

## 2

# Pathophysiology—Clinical Spectrum and Current Management

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### 2.1. Pathophysiology

The noted biological and medical writer Lewis Thomas mused in his 1983 essay, entitled ‘The Artificial Heart’:

*We do not really understand the underlying mechanism of cardiomyopathies at all, and we are not much better at comprehending the biochemical events that disable the heart muscle or its valves in other more common illnesses. But there are clues enough to raise the spirits of people in a good many basic science disciplines, and any number of engrossing questions are at hand awaiting answers. The trouble is that most of the good questions that may lead, ultimately, to methods for prevention (for example, the metabolism and intimate pathologic changes in a failing myocardium, the possible roles of nutrition, viral infection, blood-clotting abnormalities, hypertension, life-style, and other unknown factors) are all long-range questions, requiring unguessable periods of time before the research can be completed. Nor can the outcome of research on any particular line be predicted in advance; whatever turns up as the result of science is bound to be new information. There can be no guarantee that the work will turn out to be useful. It can, however, be guaranteed that if such work is not done we will be stuck forever with this insupportably expensive, ethically puzzling, halfway technology, and it is doubtful that we can long afford it.*<sup>1</sup>

Sixteen years later Willerson observed in an editorial on heart failure that it is ‘Not yet clear is what mediates the progression of heart failure after the initial injury, and how it may be influenced’.<sup>2</sup>

In order to understand more fully the mechanisms through which the process of ventricular containment is useful for the treatment of congestive

heart failure (CHF), it is crucial to have a thorough knowledge of the pathophysiology of this common heart disease. In this chapter I discuss the disease processes of CHF at a biochemical, molecular or cellular level, and at a more systemic level.

#### 2.1.1. Initiation of Heart Failure

Initial injuries or insults to the myocardium may sometimes be sub-clinical, thus producing immediate signs of heart failure only in a small group of patients. These injuries often initiate a process that leads to chronic CHF over a period of months or years. Three main forces that initiate the process of CHF are

- intrinsic myocardial damage
- abnormal load on one (particularly the left ventricle) or both ventricles
- extrinsic forces affecting the heart.

Over half the cases of intrinsic myocardial damage are due to ischaemia and/or infarction caused by ischaemic heart disease.<sup>3</sup> Myocardial damage resulting in heart failure may also be caused by auto-immune injury, infections, metabolic insults and toxic conditions.<sup>4</sup> Idiopathic dilated cardiomyopathy may be due to self-directed antibodies to myocyte antigens. Immunodulation may cause improvement in these patients.<sup>5</sup> Toxic and metabolic causes include alcohol toxicity and hyperthyroidism.

Abnormal loads on the myocardium may be due to chronic pressure overload (e.g. systemic arterial hypertension) or volume overload (e.g. aortic and mitral valve regurgitation).

Extrinsic causes of heart failure include constrictive pericardial disease, tachycardia-induced heart failure, and 'high-output' heart failure due to severe anaemia or a large arteriovenous fistula or shunt.

### 2.1.2. Progression

The underlying mechanism in the development and progression of heart failure involves an initial insult followed by ventricular remodelling. A destructive cycle is set in motion whereby the remaining normal myocardium undergoes changes in cellular metabolism, leading to hypertrophy and fibrosis. This gradually results in changes in the ultra-structure of the ventricles through a process called remodelling. Remodelling occurs initially as an adaptive response to improve cardiac performance. Unfortunately over time this response becomes counterproductive and maladaptive.<sup>6</sup>

### 2.1.3. Molecular and Cellular Basis

There are various factors that impact on the ventricles at a cellular level. For instance systemic arterial hypertension causes a reactivation of embryonic growth factors, which are normally dormant in the adult heart. These factors accelerate protein synthesis and myocyte growth, resulting in hypertrophy of the ventricle.<sup>7</sup> Diastolic dysfunction ensues and progresses to systolic dysfunction, which ends up causing a large, dilated, poorly functioning ventricle.

Myocardial infarction (MI) is another trigger for ventricular remodelling. The irreversibly injured myocardium loses contractile function, causing compensatory changes in the remaining myocardium. This functional overload on non-infarcted muscle, as well as intrinsic changes in the infarcted area (such as myocyte filament slippage), leads to remodelling. This process finally results in a dilated heart with severe dysfunction.<sup>8</sup>

The contributing mechanisms to ventricular remodelling are complex and not completely understood. Current hypotheses focus on certain cytokines and growth factors, such as tumour necrosis factor (TNF).<sup>9</sup> Elevated levels of TNF are found in the myocardium of patients with heart failure. Raised levels of TNF may cause myocyte dysfunction through a mechanism involving the induction of nitric oxide synthase (iNOS).<sup>10,11</sup>

While the maladaptive changes of heart failure can be reversed by successful treatment if instituted early enough,<sup>12</sup> further cellular changes result in apoptosis—programmed cell-death—and fibrous replacement in normal areas of the heart, causing permanent functional damage.<sup>13</sup>

The common end result of chronic congestive failure is systolic dysfunction, which translates as an inability of the left ventricle to eject its contents in systole. Left ventricular ejection fraction while a relatively weak prognostic indicator if used alone<sup>14</sup> is the most frequently used objective estimate of heart failure severity.

Diastolic dysfunction exists when the left ventricle is unable to fill at a normal rate and to a normal extent.<sup>15</sup> Systolic function may be normal in some patients with diastolic dysfunction. This condition can be caused by a variety of conditions, including severe left ventricular hypertrophy, restrictive infiltrative myocardial disease and constrictive pericarditis. There is no accurate way of quantifying diastolic dysfunction. Diastolic dysfunction can be difficult to treat effectively and may progress steadily.<sup>16</sup>

### 2.1.4. Maladaptive Systemic Responses

Chronic CHF starts off as adaptive cardiac and systemic responses in an attempt to maintain normal perfusion of systemic organs. These responses become counterproductive over time, leading to the progression of heart failure, with worsening symptoms (Figure 2.1).

