The syndrome of heart failure is still imperfectly understood. It is defined as effort intolerance caused by heart disease, often with a neuroendocrine response that leads to fluid retention and promotes an adverse vicious circle. The cause of this response is generally thought to be a low blood pressure, leading to adrenergic and renin-angiotensin activation. The result is increased peripheral vasoconstriction, which maintains the blood pressure while punishing the already failing myocardium by demanding more work against the increased afterload. The evolution of heart failure is traced out from an initial pressure or volume overload that initiates a series of growth signals to cause myocardial growth. Why the apparently well-compensated LV should degenerate into failure is not clear, but impaired coronary flow reserve and excess angiotensin II activity with fibrosis and apoptosis all probably play a role. The collagen matrix normally limits cardiac chamber expansion so that matrix remodeling under the influence of matrix metalloproteinases is required for the LV to enlarge in volume. Regarding the neuroendocrine response, excess adrenergic activity promotes failure by myocardial membrane damage and calcium overload, and by increasing the myocardial oxygen demand and the afterload. Beta-adrenergic stimulation may (unexpectedly) be anti-apoptotic and cardioprotective. Activation of the renin-angiotensin system (RAS) is clearly very harmful, as shown by numerous studies in which inhibiting agents have reduced human mortality. Specific adverse consequences of RAS activation include (1) excessive peripheral vasoconstriction; (2) aldosterone-mediated sodium retention and myocardial fibrosis; (3) increased endothelial damage; and (4) excessive angiotensin II effects at intracellular sites. Other neuroendocrine changes are increased levels of endothelin and of cytokines such as tumour necrosis factor-alpha. Ergoreflexes from the ailing skeletal muscle may further promote adrenergic and RAS activation. Conversely, increased release of natriuretic peptides from the left heart is cardioprotective by limiting fluid retention and promoting vasodilation. Current therapies of heart failure are largely based on inhibition of the neuroendocrine response.
heart and decreased force development explains the development of the all-important neuroendocrine changes, involving many receptors and signaling systems (Table 1). Of note, the diastolic and systolic components co-exist to a variable degree.

Hypothetically, the low blood pressure reflexly stimulates the adrenergic and renin-angiotensin-aldosterone systems, with increased peripheral vascular resistance and afterload. Aldosterone excess promotes fluid retention, peripheral congestion and edema so that both the preload and afterload also increase. Besides these adverse events, there is a beneficial and protective neuroendocrine change with increased release of the natriuretic peptides ANP and BNP from atria and ventricles respectively.

Clinical definition. Heart failure is a clinical syndrome characterised by exertional intolerance caused by heart disease, often but not always with a neurohumoral response and fluid retention. This simple definition, verbally proposed by Packer some years ago, has been adopted by Professor Commerford in our Cardiology Division in Cape Town. This definition allows the bedside diagnosis of heart failure even by a medical student. Congestive heart failure (CHF) is the term that encompasses sufficiently severe fluid and sodium retention (‘congestion’) to cause a raised jugular venous pressure, pulmonary changes, peripheral oedema or liver enlargement. The New York Heart Association has proposed dividing a widely used classification of heart failure into four grades, based on the severity of effort intolerance. Years ago the great British cardiologist, Sir Thomas Lewis, wrote: ‘The first indication of cardiac failure is to be found in diminished tolerance to exercise. Of the very numerous tests of cardiac efficiency....there is none that approaches in delicacy the symptom breathlessness’.

Myocardial adaptation to overload
‘All roads lead to Rome’, but it is self-evident that the starting points and routes followed are different. There are basically four mechanisms that initiate the sequence leading to myocardial contractile failure: pressure overload, volume overload, primary myocardial disease (myocarditis, cardiomyopathy) and myocardial infarction. In each case, through different mechanisms, the myocardium mechanically compensates for the primary defect before the stage of overt myocardial failure develops. In addition, complex neuroendocrine changes attempt to maintain the circulation and normal organ perfusion in the face of decreasing myocardial function. These changes involve activation of the renin-angiotensin and other systems that cause peripheral vasoconstriction, thereby maintaining the blood pressure while punishing the heart by increasing the afterload.

