cardiac hypertrophy.[85,86] Evidence that microRNAs regulate cardiac hypertrophy[87,88] is of potential therapeutic importance because short RNA segments, called small-interfering (si)RNAs, can silence specific genes. The ability of siRNAs, which are readily synthesized commercially, to block specific proliferative pathways promises
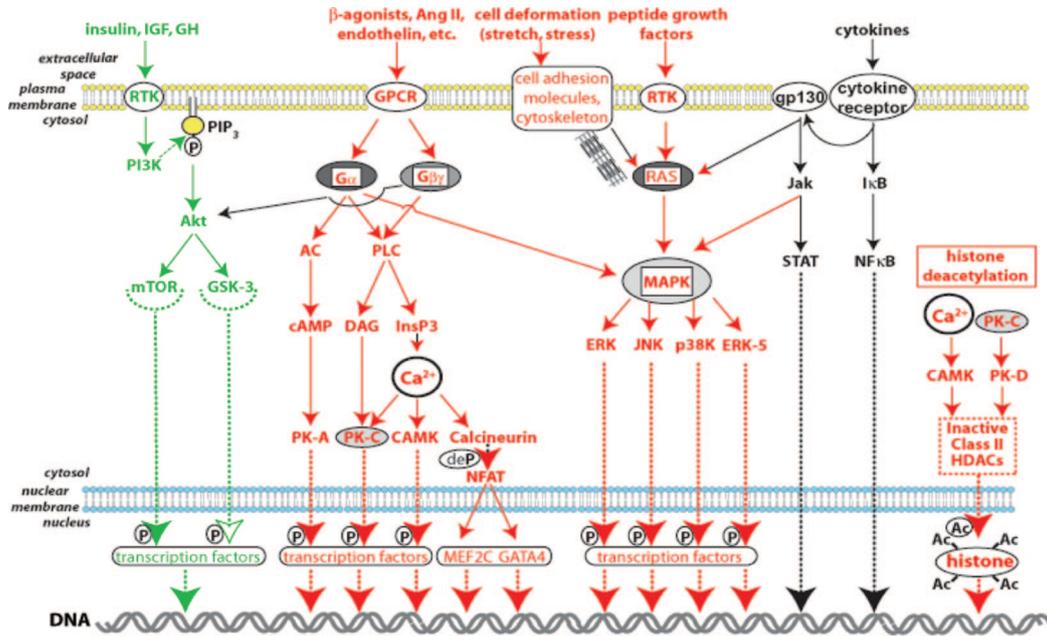
Figure 5. Proliferative signaling pathways that mediate cardiac hypertrophy. The PI3K/PIP₃/Akt pathway is activated when insulin, insulin growth factor (IGF), and growth hormone (GH) bind to receptor tyrosine kinases (RTK); the cascade begins with phosphorylation of phosphatidylinositol tris phosphate (PIP₃) by phosphoinositide 3′-OH kinases (PI3K) that activates Akt, a protein kinase that phosphorylates mammalian target of rapamycin (mTOR) and inhibits glycogen synthetase kinase 3 (GSK-3). Neurohumoral mediator binding to G-protein–coupled receptors (GPCR) activates G_α and $G_{\beta\gamma}$. $G_{\alpha s}$ activates adenylyl cyclase (AC) to form cyclic adenosine monophosphate, which stimulates protein kinase A (PK-A). $G_{\alpha q}$ and $G_{\beta\gamma}$ activate phospholipase C (PLC) to form diacylglycerol (DAG) and inositol tris phosphate (InsP₃). DAG stimulates protein kinase C (PK-C). Calcium released by InsP₃ activates protein kinase C and calcium/calmodulin kinase (CAMK). Calcium also activates calcineurin, a protein phosphatase that dephosphorylates nuclear factor of activated T cell (NFAT) so as to activate the transcription factors MEF2C and GATA4. Peptide growth factor binding to RTKs and cytoskeletal signaling pathways activate Ras, a monomeric G-protein that stimulates mitogen-activated protein kinase (MAPK) pathways; the latter include extracellular receptor-mediated kinases (ERK), c-Jun kinase (JNK), and p38 kinase (p38K). Activated cytokine receptors release an inhibitory effect of IκB on nuclear factor-κB (NFκB) and activate gp130-mediated signaling pathways that stimulate janus kinase (Jak) to activate signal transducer and activator of transcription (STAT) and MAP kinases. Calcium and protein kinase C can inactivate class II histone deacetylases (HDACs), which increase histone acetylation (Ac) that reduces an inhibitory epigenetic effect on DNA transcription. Pathways in red mediate mainly maladaptive hypertrophy; those in green, mainly adaptive hypertrophy. Cytokine-activated pathways (black) can activate both adaptive and maladaptive growth. Thin solid arrows indicate signaling pathways; dotted arrows with solid arrowheads, phosphorylations (P); and those with open arrows, dephosphorylations (deP). Modified from Katz.[40]

additional approaches to inhibiting maladaptive hypertrophy to slow deterioration of failing hearts.