Various homeostatic mechanisms are activated in CHF, such as the activation of the renin–angiotensin–aldosterone system. Decreased renal perfusion is detected by receptors in the renal arterioles, leading to renin release from the kidneys. The increased angiotensin II that is formed acts on efferent arterioles increasing glomerular filtration pressure, despite reduction in renal perfusion pressure. Aldosterone synthesis is stimulated by angiotensin II, causing retention of salt and water by the kidney. Initially, this mechanism works to preserve normal systemic and renal perfusion. However, over a longer period this process leads to edema, elevated pulmonary artery pressures and increased after-load.<sup>17</sup> Figure 2.2 illustrates these mechanisms.

Figure 2.2 shows that there is an increase in sympathetic activity, as well as vasopressin and renin

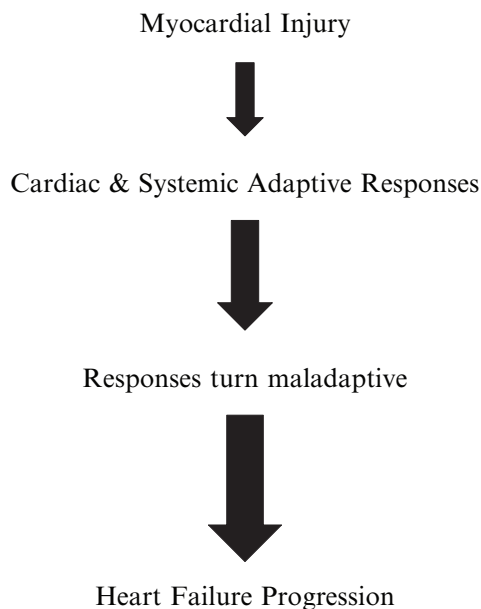


FIGURE 2.1. Mechanism of heart failure progression.

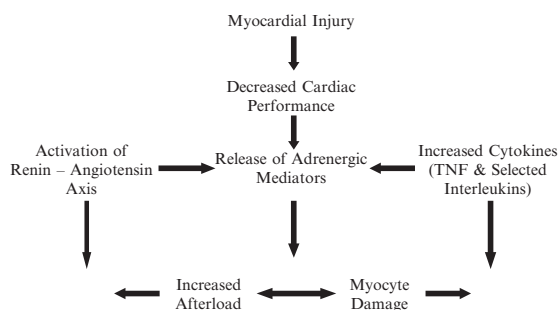


FIGURE 2.2. Cycle of heart failure progression, interacting with the renin-angiotensin axis, adrenergic system and cytokines.

release, in CHF. Neuro-endocrine activation is manifested by the release of norepinephrine, vasopressin and atrial natriuretic peptide.<sup>18</sup> The increased afterload and myocyte damage leads to a repetitive cycle of decreasing cardiac performance. Norepinephrine increases systemic vasoconstriction, chronotropy and inotropy by direct cardiac stimulation.<sup>19</sup> Over time, this increase in tissue norepinephrine activity predisposes to ventricular arrhythmias and sudden cardiac death. Higher circulating levels of plasma norepinephrine have been shown to negatively correlate with the prognosis of heart failure.<sup>20</sup> These values, while a rough guide, can be highly variable

and unreliable compared to local concentrations of norepinephrine within the heart. The levels of norepinephrine in the cardiac circulation are measured by norepinephrine spill-over, and are elevated in CHF, providing an accurate prognostic guide.<sup>21</sup>

Increased levels of endothelin are also found in CHF, promoting peripheral vasoconstriction, myocyte hypertrophy and adverse remodelling.<sup>22</sup> Furthermore, atrial and brain natriuretic peptides (ANPs & BNPs) are released by the atria in response to stretch and increased atrial pressure. Neurohormones, cytokines and nitric oxide all interact together in complex ways to create the syndrome of chronic heart failure.

#### 2.1.4.1. Fetal Gene Activation During Heart Failure

In a hypertrophied heart, myocytes are not only big in size but they also have additional sarcomeres. The manner in which these sarcomeres are added depends upon the type of load being imposed on myocytes. In situation of pressure overload, sarcomeres are added in parallel, leading to increased LV wall thickness, whereas during volume overload, they are added in series, resulting in dilation of the ventricular cavity. There are also qualitative differences in sarcomeres of hypertrophied myocytes. A great body of evidence suggest that hypertrophy of myocytes is associated with induction of a group of genes, which are usually expressed during fetal heart development. These genes include activation of  $\beta$ -myosin heavy chain (MHC), skeletal- $\alpha$ -actin and atrial natriuretic factor and the repression of  $\alpha$ -MHC and SR-CaATPase. These changes may be initially salutary for an overloaded heart; however, prolonged hypertrophy leads to myocyte dysfunction, which eventually results in heart failure. Results collected from animals studies have also indicated that the loss of  $\alpha$ -MHC content is a critical determinant of the reduced myocardial contractility during heart failure. Direct evidence in support of a causal link between the loss of  $\alpha$ -MHC and the development of heart failure came from experiments in which the  $\alpha$ -MHC gene was ablated. Data correlating even small decrements of  $\alpha$ -MHC content with changes in the intrinsic contractile characteristics of the myocardium also support the idea that a critical level of  $\alpha$ -MHC content is essential for the normal pump function of the heart.

Another possible cause of a decrease in contractile protein function is an alteration in the expression and/or activity of regulatory proteins. In animal models of heart failure, there are changes in the myosin light chain and the troponin–tropomyosin complex. Changes in myosin light-chain isoforms have been observed in heart samples of patients subjected to increased mechanical stress, and the expression of troponin-T splice variants was found to be altered in failing human myocardium. Changes in the phosphorylation status of Troponin-I have also been suggested to be involved in the loss of contractile activity of myocytes during heart failure. Moreover, defects in sarcoplasmic reticulum  $\text{Ca}^{2+}$ ATPase and  $\text{Ca}$  release channels have been suggested to be responsible for the contractile dysfunction of myocytes.