Pressure overload
In response to aortic stenosis or sustained severe hypertension, the left ventricular (LV) pressure that is developed must increase to overcome the resistance to the ejection of blood. The initial mechanism for the increase at a cellular level is probably a stretch-induced increase in the inotropic state, involving mechanoreceptors and increased cytosolic calcium. The result is that the LV systolic pressure rises, the obstruction to the outflow of blood from the left ventricle is overcome, and the cardiac output is maintained. The disadvantage of this mode of adaptation is that LV wall stress is greatly increased. This initiates a complex series of stretch-induced signals starting with locally synthesized angiotensin

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**TABLE I. RECEPTORS AND SIGNALING SYSTEMS IN SEVERE CONGESTIVE HEART FAILURE**

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-adrenergic receptors downgraded, i.e. density and activity decreased</td>
<td></td>
</tr>
<tr>
<td>β-adrenergic receptor density unchanged, functional uncoupling</td>
<td></td>
</tr>
<tr>
<td>β-adrenergic receptors relatively increased in density</td>
<td></td>
</tr>
<tr>
<td>VIP receptors decreased in density but affinity considerably more</td>
<td></td>
</tr>
<tr>
<td>G-proteins</td>
<td></td>
</tr>
<tr>
<td>Gi increased with inhibition of adenylate cyclase</td>
<td></td>
</tr>
<tr>
<td>G, normal or decreased</td>
<td></td>
</tr>
<tr>
<td>Adenylate cyclase</td>
<td>Decreased cyclase activity with less production of cyclic AMP, related to G, increase; still responds directly to forskolin</td>
</tr>
<tr>
<td>Cyclic AMP</td>
<td>Production impaired, presumably due to adenylate cyclase inhibition</td>
</tr>
<tr>
<td>Calcium transients</td>
<td>Impaired transients with low peak and delayed fall in diastole</td>
</tr>
<tr>
<td>Calcium uptake by SR unchanged or decreased in situ</td>
<td></td>
</tr>
<tr>
<td>Calcium release by SR decreased</td>
<td></td>
</tr>
<tr>
<td>Single calcium channel activity normal</td>
<td></td>
</tr>
<tr>
<td>Amount of calcium entry via calcium channel may be abnormal</td>
<td></td>
</tr>
</tbody>
</table>

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![Fig. 1. The neuroendocrine vicious circle in congestive heart failure (CHF).](image-url)
at the length limit of the Frank-Starling curve. Second, the preload increases, so that the heart functions
changes in the loading conditions and in ventricular size.

Lesion. To deal with this volume load, there are both
true sense be equated with an organic regurgitant valve
physiological volume load. Exercise training can in no
effects of severe and prolonged exercise training as a
mitral valve or the aortic valve. Some authors include the
being valvular regurgitation (incompetence) of either the

The initial event in a volume load is again haemodynamic,
overshoot the normal E/A ratio. These abnormalities of
relaxation result in part from increased interstitial connective
tissue in which collagen type I is increased. Yet at least some
of the functional changes can reverse upon acute administra-
tion of an angiotensin-converting enzyme inhibitor, enalapril, to patients with LVH resulting from severe aortic
stenosis.1 Diastolic heart failure refers to the combination of
diastolic dysfunction, with evidence of fluid retention and
congestive symptoms, but with apparently sustained systolic
function and ejection fraction (defined by a depressed
ejection above 45%).1 Direct links between LV mass and
diastolic filling abnormalities are shown by the effects of
antihypertensive therapy.7 Using Doppler tissue imaging, a
new echocardiographic technique, diastolic abnormalities
correlate to impaired exercise capacity, at least in hyper-
trophic cardiomyopathy.8

Yet in response to exercise, systolic abnormalities may
develop, especially in the presence of more severe left ven-
tricular hypertrophy.4 The proposal is that marked diastolic
abnormalities of filling and decreased distensibility lead to
inadequate end-diastolic stretch of the ventricular myocytes
so that the Frank-Starling mechanism does not operate as it
should during exercise. Furthermore, in clinical diastolic
heart failure there may be subtle abnormalities of systolic
function.13,9 Therefore it would be more correct to speak of
dominant diastolic dysfunction.

