

Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal



Journal of Clinical and Basic Cardiology 2001; 4 (3), 173

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Congestive Heart Failure – Five Decades of Progress

E. Braunwald

My first contact with patients suffering from congestive heart failure occurred in 1952, just a half century ago. As a medical student at New York University I was assigned to a heart failure clinic, one of the first devoted entirely to patients with this condition, and a haemodynamic laboratory under the leadership of Professor Ludwig W. Eichna, a pioneer clinical investigator of heart failure. The patients with heart failure whom I encountered usually had hypertension or rheumatic valvular disease (Tab. 1). The suggested underlying mechanism – “exhaustion of the overloaded ventricle” – had not changed since it had been proposed by Osler more than a half century earlier. Treatment with bed rest, digitalis, salt free diet, and intramuscular mercurylidrin was applied, more or less indiscriminately to all patients, and also had not changed for several decades.

My subsequent interest in heart failure has been in three principal areas:

Neurohormonal Disturbances

In the early 1960s my colleagues and I described the first neurohormonal disturbance in heart failure. We reported that circulating concentrations of the adrenergic neurotransmitter, norepinephrine, were abnormally elevated in patients with heart failure, particularly during exercise [1]. This was associated with elevations in the quantity of norepinephrine excreted in the urine [2], and with marked reductions in the cardiac content of the neurotransmitter [3]. Much has been learned about abnormalities in adrenergic signalling in the last four decades. Most important, from a clinical perspective, has been the realization that the hyperadrenergic state characteristic of heart failure can, on a chronic basis, impair cardiac function further, and that beta-adrenergic blockade prolongs life and reduces hospitalizations for heart failure in a large proportion of patients with systolic heart failure [4].

The second humoral system in heart failure, which I investigated, was the renin-angiotensin-aldosterone system. The Drs. Pfeffer and I found that angiotensin converting enzyme inhibition (ACEI) prevents hypertrophy and left ventricular dysfunction in spontaneously hypertensive rats [5], and prevents left ventricular dilatation and death in rats with myocardial infarction [6]. The salutary haemodynamic effect was also observed in patients with myocardial infarction [7]. These observations culminated in the SAVE trial, which was the first trial to demonstrate an improvement of survival in patients post-infarction who had left ventricular dysfunction without overt heart failure [8]. Just as was the case for beta-

blockade, ACEI has been shown to prolong life in a large proportion of patients with heart failure, and has become a cornerstone in the treatment of this condition.

The entire field of neurohormonal disturbances in heart failure has moved forward rapidly, and a variety of other blockers appear to be beneficial in the treatment of heart failure. These include angiotensin receptor II blockers, endothelin blockers as well as blockers of the neural endopeptidase that catalyzes the breakdown of atrial natriuretic peptide. In experimental heart failure preparations, blockers of arginine vasopressin and of a number of cytokines, especially tumor necrosis factor α also appear to be salutary.

Disturbances of Myocardial Function

In the 1960s there was still considerable controversy regarding the intrinsic function of the myocardium in heart failure. We created two models of heart failure. In papillary muscles removed from kittens with obstruction to right ventricular outflow and studied *in vitro*, we observed a marked disturbance of force development and velocity of contraction [9]. We created a second model of heart failure by causing prolonged tachycardia induced by several weeks of ventricular pacing and observed that when the pacing was discontinued the haemodynamic changes characteristic of heart failure, including reductions of stroke volume and ejection fraction persisted [10].

Since these early studies our understanding of disorders of contractile function in heart failure has advanced considerably. Disturbances in myocyte shape and dimensions have been reported and contractile defects at the sarcomeric level have been observed in human (as well as animal) cardiac muscle in heart failure. Moreover, it has been observed that with prolonged unloading of the heart with a left ventricular assist device, normal myocardial function may be restored in some patients [11].