#### 2.1.4.2. Myocyte Cell-Death During Heart Failure

It has been realized that in addition to muscle gene dysregulation, cardiomyocyte cell-death significantly contributes to loss of ventricular function in a failing heart. During increased workload, myocytes undergo a hypertrophic growth response to compensate for the increased demand, the initiating events of which are similar to those that drive cell cycle progression in proliferating cells. A continuous growth signal in myocytes, at some point, causes cells to malfunction and leads to cell-death. As cells die, the work load on the remaining cells increases, which further aggravates this process and eventually leads to organ failure. Both in humans and animals with different cardiac disorders, including ischaemic heart disease, idiopathic dilated cardiomyopathy, hypertensive heart disease, viral myocarditis, pacing-induced cardiomyopathy and different transgenic models of heart failure, myocyte cell-death has been implicated as a common cause of the cardiac pathology. However, the mechanism of cell-death in a failing heart remains highly disputed. Some studies have documented a role of caspases in myocyte cell-death; however, others have disputed this notion. The activation of caspases in ischaemic heart disease seems fairly accepted, but its participation in non-ischaemic diseases remains controversial. Our own studies have shown that in pressure-overloaded hearts Poly ADP Ribose Polymerase (PARP), a nuclear

enzyme mediating DNA repair is not cleaved, a marker of caspase-dependent cell-death, but rather its expression is progressively increased in relation to the degree of cardiac hypertrophy, suggesting that haemodynamic stress endangers cardiac myocytes through a mechanism that appears different from the conventional caspase-mediated apoptosis. Activation of PARP has been seen during different animal models of heart failure as well as in failing human hearts. Recent evidence suggests that prevention of cardiomyocyte cell-death by PARP inhibition and/or by changing the activity of other cell-death intermediates protects the overloaded heart from going into failure.

#### 2.1.5. Genetics of Heart Failure

Before we proceed to a discussion of the complex clinical manifestations of CHF, a brief discussion of the genetic factors at work in CHF is necessary for completion. Almost 20% of patients with dilated cardiomyopathy are likely to have an inherited genetic defect. For instance, familial hypertrophic cardiomyopathy is caused by a number of gene mutations affecting  $\beta$ -MHC, cardiac troponin-T and I, alpha tropomyosin, myosin-binding protein C and myosin light chains 1 and 2.<sup>23</sup> In certain conditions such as Duchenne muscular dystrophy, there are definite genetic associations of an abnormal gene called dystrophin with abnormal myocardial function.<sup>24</sup>

### 2.2. Clinical Spectrum

Heart failure is usually defined as the inability of the heart to generate an output sufficient to meet the metabolic requirements of the body. The left or right ventricles may fail individually or together. Heart failure may also occur in the face of normal systolic ventricular function.

Left heart failure presents with shortness of breath, which, if severe, will occur at rest. Patients are graded on their functional capacity depending on the level of activity that induces shortness of breath. This functional classification, known as the 'New York Heart Association (NYHA) classification', is widely accepted and used around the world. This functional classification is used in the assessment of patients, prognostication and in tailoring management. The classes are as follows Table 2.1:

TABLE 2.1. New York Heart Association (NYHA) classification.

NYHA Class I	Shortness of breath on unaccustomed exertion. Normal exercise tolerance.
NYHA Class II	Shortness of breath on accustomed exertion, e.g., breathlessness on walking uphill or climbing a flight of stairs.
NYHA Class III	Shortness of breath on mild exertion, e.g., symptomatic on walking a few metres.
NYHA Class IV	Symptomatic at rest or on minimal exertion.

Minor impairment of cardiac function may remain asymptomatic but as compensatory mechanisms become maladaptive, the clinical features of heart failure emerge. These relate primarily to the consequences of elevated atrial pressures and reduced cardiac output, expressed as congestion and peripheral hypoperfusion, respectively. Manifestations of left and right heart may occur separately, but in reality they often occur together in varying degrees, resulting in the broader syndrome of CHF.

### 2.2.1. Acute Left Heart Failure

This is usually caused by acute MI, but may also be due to acute aortic or mitral regurgitation, or fulminant myocarditis. The patient usually presents with sudden onset of breathlessness and may cough up pink, frothy sputum. These clinical features are hallmarks of acute pulmonary oedema although, in reality, most patients are now diagnosed on the basis of 'wet lungs' using chest x-ray. Systemic hypoperfusion supervenes, progressing to hypotension, oliguria and, in severe cases, cardiogenic shock.

### 2.2.2. Chronic Left Heart Failure

Patients usually have varying degrees of dyspnoea on exertion, the causes of which are many. For example, the elevation of left atrial pressure with exertion may be caused by

- respiratory muscle fatigue,
- metabolic factors such as acidosis and renal impairment or
- muscle fatigue due to low cardiac output and poor muscle conditioning.

Clinical examination may reveal signs of low cardiac output and reflex sympathetic stimulation, which include tachycardia, cool peripheries and, occasionally, cyanosis. Auscultation may reveal inspiratory crackles at lung bases, although this can be unreliable; they are just as likely to be retained secretions within the lungs. Pleural effusions may be present. A third heart sound may be present producing a gallop rhythm. In severe heart failure, dilatation of the cardiac base and fibroskeleton causes mitral annular dilatation and mitral regurgitation. This is manifested by a pan-systolic murmur at the apex.

### 2.2.3. Acute Right Heart failure

Acute right heart failure may be caused by pulmonary embolism or right ventricular infarction. Patients usually present with breathlessness, systemic hypotension, cool skin, elevated jugular venous pressure and occasionally an enlarged liver.

### 2.2.4. Chronic Right Heart Failure

In this condition patients complain more of fatigue, and breathlessness is common. They also complain of a bloated feeling in the abdomen and a loss of appetite. This may be due to ascites, liver congestion and edema of the gastro-intestinal tract. On examination the jugular venous pulse (JVP) is elevated. Occasionally there may be large 'v' waves in the JVP along with pulsatile hepatomegaly, suggestive of functional tricuspid regurgitation. In such patients a pan-systolic murmur can be heard at the left sternal edge. Peripheral edema and ascites may be present. Occasionally patients present with jaundice and impaired protein synthesis, due to chronic impairment of liver function.