Volume overload and LV function

The initial event in a volume load is again haemodynamic,
being valvular regurgitation (incompetence) of either the
mitral valve or the aortic valve. Some authors include the
effects of severe and prolonged exercise training as a
physiological volume load. Exercise training can in no
ture sense be equated with an organic regurgitant valve
lesion. To deal with this volume load, there are both
changes in the loading conditions and in ventricular size.
First, the preload increases, so that the heart functions
at the length limit of the Frank-Starling curve. Second,
the degree of myocardial hypertrophy. In contrast, when there is an excessive collagen response to ischaemia or endocrine signals such as angiotensin II, then compliance decreases with an increase in chamber stiffness, or a decrease in distensibility. Experimentally, the nonelastic Type 1 collagen increases more. Clinically this promotes poor diastolic relaxation and, hence, diastolic failure. The wall tension therefore rises more than expected, with a corresponding increase in the oxygen demand. This, in turn, contributes to relative ischaemia of the hypertrophied myocardium and further promotes interstitial fibrosis. Increased activity of matrix metalloproteinases (MMP), possibly caused by angiotensin II, results in decreased collagen cross-linking with weakening of the matrix, thereby allowing matrix remodeling with myocyte slippage and LV chamber enlargement. Exactly how the MMPs and the counter-balancing enzymes that inhibit them (TIMS, tissue inhibitors of MMPs) are regulated remains unclear. Presumably the balance between their activities governs the stability of the collagen network.

Apoptosis
The left ventricle undergoes progressive dilation and thinning during the development of severe heart failure. A current hypothesis is that apoptosis, a form of programmed cell death, may contribute to the attrition. Apoptosis is a gene-directed process that results in predictable cell death, as recognised by a number of indirect markers of DNA damage such as ‘laddering’. There is also new gene expression, for example of the Fas gene, and inactivation of the anti-apoptotic gene, bcl-2. Only a low incidence of apoptotic cells is found in severe heart failure. Yet if only 0.2% of the entire population of cells were lost per day, then, because the apoptotic cycle is so short, up to 50% of the total pool of myocellular cells could be lost over one year. Possibly beta-adrenergic stimulation may protect from apoptosis, while increased levels of circulating TNF-alpha (tumour necrosis factor) may enhance apoptosis (see later). Despite the fascination of the subject and its major implications, the true role of apoptosis in progression of heart failure is not yet fully accepted.

Myocyte calcium overload
Altered regulation of cytosolic calcium in the failing heart has been suspected since at least 1913, when Clark found that the hypodynamic frog’s heart ‘loses its power of combining with calcium’. Recent studies on heart tissue removed at the time of transplantation or insertion of an LV assist device, together with data from increasingly sophisticated animal models, suggest that Clark was right and that calcium abnormalities are fundamental in the defective systolic function of the LV. Possible factors causing calcium overload in congestive heart failure include sarcolemmal damage and enhanced membrane permeability, microfoci of ischaemia; excess circulating catecholamines and microvascular spasm, and defective calcium cycling.