Conclusions

The extent to which therapy for heart failure is now changing is documented in Figure 6, which shows how management of heart failure has evolved over the past 40 years. The remarkable progress in understanding the pathophysiology and clinical management of this syndrome not only illustrates the increasing pace of scientific discovery[1] but also how great discoveries emerge from unexpected directions.
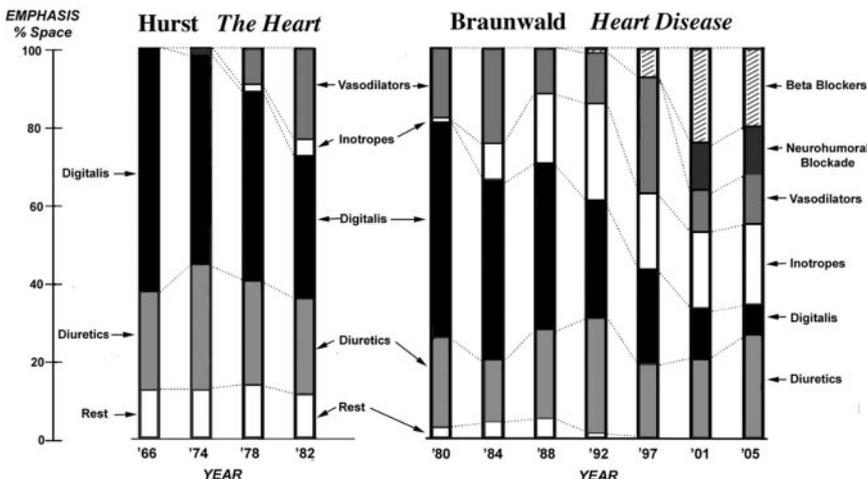

Figure 6. Changing management of heart failure over the past 40 years. Pages devoted to various treatments were estimated in several editions of Hurst's *The Heart* and Braunwald's *Heart Disease*. (Electronic and mechanical devices and surgical therapies are not included.) From Katz and Konstam.[89]

A.V. Hill, in a book based on lectures given in 1926 to school children in London, described how Röntgen, while studying the conduction of electricity through gases, discovered x-rays:

> Imagine fifty years ago a prize offered to anyone who could photograph the inside of the body of a living child. He or any who tried to win the prize would only have been laughed at for their pains. Certainly those who set out to win it would have been most unlikely to succeed. Success came from a totally different direction, from the work of men who to their severely practical brothers may have seemed to be investigating things of little importance. Often in science, as in life, it is the by-products which turn out in the end to be more important than the things we set out to find. . . . One never knows where scientific investigations will lead, but experience has made it certain that a disinterested and honest study of nature, an attempt to understand the real facts behind the shadow, will lead at intervals to discoveries of the first importance for the comfort and well-being, mental, moral, and material, of the race.[90]

Thirty years later, in a lecture delivered on the occasion of the presentation of a copy of Harvey's *De Motu Cordis* to the John Crerar Library in Chicago, my father stated:

> Research is a dignified profession, to be pursued only by the consecrated and inspired, in quietude, at a leisurely pace, and away from prying eyes. It cannot be placed on a business footing where one new fact is to be returned for each quantum of dollars invested. I have actually heard some persons propose to set up a committee to find out what needs to be done in discovering a cure for some specified malady. I have heard them suggest gathering all of the eminent scientists together and putting them to work so that the cure will come in their lifetime. Of course these individuals, worried about themselves, would like to hurry the process. Since industry had been successful in harnessing men together, the uninitiated naturally believe that research results can be accomplished in the same way. Unfortunately this is not necessarily so. Great discoveries are not produced on the assembly line. Only duplicates can be so manufactured. The original must come about through the deliberate activity of a creative mind. And a creative mind works best away from artifices and prodding. Great discoveries evolve—they are not delivered on call. This was the case with Harvey.[91]

Looking back at the work of the many scientists, both basic and clinical, whose efforts provided the knowledge that is of such enormous benefit to patients with heart failure, we cannot but marvel at the way that a dispassionate study of nature and human disease has benefited humanity.

Disclosures

None.

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