### 2.2.5. Complications

A variety of cardiac arrhythmias occur in heart failure, especially atrial fibrillation which causes varying degrees of haemodynamic deterioration. Ventricular arrhythmias occur later in the course of the disease and are more sinister, often causing sudden death. Arrhythmias and cardiac dilatation predispose to thrombus formation within cardiac chambers, which can then embolise into the

pulmonary or systemic circulations. Chronic congestion of the lungs also provides a fertile ground for chest infections. Deep vein thromboses as a result of sluggish flow in the veins of the legs and pelvis may progress to pulmonary embolism and sudden death.

Advanced heart failure also causes progressive failure of major organs such as the liver and kidneys.

### 2.2.6. Diagnosis

As I have described CHF can present with a variable clinical picture. However, a variety of investigations can help confirm the diagnosis, such as electrocardiogram (ECG), chest X-ray, echocardiography, cardiac catheterization, radionuclide ventriculography (RNVG), magnetic resonance imaging (MRI) and cardio pulmonary exercise testing. Such investigative tools are useful for mapping the course and progression of the disease.

## 2.3. Current Treatment Options for CHF

CHF is a complex medical condition requiring therapeutic interventions at multiple levels. It is the most common cause of medical admissions in Australia, the United States, Canada and the UK. The biggest advance in the treatment of heart failure has been the establishment of 'Heart Failure Clinics' and heart failure groups in hospitals, serviced by people interested in investigating, understanding and managing heart failure.<sup>25</sup>

Multi-disciplinary heart failure programmes that run cardiac rehabilitation courses after MI or cardiac surgery have been effective in reducing heart failure-related admissions.<sup>26</sup> Symptomatic improvement has also been noticed, along with reduced hospitalisation in patients with cardiomyopathy who attend a specialised clinic.<sup>27</sup>

Prevention also plays a very important role. The West of Scotland Study showed that primary prevention, by advocating drug therapy with pravastatin, prevented MI and reduced the incidence of heart failure in a population at risk.<sup>28</sup> The 4S Study (Scandinavian Simvastatin Survival Study) followed patients with coronary artery disease, some of whom were randomly assigned to a placebo group and some to a group treated with

simvastatin. Secondary prevention in the 4S Study showed that occurrence of heart failure at 5-year follow-up was significantly higher in the placebo than in the simvastatin group.<sup>29</sup>

Exercise programmes to improve general fitness and the level of exercise tolerance have been shown to significantly improve the functional status of patients with heart failure.<sup>30</sup> Bed rest, which was a cornerstone of traditional therapy for CHF, is therefore no longer advocated for these patients.

Despite these improvements in treatment and prevention, the effective management of heart failure continues to be a pressing concern. Before discussing my research into the utility and efficacy of ventricular containment, this next section will review current approaches to the treatment of CHF, both medical and surgical.

### 2.3.1. Drug Therapy

#### 2.3.1.1. Inotropic Agents

Digoxin, a drug that exerts a direct inotropic effect on the heart, has been a therapeutic mainstay in CHF for many years. Despite this, the DIG (Digitalis Investigation Group) trial found that there was no significant impact on mortality in patients treated with digoxin.<sup>31</sup> However, this study demonstrated that patients treated with digitalis required less hospitalisation for worsening heart failure. The newer inotropic agents have also failed to lower the mortality rate of CHF sufferers. The PROMISE (Prospective Randomised Milrinone Survival Evaluation) trial, for example, did not live up to its name. Indeed there was a 28% higher all-cause mortality in patients randomly treated with 40mg/day of milrinone compared to the placebo group.<sup>32</sup>

#### 2.3.1.2. Vasodilators

The first Veteran Administration Co-operative Vasodilator-Heart Failure Trial (V-HeFT I) was published in 1986. The report showed that the addition of the vasodilators hydralazine (300mg/day) and isosorbide dinitrate (160mg/day) to a digoxin and diuretic regime resulted in a reduction in mortality of 38% after 1 year, 25% after 2 years, and 28% over the entire follow-up period (a mean of 2.3 years).<sup>33</sup> In 1991, the V-HeFT II study (conducted by the same group) reported that the angiotensin-converting enzyme (ACE) inhibitor

enalapril was 18% better than the combination of the two direct vasodilators.<sup>34</sup> However, the hydralazine-isosorbide combination was associated with improved ventricular function and better oxygen consumption at peak exercise.

### 2.3.1.3. Calcium Channel Blockers

Calcium channel blockers have been associated with worsening heart failure and a rise in mortality,<sup>35</sup> with the exclusion of amlodipine. The PRAISE (Prospective Randomised Amlodipine Survival Evaluation) trial found that while amlodipine had no impact on mortality, it diminished the combined risk of non-fatal and fatal events by 31% in patients with non-ischaemic cardiomyopathy.<sup>36</sup>

### 2.3.1.4. Beta-Adrenoceptor Blockade

The sympathetic system is activated in patients with CHF. Another way of dealing with the adverse effects of neurohumoral activation is through beta-adrenoceptor blockage. Carvedilol, for example, is a non-selective beta-receptor antagonist that also blocks alpha-1 receptors and has antioxidant effects. In a recent trial carvedilol reduced mortality, 6–12 months after treatment, by 65% in patients with CHF.<sup>37</sup> An Australian trial also showed improvement in ejection fraction, cardiac mortality and morbidity in patients treated with carvedilol.<sup>38</sup>

### 2.3.1.5. Angiotensin-Converting Enzyme Inhibitors

There is now a large volume of work supporting the role of ACE inhibitors in heart failure and these agents have become a cornerstone of first-line therapy. Treatment with ACE inhibitors improves haemodynamic profiles as well as functional status, with benefits in exercise performance, dyspnea, fatigue and edema. The Survival and Ventricular Enlargement (SAVE) trial showed improvement in all-cause mortality and reduced cardiovascular morbidity in patients with asymptomatic LV dysfunction after MI, who were treated with captopril.<sup>39</sup> The SOLVD (Studies of Left Ventricular Dysfunction) trial showed that enalapril reduced the risk of death and hospitalisation for worsening failure compared to the placebo group.<sup>40</sup>

There are many other studies showing the efficacy of various ACE inhibitor drugs in heart failure

as a consequence of MI. However, while most of these drugs delay progression of heart failure for a while and provide a solid bedrock of therapy, each of them has a significant incidence of complications. Despite best medical therapy, patients tend to worsen gradually as the ventricle dilates inexorably.