Abnormal calcium transients
Typically in failing hearts there are multiple abnormalities of calcium cycling. In terminal human heart failure, there is a decreased rise of internal calcium, followed by prolonged slowly falling calcium transient. Particularly when the heart rate is fast, there is not enough time for the internal calcium to fall to baseline levels, which may explain why tachycardia is so badly tolerated in heart failure and why sustained tachycardia can actually cause heart failure – tachycardia-induced cardiomyopathy. The impaired calcium transients reflect at least two defects in the sarcoplasmic reticulum. First, the calcium uptake pump, SERCA, is expressed at a lower level, and, secondly, calcium-induced calcium release is impaired. As SERCA2a, the specific isof orm involved, is down-regulated, the relative abundance of phospholamban in its unphosphorylated form progressively inhibits calcium uptake by the SR. Regarding calcium release by the ryanodine receptor RyR2, that too is faulty in heart failure in that the receptor is hyperphosphorylated probably in response to excess beta-adrenergic stimulation. Therapy with beta-blocking drugs restores the RyR2 function towards normal, perhaps by lessening the degree of hyperphosphorylation. Therefore calcium overload could be one of the consequences of excessive beta-adrenergic stimulation.

Catecholamines and beta-receptors in heart failure
It is not clear just when along the course of development of congestive heart failure the sympathetic adrenergic stimulation starts. Experimentally, it is closely associated with failure of myocardial contractility. We know that in severe heart failure, plasma norepinephrine is elevated, that the degree of elevation bears a relation to the severity of heart failure, and that the plasma level of norepinephrine is powerfully related to the prognosis, such as the increase in heart rate or fall in heart work. Therefore, it is reasonable to suppose that myocardial failure results in sympathetic activation and that such activation has adverse consequences (Fig. 3). The origin of the increased whole-body adrenergic stimulation is complex. In patients with established con-
gestive heart failure, there is increased adrenergic turnover in the subcortical and suprabulbar brain regions. Vasomotor centres are, however, at bulbar (medullary) level. Perhaps it all starts with a low blood pressure activating the baroreceptors and hence the sympathetic nervous system, via bulbar vasomotor centres that in turn activate renin-angiotensin II, which then stimulates suprabulbar adrenergic mechanisms.

**Excess catecholamine stimulation**

Excess catecholamine stimulation, such as found in severe congestive heart failure, could have a direct ‘toxic’ effect on the failing myocardium, but proof of this proposal is still lacking. The sum total of the potential harm of excess catecholamine stimulation is serious and includes (1) enhanced sarcolemmal permeability, (2) intracellular calcium overload and a delayed diastolic fall in calcium, (3) arrhythmogenic mechanisms that follow excess cAMP or calcium stimulation, (4) impaired mechanical function, possibly with impaired diastolic relaxation, and (5) myocardial oxygen wastage. The ultimate effects of excess catecholamines and of calcium overload are likely to be harmful and contribute to the process of accelerating myocardial failure.

The major haemodynamic consequences of excess sympathetic stimulation include: (1) beta-mediated sinus tachycardia and alpha-mediated peripheral vasoconstriction, both of which have potentially harmful effects on the failing myocardium, the former by decreasing the diastolic filling time and the latter by increasing the afterload. (2) A potential positive inotropic effect, which only in part compensates for decreased stroke volume and the inherent contractile failure of the myocardium, because of beta-receptor downregulation. It is not clear whether such excessive and prolonged myocardial sympathetic stimulation leads directly to beta-adrenergic receptor downgrading or whether genetic reprogramming is involved; the end-result is a lesser degree of inotropic response to catecholamines. This impaired response to catecholamines is relatively specific to the myocardium so that increased sympathetic stimulation of the kidneys leads to increased renin release with the consequent formation of vasoconstrictive angiotensin II.

**Compensatory role of beta2- and alpha1-adrenergic, and VIP receptors**

Sizeable amounts of beta2-adrenergic receptors are found in the non-failing human ventricle, amounting to about 15% of the combined beta, plus beta2-adrenergic receptor population. These beta2-adrenergic receptors may (1) physiologically help to sustain the full and maximal inotropic response to catecholamine stimulation, and (2) pathologically come into greater prominence as the beta1-adrenergic receptors are downgraded and hence the beta2-receptors are relatively upgraded in severe congestive heart failure. Some data suggest that beta2-adrenergic stimulation exerts an anti-apoptotic protective effect in heart failure by unexpectedly signaling via the inhibitory G-protein G1, to the pathways that promote cell survival. Nonetheless, the beta2-adrenergic receptors are also not normal in that they are uncoupled from the G-proteins.

