The Treatment of Heart Failure: The Role of Neurohumoral Activation

Holly R. Middlekauff and Allyn L. Mark

Neurohumoral activation refers to increased activity of the sympathetic nervous system, renin-angiotensin system, vasopressin and atrial natriuretic peptide. It is now known that neurohumoral activation contributes to the transition from ventricular dysfunction to clinical heart failure, and is an independent predictor of poor prognosis in heart failure. Although the treatment of heart failure has traditionally focused on drugs to improve ventricular function, there is increasing evidence that therapeutic modulation of neurohumoral activation is a key to successful treatment of heart failure. For example, there is mounting evidence that angiotensin converting enzyme inhibitors (the unquestioned cornerstone for treatment of heart failure), beta receptor blockers, digitalis, and endurance exercise training exert their benefit in heart failure in large part through neurohumoral modulation. This observation – discussed in this brief review – highlights the concept that compensatory neurohumoral activation to decreased cardiac function may itself contribute to the development of heart failure and its poor prognosis.

Key words: sympathetic nervous system (SNS), renin-angiotensin system, angiotensin converting enzyme inhibitors (ACEI), beta receptor blockers, digitalis, exercise training

Introduction

In the past, treatment of heart failure focused on improving left ventricular function directly with positive inotropic drugs. Therefore, it may seem counterintuitive that most positive inotropic therapies increase mortality, whereas negative inotropic beta-adrenergic blockers appear to have beneficial effects in heart failure.

In contrast to the disappointing effects of many positive inotropic drugs, controlled clinical trials demonstrated that therapy with angiotensin converting enzyme inhibitors (ACEI) improve survival in patients with heart failure. Indeed, the striking benefit with ACEI now mandates administration of ACEI to all patients with left ventricular dysfunction in the absence of intolerable side effects. Initially, the benefit of ACEI was attributed to their vasodilator actions, but evidence is mounting that their benefit is largely due to neurohumoral rather than vasodilator actions.

This emphasizes the importance of neurohumoral activation in heart failure. But what is meant by neurohumoral activation? What is the evidence that it is detrimental in heart failure? What causes it? Finally, how does treatment modify it?

What is “neurohumoral activation?”

In simplest terms, neurohumoral activation characterizes a state in which the neural and hormonal systems designed to maintain adequate organ perfusion are turned on to excessively high levels. This activation may include the sympathetic nervous system (SNS), renin-angiotensin-aldosterone-system, vasopressin, and atrial natriuretic peptide. Although initially this is an adaptive response to cardiac injury, prolonged activation of these support systems inevitably leads to progressive heart failure symptoms and ultimately cardiac death. Heart failure patients with the greatest SNS activation, as estimated by plasma norepinephrine levels, have the worst overall survival.

SNS activation is present early in the course of left ventricular dysfunction. In an animal model of early left ventricular dysfunction without overt heart failure, plasma norepinephrine levels are elevated, indicative of early SNS activation. Power spectral analysis of heart rate variability suggests that there is sympathetic activation early in the course of left ventricular dysfunction in a canine model of heart failure. This finding of sympathetic activation with ventricular dysfunction in the absence of heart failure has also been demon-
Neurohumoral Activation in Heart Failure

Figure 1. Evidence for increases in plasma norepinephrine (NE) in patients with left ventricular dysfunction (LVD) even before symptoms of heart failure (HF). There is a further increase in NE in patients with symptomatic heart failure (4).

Figure 2. Evidence for increased cardiac sympathetic activity before generalized sympathetic excitation and before sympathetic activation to the kidney in patients with heart failure. Individual and mean ± SEM values for cardiac norepinephrine (NE) spillover, renal NE spillover, total-body NE spillover in healthy controls and in patients with mild to moderate and severe heart failure (CHF) are presented (adapted from Rundqvist et al (5)).

In what way is sympathetic nervous system activation detrimental?

Initially an adaptive response to cardiac injury, prolonged activation of the sympathetic nervous system may have adverse sequelae (Fig. 3) (9). These include increased myocardial wall tension and ischemia. Norepinephrine is directly cardiotoxic, and may lead to detrimental cardiac remodeling. Peripheral vasoconstriction leads to increased afterload and diminished cardiac output and renal perfusion, leading, in turn, to increased sodium and fluid retention. The renal sympathetic nerves also act directly on the renal tubules to promote sodium retention. Finally, sympathetic nerve activation decreases ventricular fibrillation threshold, predisposing to sudden death. As noted above, heart failure patients with the greatest sympathetic...
Detrimental Sequelae of 
Sympathetic Activation in Heart Failure

- Wall Tension
- Ischemia
- Myocyte Toxicity
- Cardiac Remodeling
- Vent. Fib. Threshold
- Vasoconstriction
- Muscle Perfusion
- Renin Release
- Tubular Na Resorption
- Renal Vasoconstriction

Figure 3. Adverse sequelae of sympathetic activation in heart failure.

activation have the poorest prognosis (1).

What are the mechanisms underlying sympathetic activation in heart failure?

Although there is agreement that the SNS is activated in heart failure, there is controversy about the mechanisms underlying this activation. Possible mechanisms implicated include 1) attenuation of tonically inhibitory input to the central nervous system; 2) activation of excitatory input to the central nervous system; and/or 3) changes in humoral or local brain factors affecting central neural sympathetic regulation (Fig. 4).