## 2.3.2. Surgical Therapy

Apart from first-line treatment with drug therapy, a number of surgical techniques have also been developed to treat heart failure. These include the following.

### 2.3.2.1. Left Ventricular Assist Devices

Occasionally, in patients with cardiomyopathy due to either idiopathic or reversible causes, ventricular assist devices may be used on a long-term basis until the patients recover.<sup>41</sup> Despite many favourable reports<sup>42</sup> use of these devices has been bedevilled by a high rate of bleeding, infection and haemolysis,<sup>43</sup> as well as thrombo-embolism.<sup>44</sup> They work reasonably well in the short and intermediate term to tide patients over until transplantation.<sup>45</sup> However, ventricular devices are expensive and cumbersome. Because of the financial constraints, these are usually reserved for young patients in NYHA class IV heart failure who are likely to undergo a heart transplant.

### 2.3.2.2. Cardiomyoplasty

Dynamic cardiomyoplasty was first performed in 1985, utilising the left latissimus dorsi on an intact neurovascular pedicle. The skeletal muscle was transformed to fatigue resistance by long-term electrical stimulation, utilising Pette's elegant finding in muscle physiology.<sup>46</sup>

Skeletal muscle transformed in this way was used experimentally in an attempt to augment cardiac function<sup>47</sup> and as an implantable extra-aortic balloon assist device.<sup>48</sup> Despite much enthusiasm for this technique, early experiences were marred by high mortality and morbidity rates.<sup>49</sup> A randomised study to demonstrate the efficacy of cardiomyoplasty was commenced quite late; by the time the study was completed the cardiomyostimulators had already been withdrawn from the market. However, the results of the randomised study showed that

patients with NYHA class III heart failure who underwent cardiomyoplasty received symptomatic benefit.<sup>50</sup> Unfortunately, the results of this study came too late to resurrect this procedure.

#### 2.3.2.3. Mitral Valve Annuloplasty

Bolling and his colleagues from Ann Arbor, Michigan, have advocated an aggressive approach to patients with dilated cardiomyopathy and mitral regurgitation. They have shown good intermediate term results with mitral valve repair, usually in the form of a radical annuloplasty to reduce the size of the mitral annulus.<sup>51</sup> This works well only if the mechanism of de-compensation is moderate to severe mitral regurgitation.

The Cleveland Clinic heart failure group, headed by Dr McCarthy, has reported good results with the Alfieri-type edge-to-edge mitral valve repair, along with an annuloplasty, in patients with mitral insufficiency in the setting of a cardiomyopathy.<sup>52</sup>

#### 2.3.2.4. Partial Left Ventriculectomy (Batista Procedure)

As discussed previously, Dr Randas Batista was one of the first cardiac surgeons to demonstrate the beneficial possibilities of ventricular volume reduction surgery. Batista, working in a relatively impoverished area of Brazil, designed a procedure to reduce the size of dilated ventricles by resecting a portion of the left ventricular myocardium between the papillary muscles. He also advocated an Alfieri-type mitral valve repair. In 1997, he reported good results using this combined procedure.<sup>53</sup> There has been a lot of interest in the procedure with McCarthy, from the Cleveland Clinic, performing a careful evaluation of its efficacy. His findings showed that, in spite of a significant early morbidity and mortality, patients who survived had significant improvement in haemodynamics and ventricular function in the short-term.<sup>54</sup> Unfortunately, most patients had recurrent dilatation, which steadily progressed either to death or transplantation.<sup>55</sup>

#### 2.3.2.5. Left Ventricular Aneurysm Repair

Reconstruction of scarred left ventricles in the setting of large left ventricular aneurysms is being performed with increasing frequency. Left ventricular

aneurysms may be large saccular thin-walled scars or small dyskinetic scarred segments. In either case there is usually underlying cardiac dilatation. Early repairs of left ventricular aneurysms were performed in a linear fashion,<sup>56</sup> producing distortion of an already abnormal ventricle and often marginal results.<sup>57</sup> The importance of maintaining a geometric shape similar to that of a ventricle was demonstrated by various groups and resulted in the development of endo-aneurysmorrhaphy.<sup>58</sup>

In 1989 Dor<sup>59</sup> showed that endo-ventricular patch repair had physiologic merit and Jatene<sup>60</sup> demonstrated the importance of reducing the size of the defect after aneurysm resection. Late haemodynamic results are also favourable when patch repair of remodelled ventricular segments is performed in association with coronary artery grafting.<sup>61</sup>

In 1992 Dor went further and advocated reconstruction of post-ischaemic akinetic ventricular dilatation.<sup>62</sup> This was based on the observation that full-thickness scarring is prone to a variety of unpleasant sequelae, such as calcification, dykinesis, Dressler syndrome, and progressive dilatation of the remaining ventricular cavity.<sup>63</sup> A modification of this technique has also been developed for treatment of refractory ischaemic ventricular tachycardia by endo-ventricular patch plasty.<sup>64</sup> More recently, McCarthy reported on a series of patients undergoing 'cardiac reshaping' (which is akin to the Jatene procedure or the Dor procedure, but without the patch) for ischaemic dilated cardiomyopathy. This produced excellent results.<sup>65</sup> Buckberg is currently co-ordinating an international trial called SAVE (Surgical Anterior Ventricular Infarct Exclusion) to evaluate the efficacy of excluding the dyskinetic infarcted anterior segment of hearts in these patients.<sup>66</sup> Finally I would add that, to date, my personal experience with geometric endo-ventricular repair<sup>67</sup> has been very satisfactory in repairing anterior and inferior left ventricular scars. This technique incorporates features of the Cooley and the Dor repair without using a purse-string suture, but utilising a measured pericardial patch.