**Alpha1-adrenergic receptor** stimulation, in general, helps to mobilize internal calcium and enhances transsarcolemmal calcium influx independently of cAMP. In severe congestive heart failure, there is a relative increase in alpha1-adrenergic receptor density.

**Vasoactive intestinal peptide** (VIP, a 28-amino acid peptide neurotransmitter) acts on receptors that are coupled to adenylate cyclase. In the failing human heart, ventricular VIP receptors become much more sensitive to VIP. This may therefore be one mechanism to help maintain contractility despite the downgraded beta2-adrenergic receptors.

**Beta2-adrenergic receptors.** Besides their important role in adipose tissue, these receptors may have a cardiac function. The proposal is that they respond to adrenergic stimulation by an unexpected negative inotropic response, which leads to the further suggestion that their relative overexpression in the failing heart could exaggerate the already poor mechanical function.

**G-proteins and adenylate cyclase.** The content of the inhibitory G protein increases, whereas Gs is either unchanged or decreased in human heart tissues with heart failure. In general, the increase in Gi is accompanied by a decreased activity of adenylate cyclase and possible anti-apoptotic effects. This may be a protective pathway (see beta2-adrenergic section).

**Cyclic AMP generation in heart failure.** Another significant abnormality in end-stage heart failure is poor generation of cAMP in response to both beta-agonist agents and (unexpectedly) to the phosphodiesterase inhibitors, agents that inhibit the breakdown of cAMP. Whereas the failure of beta-agonists to be fully effective can be explained by receptor downgrading and the inhibition of adenylate cyclase by Gi, the explanation for the failure of phosphodiesterase inhibition to increase cAMP is obscure. Possibly, intracellular compartmentation of cAMP could be invoked.

**Angiotensin II and other vasoconstrictive peptides**

In severe heart failure, an increased afterload is a prominent adaptation. Both the low renal perfusion pressure and increased beta-adrenergic stimulation contribute to renin release. The result is ultimately excessive angiotensin-mediated vasoconstriction added to that mediated by the activated sympathetic nervous system. Angiotensin II directly constricts the peripheral vessels and enhances the degree of sympathetic alpha-adrenergic activation. Angiotensin II also evokes the release of aldosterone, with an increase of body fluid volume and retention of sodium and water. Sodium and water retention, resulting from aldosterone secretion, tends to reverse the low renal perfusion pressure and, by maintaining the blood pressure, lessens the reflex sympathetic stimulation. The causes of increased renin secretion are, therefore, subject to feedback, which may explain why in nearly half of all patients with severe cardiac oedema, renin and aldosterone levels are normal. Other adverse effects of angiotensin II are increased endothelial damage and intra-
cellular damage caused by increased oxidative damage to blood vessels.

The low blood sodium resulting from excess volume retention is a serious prognostic sign and reflects the inappropriate non-osmotic secretion of the antidiuretic hormone (also called arginine vasopressin) from the pituitary gland. This renal effect is mediated by the vasopressin V2 receptors. The increased fluid retention increases cardiac work by volume overload. The antidiuretic hormone may also further increase the afterload by acting on vascular V1 receptors to cause peripheral vasoconstriction.

**Endothelin in heart failure**

Circulating levels of endothelin are increased in severe heart failure. The source of the endothelin is at least in part the myocardium in which there are increased levels of pre-pro-endothelin-1. The mechanism of increased formation is partly in response to increased angiotensin II. In the progression from compensated experimental LVH to heart failure, endothelin may also be formed independently of angiotensin II, and such endothelin may play a role in the transition to heart failure. Endothelin in excess has a direct toxic myocardial effect, perhaps by promoting calcium overload. Administration of an endothelin receptor antagonist lessens mortality in experimental heart failure and improves haemodynamics in humans.