Myocardial Energetics

Table 2 shows six postulated pathogenetic mechanisms for the development of heart failure. I have been particularly interested in the fourth of these, ie a reduction of the availability of high-energy phosphate stores. In both of the aforementioned models of heart failure – the kitten with chronic right ventricular pressure overload [9] as well as the dog with pacing induced tachycardia [10] – the total stores of high energy phosphates and the ratio of creatine phosphate to adenosine triphosphate were found to be reduced [12]. Since then such reductions have been described in patients with heart failure secondary to mitral regurgitation [13] and dilated cardiomyopathy [14]. The lack of energy stores appears to play a role in the pathogenesis of heart failure in conditions other than

Table 1. Heart failure in 1951

Etiologies	Hypertension, valvular HD
Mechanism	“Exhaustion” of overloaded ventricle
Goals of Rx	Reduce symptoms by ↓ fluid accumulation Improve haemodynamics
Management	Similar therapy for all Digitalis Bed rest Strict Na ⁺ restriction Mercurial diuretics I.v. catecholamines for acute pump failure
Attitude	Hopelessness

Table 2. Mechanisms of heart failure – 2001

- Reintroduction of fetal expression of sarcomeric proteins
- Myocyte Ca²⁺ overload
- Myocyte apoptosis
- Abnormalities of cytoskeletal proteins
- Impaired energy metabolism (including chronic stunning)
- Interstitial fibrosis

coronary obstruction. However, in 1982 we postulated that in the latter condition, heart failure may be caused by chronic stunning, ie repetitive episodes of myocardial ischaemia not severe enough to cause myocardial necrosis [15]. Chronic stunning can lead to ischaemic cardiomyopathy, a very common form of heart failure which may not be associated with signs of overt ischaemia, such as angina or electrocardiographic changes. When this condition is recognized it may be treated successfully by coronary revascularization. Indeed, revascularization of ischaemic cardiomyopathy is now the most common method of permanently reversing heart failure [16].

Conclusions

It has been my good fortune in the last half century to witness, often at close range, many important developments in heart failure and to participate in several of them. The view of

the condition has changed enormously in the past fifty years (Tab. 3). While there has been substantial progress in management, both the incidence and prevalence of heart failure are increasing rapidly, in large part because of the progressive aging of the population. However, there now exist several areas of special opportunity (Tab. 4). These include the prevention of heart failure – by preventing its most common cause – ischaemic heart disease. Several new areas of therapy, including newer blockers of neurohumoral and cytokine causes of cardiac damage appear promising. Sudden cardiac death, responsible for about half of the mortality of heart failure can be largely prevented by the implantation of internal cardioverter defibrillators. Cardiac replacement with a totally implanted artificial heart or by xenotransplantation is undergoing rapid development. Finally, I believe that myocardial regeneration, using stem cell based therapy, holds out the greatest promise.

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Table 3. Changes in focus on heart failure (modified from *Eur Heart J* 2001; 22: 825–36)

	1951	2001
Etiologies	Hypertension Valvular HD	Ischemic HD Cardiomyopathies
Mechanisms	"Exhaustion" of overloaded ventricle	Molecular mechanisms Abnormal gene expression
Goals of Rx	Reduce symptoms by: ↓ fluid accumulation ↑ contractility ↓ vent. rate in AF	Improve quality and duration of life Prevent deterioration of pump function Prevent fatal arrhythmias Shorten hospitalization
Management	Similar therapy for all Digitalis Bed rest Na ⁺ restriction Mercurial diuretics	Individualized therapy Aggressive manage- ment plan, close followup in HF centers ACE inhibitors, β-blockers, loop diuretics, moderate exercise Spironolactone, digitalis, anticoagulants LVAD, ICD, transplantation
Encouraging experimental therapies	I.v. catecholamines for acute pump failure	AT1 receptor blockers, endothelin blockers, TNF I blockers, vasopeptidase inhibitors
Attitude	Hopelessness	Guarded optimism

Table 4. Heart failure: future directions

- Greater application of established therapies
- Additional blockade of activated neurohormonal/cytokine systems
- Prevention of HF through genetically-targeted prevention of ASCVD
- Prevention of sudden cardiac death
- Prolonged mechanical unloading
- Cardiac replacement: artificial ht., xeno-transplantation
- Myocardial cell replacement, myocardial regeneration

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