*Cardiac transplantation is the accepted gold standard treatment for selected patients with refractory heart failure. Despite a 10-year survival of 65–70%, a shortage of donors means that it is available only for a very small subset of patients.*<sup>68</sup>

### 2.3.3. Other Ancillary Therapies

#### 2.3.3.1. Pacing

Pacing may be required to treat patients with symptomatic bradyarrhythmias or loss of atrioventricular synchrony. These pacemakers should be dual chambered and rate responsive.<sup>69</sup>

Biventricular pacing is a promising new approach to re-synchronise cardiac contraction in patients with systolic heart failure and left bundle branch blocks.<sup>70</sup> This approach is the subject of many international trials.

In selected patients with a propensity for ventricular arrhythmias, intra-cardiac cardioverter-defibrillator devices may be implanted, reducing the risks of out-of-hospital cardiac arrests.<sup>71</sup>

#### 2.3.3.2. Exercise Training

In the 1990s there were various groups that showed the efficacy of low-intensity exercise training in patients with CHF.<sup>72</sup> On the basis of this experience, some groups have shown improvement in muscle strength<sup>73</sup> and haemodynamics with resistance training.<sup>74</sup> Whatever the intensity or mode, there is enough body of evidence now suggesting the beneficial effects of exercise in heart failure,<sup>75,76</sup> that most heart failure groups and clinics have an integrated programme that includes some form of physical exercise in addition to the general rehabilitative measures as treatment in patients with CHF.

## 2.4. Constraining the Heart—Prevention of Further Cardiac Dilatation

While some of the procedures mentioned so far help to reduce the size of the dilating ventricles (apart from cardiomyoplasty) none of them actually prevent further dilatation of the heart. In CHF, the natural tendency is for the heart to gradually enlarge over time. Our interest, then, was in developing a technique for not only reducing but also containing the size of the ventricle. We therefore decided to study the concept of ventricular containment based on what we thought was the presumed mechanism behind cardiomyoplasty. Fortunately there were a couple of papers that supported our premise that the muscle in myoplasty acted

as a girdle<sup>77</sup> and that stimulation of the muscle actually gave it a bit of tension that improved the constraint.<sup>78</sup> Furthermore, a contemporaneous study reported good results using a Gore-Tex sheet wrapped around a dilating heart.<sup>79</sup> Raman and Power, working at the Austin Hospital, Melbourne, Australia, showed that this procedure could be adapted to various stages of progressive ventricular dilatation in an animal model, and this was adapted in human patients with encouraging results.<sup>80</sup> This proved the basis for various devices such as the Acorn cardiac support device, the Paracor device, etc, which will be discussed in Chapter 13.

## Key Points to Remember

- Congestive heart failure is a complex clinical syndrome due to failure of the heart to meet the metabolic demands of the body.
- A variety of mechanisms get triggered initially from compensatory mechanisms in the cells of the heart.
- Over a period of time, these mechanisms take a life of their own to cause the various manifestations of heart failure.
- The clinical spectrum of heart failure is variable but is based on the underlying cellular, molecular mechanisms and end up causing a range of clinical manifestations.

## References

1. Thomas L. The artificial heart. In: *Late Night Thoughts on Listening to Mahler's Ninth Symphony*. Viking Penguin, New York; 1983.
2. Willerson JT, Delgado R III, Mann D. Treating relentlessly progressive congestive heart failure: What next? *Tex Heart Inst J*. 1998;25:235-237.
3. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: A manifestation of coronary artery disease. *Circulation*. 1998;97:282-289.
4. Willerson JT. Other cardiomyopathies. In: Willerson JT, Cohn JN eds. *Cardiovascular Medicine*. New York: Churchill Livingstone; 1995:888-894.
5. Luppi P, Rudert WA, Zanone MM, Stassi G, Finegold D, et al. Idiopathic dilated cardiomyopathy: A superantigen driven autoimmune disease. *Circulation*. 1998;98:777-785.