**Cytokines in heart failure**

Cytokines are locally acting autacoid polypeptide mediators (from two Greek words, _autos _= self and _akos _= remedy). This group of poorly understood agents interacts as a class with receptors that are phospholipase C-linked, and mediates vasoconstriction through release of calcium from the sarcoplasmic reticulum. Cytokines act locally in one of several manners: autocrine – active on the cells of origin, paracrine – acting on neighboring cells, or justacrine – acting on adjacent cells. Examples are the inflammatory cytokines, such as the interleukins, derived from macrophages and leukocytes. Such cells are especially found in the myocardium in infective cardiomyopathies, but also after myocardial infarction and following reperfusion. Tumour necrosis factor-α (TNF-α) and another cytokine, interleukin-6, increase the formation of soluble ICAM-1 (intercellular adhesion molecule-1). They also appear to be linked, as does interleukin-1, to the myocardial nitric oxide signaling system, which is upregulated in response to inflammatory mediators. In the case of septic shock, cytokines are thought to exert excess negative inotropic influences by the formation of myocardial cyclic GMP. Additionally, TNF-α also induces experimental apoptosis, an effect still to be proven in patients.

**Ergoreflexes in severe heart failure**

These are intramuscular reflexes stimulated into activity by metabolites formed during skeletal muscular activity. The reflex arc acts centrally to stimulate the sympathetic nervous system, thereby being one of the factors enhancing the heart rate and blood pressure response to exercise. In CHF, according to the ‘Coats hypothesis’, there is enhanced activity of these receptors, which contributes to the excessive neuroendocrine response.

**Atrial and brain natriuretic peptides**

Thus far, many of the adaptations discussed have been potentially harmful to the failing myocardium, either directly or by increasing the afterload and preload. However, release of atrial natriuretic peptide (ANP) from the atria and brain natriuretic peptide (BNP) from the ventricles has beneficial properties for the circulation in heart failure (Fig. 4). Cardiac BNP is normally only found in the foetal and neonatal heart. In heart failure, the adult myocardium reverts to a foetal genetic pattern that is able to synthesize proteins and peptides such as BNP. ANP is both synthesized more and released in greater amounts, the latter being a pressure-sensitive event resulting from increased left atrial pressure. ANP is viewed as the acutely responsive hormone, whereas BNP is a backup hormone activated only by prolonged ventricular overload, when BNP levels exceed those of ANP. Both ANP and BNP have diuretic activity, vasodilate and inhibit aldosterone secretion. ANP is an endogenous antagonist to angiotensin II, and binding sites for these two compounds overlap. ANP inhibits the release of norepinephrine from terminal neurons, which also leads to vasodilation. This increase and that of BNP helps to slow the progression from asymptomatic left ventricular dysfunction to overt heart failure.

In congestive heart failure the potentially beneficial effects of ANP and BNP are shown by the worsening of signs when monoclonal anti-ANP antibodies are given in experimental heart failure. The increased levels of ANP and BNP in congestive heart failure are overcome by the drives to vasoconstriction and sodium retention resulting from renin-angiotensin-aldosterone activation. In addition, the atrial stretch receptors involved in the secretion of ANP

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**Fig. 4. Release of natriuretic peptides (NP) from the failing left ventricle. ANP = atrial, BNP = brain, AII = angiotensin II, Et = endothelin, Aldo = aldosterone. Figure copyright L.H. Opie, modified from The Heart, Physiology from Cell to Circulation, 3rd edition, Lippincott-Raven, Philadelphia, 1998.**
become downgraded, and vascular ANP receptors decrease their reaction to circulating ANP stimulation.\textsuperscript{43,45} Likewise the response to BNP is attenuated.\textsuperscript{44}

