Influence of medical intervention on sympathetic activity in heart failure

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Chapter II

Heart failure, pathophysiology and compensatory mechanisms
Introduction

The concept of the pathophysiological mechanisms operative in the syndrome of heart failure has changed dramatically in the past 20 years. For many years, heart failure was considered a hemodynamic problem of pure pump dysfunction. Nowadays, heart failure is seen as a clinical syndrome consisting of a complex interplay of systolic and diastolic dysfunction, neuroendocrine activation and altered peripheral vascular and muscular responses. These changes in the concept of heart failure were paralleled by changes in medical therapy. Drugs designed to influence systolic function were shown to be deleterious or had a neutral effect on the disease process. In contrast, drugs that modulate the activated compensatory mechanisms in heart failure show beneficial effects on both morbidity and mortality. With these new treatment modalities, the vision that myocardial failure is an irreversible and progressive process is no longer valid. As stated by Eichhorn and Bristow, interventions such as treatment with ACE inhibition and β-blockade that are primarily aimed at a reduction in the harmful long-term consequences of neuro-endocrine activation can improve the biological properties of the chronically failing heart irrespective of the cause of myocardial dysfunction. These treatment modalities open a new era in the treatment of heart failure as was recently shown in several large trials with ACE-inhibitors, β-blockers and spironolactone.

Pathophysiology of heart failure

Generally speaking, heart failure is the result of an insult to myocytes resulting in a decline in systolic and diastolic performance of the myocardium. This myocardial dysfunction is best demonstrated by a downward and rightward shift in the Frank-Starling relation. The index events that lead to heart failure may include subclinical alterations of contractile function, perhaps at the level of contractile proteins within the myocyte, an acute inflammatory response, or sudden loss of myocardial tissue as a result of acute myocardial infarction. Table 1 summarizes different

Table 1 Etiology of heart failure

- myocardial infarction
- chronic myocardial ischemia
- hemodynamic overload
  - hypertension
  - valvular disease
- inflammation
- genetic
- idiopathic
- miscellaneous
- toxins (alcohol, adriamycin)
- infiltrative disease (amyloidosis, neoplastic)
- metabolic (diabetes)
- post partum
- tachycardia induced
Figure 1 Pathogenesis of heart failure. Heart failure begins after an index event produces an initial decline in pumping capacity of the heart. This initial decline in systolic function and diastolic properties will result in increased loading conditions and decreased systemic perfusion. A variety of compensatory mechanisms are activated, including the (para)sympathetic nervous system, the renin-angiotensin system and the cytokine system. Besides systemic activation of these compensatory mechanisms, local activation at the myocardial level occurs, including the so-called aldosterone escape. Overexpression of these biologically active molecules can attribute to disease progression independently of the hemodynamic status of the patient. Ultimately, myocardial apoptosis and necrosis occur, thus further aggravating progressive pump failure.

etologies of heart failure. Among several causes of heart failure, coronary artery disease is the most frequently encountered in the western world. The decline in contractile function of the myocardium will result in activation of compensatory mechanisms to preserve cardiac output. These may be located within the myocardium (e.g., hypertrophy, cardiac sympathetic activation, parasympathetic modulation) and at the systemic level (e.g., renin-angiotensin, adrenergic stimulation). These compensatory mechanisms can initially be considered as beneficial to support cardiac function but eventually they aggravate the disease process because of their adverse biological effects on the long term (Figure 1). Apart from their influence on myocardial function, activation of these compensatory mechanisms also influences peripheral muscle function and blood supply thus contributing to the clinical manifestations of heart failure. The myocardial signaling pathways involved in progressive myocardial dysfunction are summarized in table 2.
Hear failure, pathophysiology and compensatory mechanisms

Table 2 signaling pathways involved in progressive myocardial dysfunction and remodelling

<table>
<thead>
<tr>
<th>signaling pathway</th>
<th>compensatory effect</th>
<th>adverse biological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>neurotransmitters</td>
<td>adrenergic</td>
<td>increase heart rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>increase contractility</td>
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<td></td>
<td></td>
<td>increase preload</td>
</tr>
<tr>
<td></td>
<td></td>
<td>myocyte hypertrophy</td>
</tr>
<tr>
<td>growth factors</td>
<td>angiotensin II</td>
<td>increase preload</td>
</tr>
<tr>
<td></td>
<td></td>
<td>myocyte hypertrophy</td>
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<tr>
<td></td>
<td></td>
<td>myocyte hypertrophy</td>
</tr>
<tr>
<td>endothelin</td>
<td></td>
<td>myocyte hypertrophy</td>
</tr>
<tr>
<td>insulin like growth factor</td>
<td></td>
<td>myocyte hypertrophy</td>
</tr>
<tr>
<td>fibroblast growth factor</td>
<td></td>
<td>myocyte hypertrophy</td>
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<tr>
<td>cytokines</td>
<td>TNF-alfa</td>
<td>myocyte hypertrophy</td>
</tr>
<tr>
<td>mechanical strain</td>
<td>wall stretch</td>
<td>increase preload</td>
</tr>
<tr>
<td></td>
<td></td>
<td>myocyte hypertrophy</td>
</tr>
</tbody>
</table>