6. Cohn JN. Overview of pathophysiology of clinical heart failure. In: Hosenpud JD, Greenberg BH eds. *Congestive Heart Failure: Pathophysiology, Diagnosis and Comprehensive Approach to Management*. New York: Springer-Verlag; 1994:11-16.
7. Katz AM. The cardiomyopathy of overload: An unnatural growth response in the hypertrophied heart. *Ann Intern Med*. 1994;121:363-371.
8. McKay RG, Pfeffer MA, Pasternak RC, et al. Left ventricular remodelling after myocardial infarction: A corollary to infarct expansion. *Circulation*. 1986;74:693-702.
9. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Pro-inflammatory cytokine levels in patients with depressed left ventricular ejection fraction: A report from the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol*. 1996;27:1201-1206.
10. Haywood GA, Tsao PS, von der Leyden HE, et al. Expression of inducible nitric oxide synthase in human heart failure. *Circulation*. 1996;93:1087-1094.
11. Oral J, Kapadia S, Nakano M, et al. Tumour necrosis factor- $\alpha$  and the failing human heart. *Clin Cardiol*. 1995;18(suppl 4):IV20-IV27.
12. Li G, Willerson JT. Molecular biologic alterations in heart failure. In: Frazier OH ed. *Support and Replacement of the Failing Heart*. Philadelphia: Lippincott-Raven; 1996:69-74.
13. Anversa P, Kajstura J, Olivetti M. Myocyte death in heart failure. *Curr Opin Cardiol*. 1996;11:245-251.
14. Hosenpud JD, Greenberg BH, eds. *Congestive Heart Failure: Pathophysiology, Diagnosis and Comprehensive Approach to Management*. New York: Springer-Verlag; 1994:623-624.
15. Bonow RO, Udelson JE. Left ventricular diastolic dysfunction as a cause of congestive heart failure: Mechanisms and management. *Ann Intern Med*. 1992;117:502-510.
16. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: An epidemiologic perspective. *J Am Coll Cardiol*. 1995;26:1565-1574.
17. Willerson JT, Cohn JN, eds. *Cardiovascular Medicine*. New York: Churchill-Livingstone; 1995:952-953.
18. Benedict CR. Neurohumoral aspects of heart failure. *Cardiol Clin*. 1994;12:9-23.
19. Hosenpud JD, Greenberg BH, eds. *Congestive Heart Failure: Pathophysiology, Diagnosis and Comprehensive Approach to Management*. New York: Springer-Verlag; 1994:13-14.
20. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med*. 1984;311:819-823.
21. Meredith IT, Eisenhofer G, Lambert GW, Dewar EM, Jennings GL, Esler M. Cardiac sympathetic nervous activity in congestive heart failure: Evidence for increased neuronal norepinephrine release and preserved neuronal uptake. *Circulation*. 1993;88:136-145.
22. Wei CM, Lerman A, Rodeheffer RJ, et al. Endothelin in human congestive heart failure. *Circulation*. 1994;89:1580-1586.
23. Mestroni L, Giacca M. Molecular genetics of dilated cardiomyopathy. *Curr Opin Cardiol*. 1997;12:203-209.
24. Towbin JA, Hejtmancik JF, Brink A, et al. X-linked dilated cardiomyopathy: Molecular genetic evidence of the Duchenne muscular dystrophy (dystrophin) gene at Xp21 locus. *Circulation*. 1993;87:1854-1865.
25. Cintron G, Bigas C, Linares E, Aranda JM, Hernandez E. Nurse practitioner role in a chronic congestive heart failure clinic. In hospital time, costs and past satisfaction. *Heart Lung*. 1983;12:237-240.
26. Rich MW, Beckman V, Wittenber C, Level CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med*. 1995;33:1190-1195.
27. Smith LE, Fabri SA, Pai R, Ferry D, Heywood T. Symptomatic improvement and reduced hospitalization for patients attending a cardiomyopathy clinic. *Clin Cardiol*. 1997;20:949-954.
28. Shepherd J, Cobbe SM, Ford I, et al., for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-1307.
29. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4,444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study(4S). *Lancet*. 1994;344:1382-1389.
30. Squires RW, Lavie CJ, Brandt TR, Gau GT, Bailey KR. Cardiac rehabilitation in patients with severe left ventricular dysfunction. *Mayo Clin Proc*. 1987;62:997-1002.
31. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997;336:523-533.
32. Packer M, Carver JR, Rodeheffer RJ, et al. for the PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med*. 1991;325:1468-1475.
33. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: Results of a Veterans' Administration Co-operative Study. *N Engl J Med*. 1986;314:1547-1552.

34. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide nitrate in the treatment of chronic congestive heart failure. *N Engl J Med*. 1991;325:303-310.
35. The Multi-center Diltiazem Post-infarction Research Group. The effect of diltiazem on mortality and re-infarction after myocardial infarction. *N Engl J Med*. 1988;319:385-392.
36. Packer M, O'Connor CM, Ghali JK, et al., for the Prospective Randomized Amlodipine Survival Evaluation Study. Effect of Amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med*. 1996;335:1107-1114.
37. Packer M, Bristow MR, Cohn JN, et al., for the U.S. Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334:1349-1355.
38. Australia/New Zealand Heart Failure Research Collaborative Group. Randomized, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet*. 1997;349:375-380.
39. Pfeffer MA, Braunwald E, Moye LA, et al, on behalf of the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med*. 1992;327:669-677.
40. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med*. 1992;327:685-691.
41. Westaby S, Coats AFS. Mechanical bridge to recovery. *Eur Heart J*. 1998;19:541-547.
42. Schmid C, Hammel D, Deng MC, et al. Ambulatory care of patients with left ventricular assist devices. *Circulation*. 1999;100(suppl. II):II-224-II-228.
43. Mueller J, Wallukat G, Weng YG, et al. Weaning from mechanical cardiac support in patients with idiopathic dilated cardiomyopathy. *Circulation*. 1997;95:542-549.
44. Schmid C, Weyand M, Hammel D, Deng MC, Nabavi D, Scheld HH. Cerebral and systemic embolization during left ventricular support with the Novacor N100 device. *Ann Thorac Surg*. 1998;65:1703-1710.
45. Levin H, Chen J, Oz M, et al. Potential for left ventricular assist devices as outpatient therapy with awaiting transplantation. *Ann Thorac Surg*. 1994;58:1515-1520.
46. Pette D, Smith ME, Staudte HW, et al. Effects of long-term electrical stimulation on some contractile and metabolic characteristics of fast rabbit muscles. *Pfluegers Arch*. 1973;338:257-261.
47. Chachques JC, Grandjean PA, Carpentier A. Dynamic cardiomyoplasty: Experimental cardiac wall replacement with a stimulated skeletal muscle. In: Chiu RC-J ed. *Bio-mechanical Cardiac Assist: Cardiomyoplasty and Muscle-Powered Devices*. Mt Kisco, NY: Futura Publishing Co; 1986:59-84.
48. Chiu RC-J, Walsh GL, Dewar ML, et al. Implantable extra-aortic balloon assist powered by transformed fatigue-resistant skeletal muscle. *J Thorac Cardiovasc Surg*. 1987;94:694-698.
49. Magovern JA, Furnary AP, Christlieb IY, Kao RL, Park SB, Magovern GJ. Indications and risk analysis for clinical cardiomyoplasty. *Seminars in Thoracic & Cardiovascular Surgery*. 1991;3(2):145-148.
50. Young JB, Kirklin JB. Cardiomyoplasty-Skeletal Muscle Assist Randomized Trial (C-SMART): 6 month results. *Circulation*. 1999;100[18(suppl. I)]:514.
51. Bolling SF, Deeb GM, Brunsting LA, et al. Early outcome of mitral valve reconstruction in patients with end-stage cardiomyopathy. *J Thorac Cardiovasc Surg*. 1995;104:676-683.
52. Bishay ES, McCarthy PM, Cosgrove DM, et al. Mitral valve surgery in patients with severe left ventricular dysfunction. *Eur J Cardiothorac Surg*. 2000;17:213-221.
53. Batista RJV, Nery P, Bocchino L, et al. Partial left ventriculectomy to treat end stage heart disease. *Ann Thorac Surg*. 1997;64:634-638.
54. Dowling RD, Koenig SC, Ewert DL, Cerrito P, Laureao MA, Gray LA. Does partial left ventriculectomy improve left ventricular systolic and diastolic function? *Circulation*. 1999;100[18(suppl. 1)]:801.
55. Starling RC, McCarthy PM, Hoercher KJ, Buda T, Goormastic M, Young JB. Partial left ventriculectomy for dilated cardiomyopathy: A viable option for end-stage heart failure? *Circulation*. 1999;100[18(suppl. 1)]:801.
56. Reddy SB, Cooley DA, Duncan JM, et al. Left ventricular aneurysm : Twenty-year surgical experience with 1572 patients at the Texas Heart Institute. *Cardiovasc Dis Bull Tex Heart Inst*. 1981;11:165-186.
57. Kesler KA, Fiore AC, Naunheim KS. Anterior wall ventricular aneurysm repair: A comparison of linear versus circular closure. *J Thorac Cardiovasc Surg*. 1992;103:841-848.
58. Jatene AD. Surgical treatment of left ventricular aneurysm. In: Baue AE, Geha AS, Hammond GL, Laks H, Naunheim KS eds. *Glenn's Thoracic & Cardiovascular Surgery*. Vol. 2. 5th ed. Norwalk, CT: Appleton & Lange; 1991:1829-1836.
59. DiDonato M, Dor V, Sabatier M, et al. Outcome of left ventricular aneurysmectomy with patch repair in