Besides being acutely secreted from the atria, ANP can also be formed and secreted from diseased ventricles. ANP gene reprogramming may occur at the onset of ventricular hypertrophy.\textsuperscript{46} In the LV, volume or pressure overload promotes release of ANP or its precursors, especially from the endocardial layers.\textsuperscript{40} Ventricles are also a source of ANP in severe experimental heart failure, the model being hereditary hamster cardiomyopathy.\textsuperscript{51} In general, however, it remains true that it is the atria and not the ventricles that are the major source of ANP.

Circulating levels of ANP are increased in heart failure in proportion to the atrial pressure.\textsuperscript{52} BNP levels also increase in heart failure and are diagnostically superior to ANP.\textsuperscript{44} Specifically, BNP levels reflect an increase in echocardiographic diastolic dysfunction even when systolic function is normal.\textsuperscript{53} In the presence of combined systolic and diastolic dysfunction, BNP levels reflect the severity of the heart failure and the prognosis.\textsuperscript{54}

**Adrenomedullin**

This newly identified peptide, first found in extracts of human pheochromocytoma, has potent vasorelaxing and natriuretic properties, and in this way it resembles ANP. Furthermore, in severe human heart failure, it is found in the circulation and secreted by the heart.\textsuperscript{55} Presumably it joins ANP and BNP as self-protecting peptides made by the failing myocardium.\textsuperscript{56}

**Principles of therapy for congestive heart failure**

The principles of conventional therapy are intimately bound up with the neuroendocrine response. First, diuretic therapy, by increasing output of urine and sodium, relieves the fluid retention and pulmonary congestion, thereby reducing the preload on the heart. Unfortunately diuretic therapy promotes the secretion of renin, which helps to cause angiotensin-induced vasoconstriction. Second, angiotensin-converting enzyme (ACE) inhibition has several benefits. Most obviously, it relieves the vasoconstriction and excess afterload resulting from excess activation of the renin-angiotensin system. More hidden benefits might lie in the improvement of diastolic function and in countering myocardial fibrosis. Third, beta-blockers given to ACE inhibitor-treated patients in a stable state are protective, presumably by opposing the detrimental effects of excess circulating catecholamines. Fourth, added aldosterone antagonists also lessen mortality, perhaps acting in part by decreasing myocardial fibrosis. Fifth, positive inotropic agents, including digoxin, stimulate the myocardium to contract and move it to a higher Starling curve. Such agents have not decreased mortality, and in some cases have lessened survival, perhaps because of the adverse effects of an increased cytosolic calcium level. Nonetheless, digoxin also acts in an endocrine manner to decrease sympathetic outflow, which may explain why digoxin reduces hospitalisation in heart failure. Finally, vasodilators such as nitrates and hydralazine relieve the preload and afterload respectively.

However, it must not simplistically be thought ‘the more the better’ in relation to therapeutic neuroendocrine inhibition. When angiotensin receptor blockers are added to prior therapy with both ACE inhibitors and beta-blockers, the prognosis worsens rather than improves. Therefore ACE inhibitors plus beta-blockade plus spironolactone remain the basic life-saving therapy for severe heart failure. In the future, when gene therapy becomes more accepted, the induction of upgraded myocardial calcium uptake pumps to transfer more calcium from the cytosol into the sarcoplasmic reticulum may be possible and should alleviate the beta-adrenergic-associated calcium overload in the cytosol.

First, I thank Professor Andries Brink who many years ago suggested to me that a research career in metabolic cardiology would be challenging and satisfying (so it has been and still is). Second, I thank Professor P. Commerford, Head, Cardiac Clinic, Groote Schuur Hospital and University of Cape Town, for stimulating my interest in heart failure. Third, I thank Professor Michael Sack and many colleagues in the Hatter Institute of Cardiology Research who have promoted my interest in basic research in heart failure.

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