Short term compensatory mechanisms

In response to an insult to pump function, two, interrelated neuroendocrine systems are activated. Through activation of the adrenergic nervous system, an increase in heart rate and contractility is established. Activation of the renin-angiotensin-aldosterone system is the consequence of inadequate renal perfusion in heart failure resulting in the generation of angiotensin I. This peptide is converted by the angiotensin converting enzyme into angiotensin II. Angiotensin II is a potent vasoconstrictor, induces myocardial hypertrophy and facilitates the release of aldosterone which results in sodium and water retention and a subsequent increase in cardiac loading conditions. Both the activated adrenergic system and the renin-angiotensin-aldosterone system evoke an increase in preload and cardiac myocyte hypertrophy. In order, heart rate and contractility increases are quickly operating mechanisms, whereas increase in preload and myocyte hypertrophy are a relatively late phenomenon though beneficial to maintain cardiac output.
Long term effects of activated compensatory mechanisms on cardiac myocytes

Continued cardiac stimulation by neurotransmitters, growth factors and cytokines will result in deleterious effects on cardiac myocytes, matrix and geometry of the ventricles, a process known as remodeling of the ventricles (table 2).

Cardiac myocyte loss is a common feature of advanced states of heart failure irrespective of the cause and should be considered an intrinsic part of the disease process.\(^{17-19}\) Cell loss occurs via two mechanisms: necrosis and apoptosis. Cardiac norepinephrine release\(^{20}\) and exposure to angiotensin II\(^{21}\) can produce cell necrosis in models of heart failure. Besides, cell necrosis can occur in the setting of an acute event, such as interruption of myocardial blood supply or severe inflammation. Apoptosis, the process of programmed cell death is intensified in heart failure and contributes to cell loss.\(^{22}\) Exact mechanisms in human hearts are unknown but the intermediates responsible for apoptosis appear to be upregulated in the failing heart. Further upregulation is possibly accomplished through elevated tissue levels of angiotensin II and norepinephrine.\(^{23}\)

Apoptosis induced by norepinephrine is probably mediated mainly through \(\beta_1\)-adrenergic receptors as demonstrated in rat ventricular myocytes.\(^{24}\) In addition, elevated levels of tumor necrosis factor-\(\alpha\) can also induce cell apoptosis in the myocardium.\(^{25}\) Since cardiac myocytes do not divide, cardiac cell loss is part of the vicious circle leading to a further decline in cardiac function.

Deposits of collagen matrix accompany the loss of cardiac myocytes. Patients with non-ischemic etiology of their cardiomyopathy have higher than normal amounts of interstitial matrix. Whether these increased collagen deposits are due to synthesis of new collagen or inhibition of collagen breakdown is unknown.

The net result of the remodeling process is a reduction in the number of cardiac myocytes, side to side slippage of myocytes, a reduction in contractile filament mass, and proliferation of interstitial matrix, which includes focal and perivascular fibrosis.\(^{26}\) In addition, endothelium-dependent NO-mediated vasodilation in response to hormonal agonists and shear stress during exercise is decreased in the skeletal muscle and coronary circulation of patients with heart failure (irrespective of the etiology) compared with normal subjects.\(^{27-29}\) It was recently demonstrated that a specific decrease in synthetic activity of the L-arginine-N0 metabolic pathway plays an important role in this disturbance of vasodilation\(^{30}\) possibly contributing to the syndrome of heart failure.

Finally, it is becoming increasingly clear that disturbances in calcium homeostasis accompany heart failure.\(^{31-34}\)

Peripheral effects of activated compensatory mechanisms

Exercise intolerance and fatigue are among the most frequent and debilitating symptoms in patients with mild, moderate and more severe congestive heart failure. These symptoms are partially caused by a decreased cardiac output. However, the severity of these symptoms correlates poorly with indexes of cardiac function such as ejection fraction and hemodynamic measurements.\(^{35-37}\)
This discordance has focused attention on peripheral pathophysiological mechanisms to explain the impaired exercise capacity both at the maximal and the submaximal level assuming that exercise is limited in part by alterations in peripheral blood flow, muscle sympathetic nerve activity and intrinsic skeletal muscle architecture. These alterations occur either as a manifestation of the syndrome of heart failure or as a consequence of the resulting decrease in activity.

Peripheral blood flow
The question whether abnormalities in peripheral blood flow with reduced oxygen delivery to exercising muscle play a role remains uncertain. Abnormalities in peripheral blood flow have been demonstrated\(^\text{18,39}\) but also disputed recently.\(^\text{40-41}\) These blood flow limitations during exercise limit oxygen uptake and augment glycolysis. Early exertional fatigue may, to some extent, be attributed to this mechanism, especially during maximal exercise.

Muscle sympathetic nerve activity
Increased sympathetic outflow has been demonstrated in heart failure. An inverse relationship between peak oxygen uptake and exercise limitation on the one side and resting sympathetic nerve traffic to muscle on the other side has been proposed to add to peripheral limits in exercise.\(^\text{42}\) However, the importance of this finding remains unclear. It might well be an epi-phenomenon of neurohormonal overactivity.

Intrinsic muscle abnormalities
Several changes in muscle architecture and metabolism are being recognized in recent years. These include muscle atrophy, changes in fiber type distribution, reduced oxidative capacity and decreased capillary density in skeletal muscle. In addition, major metabolic disturbances are increasingly recognized in congestive heart failure leading to the concept of cardiac cachexia.\(^\text{43,44}\) These changes can be considered as secondary peripheral manifestations of the syndrome of heart failure and are probably partly mediated by neurohormonal overactivity.\(^\text{45}\)

References


44. Anker SD, Coats A. Cardiac cachexia: A syndrome with impaired survival and immune and neuroendocrine activation. *Chest.* 1999;115:836-847.