- patients with severely depressed pump function. *Am J Cardiol*. 1995;76:557-561.
60. Cox JL. Surgical management of left ventricular aneurysms by the Jatene technique. In: Cox JL, Sundt TL, eds. *Operative Techniques in Cardiac & Thoracic Surgery—A Comparative Atlas*. Vol. 2. WB Saunders, Elsevier Publishing, Orlando FL; 1997:132-138.
  61. Dor V, Sabatier M, DiDonato M, et al. Late hemodynamic results after left ventricular patch repair associated with coronary grafting in patients with post-infarction akinetic or dyskinetic aneurysm of the left ventricle. *J Thorac Cardiovasc Surg*. 1995;110:1291-1301.
  62. Dor V. Reconstructive left ventricular surgery for post-ischemic akinetic dilatation. *Semin Thorac Cardiovasc Surg*. 1997;9(2):139-145.
  63. Klein M, Herman M, Gorlin R. A hemodynamic study of left ventricular aneurysms. *Circulation*. 1967;35:614-630.
  64. Dor V. The treatment of refractory ischemic ventricular tachycardia by endo-ventricular patch plasty reconstruction of the left ventricle. *Semin Thorac Cardiovasc Surg*. 1997;9(2):146-155.
  65. Judd RM, Kim RJ, Chen E-L, et al. Contrast enhanced magnetic resonance imaging defines the pre-operative location and extent of myocardial scar prior to the Dor procedure. *Circulation*. 1999;100[18(suppl. 1)]:798.
  66. Buckberg GD. Defining the relationship between akinesia and dyskinesia and the cause of left ventricular failure after anterior infarction and reversal of remodelling to restoration. *J Thorac Cardiovasc Surg*. 1998;116:47-49.
  67. Raman J, Dixit A, Storer M, Hare DL, Buxton BF. Geometric endo-ventricular patch repair of inferior left ventricular scars improves mitral regurgitation and clinical outcome. *Ann Thorac Surg*. 2001;72:1055-1058.
  68. Dabol R, Edwards NM. Cardiac transplantation and other therapeutic options in the treatment of end-stage heart disease. *Compr Ther*. 2000;26:109-113.
  69. Krum H, on behalf of the National Heart Foundation of Australia Chronic Heart Failure Clinical Practice Guidelines Writing Panel. Guidelines for management of patients with chronic heart failure in Australia. *Med J Aust*. 2001;174:459-466.
  70. Barold SS. Biventricular cardiac pacing: Promising new therapy for congestive heart failure. *Chest*. 2000;118:1812-1819.
  71. Hauer RN, Aliot E, Block M, et al. Indications for implantable cardioverter-defibrillator (ICD) therapy. Study Group on Guidelines on ICDs of the Working Group on arrhythmias of European society of cardiology. *Eur Heart J*. 2001;22:1074-1081.
  72. Adamopoulos S, Coats A, Brunotte F, et al. Physical training improves skeletal muscle metabolism in chronic heart failure. *J Am Coll Cardiol*. 1993;21:1101-1106.
  73. Hare DL, Ryan TM, Selig SE, Pellizzer A, Wrigley TV, Krum H. Resistance exercise training increases muscle strength, endurance and blood flow in patients with chronic heart failure. *Am J Cardiol*. 1999;83:1674-1677.
  74. McKelvie RS, McCartney N, Tomlinson C, Baier R, MacDougall JD. Comparison of hemodynamic responses to cycling and resistance exercise in congestive heart failure secondary to ischemic cardiomyopathy. *Am J Cardiol*. 1995;76:977-979.
  75. Honig B, Maier V, Drexler H. Physical training improves endothelial function in patients with chronic heart failure. *Circulation*. 1996;93:210-214.
  76. Katz SD, Yuen J, Bijou R, LeJemtel TH. Training improves endothelium-dependent vasodilatation in resistance vessels of patients with heart failure. *J Appl Physiol*. 1997;82:1488-1492.
  77. Copuya ER, Gerber RS, Drinkwater DJ, et al. Girdling effects of non-stimulated cardiomyoplasty on left ventricular function. *Ann Thorac Surg*. 1993;56:867-870.
  78. Patel HJ, Polidori DJ, Pila JJ, et al. Stabilisation of chronic remodelling by asynchronous cardiomyoplasty in dilated cardiomyopathy: Effects of a conditioned muscle wrap. *Circulation*. 1997;96:3665-3671.
  79. Vaynbalt M, Chiavarelli M, Shah HR, et al. Cardiac binding in experimental heart failure. *Ann Thorac Surg*. 1997;64:81-85.
  80. Raman J, Power JM, Buxton BF. Ventricular containment as an adjunct to conventional cardiac surgery. *Ann Thorac Surg*. 2000;70:1124-1126.



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