Attenuation of the normal inhibitory baroreflex restraint on the SNS would lead to SNS activation. We will focus on the evidence supporting this mechanism since this is the most investigated, and the most probable, mechanism.

Baroreceptors are sensory receptors that sense changes in mechanical stretch such as those produced by changes in pressure. Their activity may also be influenced by local ionic or humoral mechanisms. Arterial baroreceptors, located in the aortic arch and carotid sinus, and cardiopulmonary baroreceptors, located preferentially in the left ventricle, tonically inhibit central sympathetic neural outflow. In heart failure, baroreflex control of sympathetic nerve activity is abnormal (10, 11). Dibner-Dunlap and Thames (10) recorded renal sympathetic nerve activity in sinoaortic denervated dogs with pacing-induced heart failure. During volume expansion, there was impairment of cardiopulmonary baroreceptor mediated suppression of renal sympathetic nerve activity (10). DiBona and Sawin (11) measured baroreceptor nerve activity directly in a rat model of heart failure. During changes in arterial pressure or left ventricular filling pressure, arterial and cardiopulmonary baroreceptor activity was significantly depressed (11). These studies, and others, are consistent with abnormal baroreflex control of sympathetic nerve activity in heart failure. This abnormality would lead to heightened sympathetic activity.

In humans, there is also compelling evidence that abnormal baroreceptor restraint contributes to heightened sympathetic activity in heart failure. First, sympathetic nerve activity is elevated only to those organs and tissues subject to baroreflex restraint in heart failure and not to all organs and tissues (12, 13). For example, SNS activation directed to muscle circulation, which is under baroreflex control, is elevated (6, 12, 14). In contrast, sympathetic neural responses to baroreceptor modulation are abnormal in heart failure patients (15), even those with mild heart failure (6). This blunted baroreflex restraint would lead to elevated sympathetic traffic.

In summary, animals and humans with heart failure have marked sympathetic activation at rest, and attenuated baroreflex control of sympathetic nerve activity. These findings are present early in the course of left ventricular dysfunction, and are consistent with the concept that abnormal baroreflex control of sympathetic nerve activity underlies the sympathetic excitation that characterizes heart failure.

What is the effect of ACEI on survival in heart failure?

Although much remains to be learned about the mechanisms of the neurohumoral activation in heart failure, it is firmly
Figure 4. Potential mechanisms of SNS activation in heart failure. These include impairment in inhibitory influences on the SNS such as arterial and cardiopulmonary baroreflexes. An alternative but less likely possibility is augmentation of excitatory influences on the SNS such as peripheral chemoreceptors and somatic afferents from muscle. Finally, alterations in local or humoral factors acting in the central nervous system could increase SNS. These include angiotensin II; norepinephrine; epinephrine; ouabain-like activity; nitric oxide; and opioids.

Figure 5. Direct intraneural recordings of muscle and skin sympathetic nerve activity (SNA). Simultaneous muscle and skin neurograms in a representative control subject (top two tracings) and in a representative heart failure patient (bottom two tracings) are shown. Muscle sympathetic nerve activity is markedly increased in the heart failure patient compared with the control subject. In contrast, skin sympathetic nerve activity is not increased in the heart failure patient (from Middlekauff, et al (10)).
established that ACEI improve survival in heart failure, mandating ACEI therapy in all patients with left ventricular dysfunction in whom these drugs are tolerated and not contraindicated (Table 1). The Cooperative North Scandinavian Enalapril Survival Study-I (CONSENSUS I) was the first randomized controlled trial to demonstrate that enalapril improved survival in advanced heart failure (16). The Veterans Administration Heart Failure Trial II (V-HeFT II) showed that enalapril was superior to hydralazine and isosorbide dinitrate in improving survival in mild to moderate heart failure (17). The Hydralazine-Captopril (Hy-C) trial extended these findings to patients with advanced heart failure; this study demonstrated improved survival with captopril compared to hydralazine despite similar hemodynamics on each therapy (18). The Studies of Left Ventricular Dysfunction (SOLVD) treatment trial (19) found that enalapril compared to placebo improved survival in patients with symptomatic left ventricular dysfunction (LVEF <35%). In the SOLVD prevention trial, enalapril decreased the progression to heart failure in patients with left ventricular dysfunction without overt heart failure (20); these patients have sympathetic overactivity as evidenced by elevated plasma norepinephrine even in the absence of symptomatic heart failure (4).

The Survival and Ventricular Enlargement (SAVE) trial demonstrated that following a myocardial infarction, patients with left ventricular dysfunction (left ventricular ejection fraction <40%) who were treated with captopril compared to placebo had improved survival (21). The results of ISIS-4 and GISSI-3 demonstrated improved survival in all survivors of myocardial infarction (regardless of ventricular function) who were randomized to ACEI compared to placebo; these studies further extended the indications for ACEI (22, 23).

\[ \text{In summary, in the above trials, and numerous others (24-27), ACEI have 1) prevented progression to heart failure in} \]

\[ \text{Table 1. Controlled Clinical Trials of ACEI for Patients with Ventricular Dysfunction or Myocardial Infarction} \]

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>Patients (n)</th>
<th>NYHA Functional Class</th>
<th>Follow Up (Months)</th>
<th>Total Mortality (ACEI vs Control)</th>
<th>Reduction in Sudden Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS (16)</td>
<td>enalapril vs placebo</td>
<td>253</td>
<td>IV</td>
<td>6</td>
<td>20% vs 44% RR 40%, ( p = 0.002 )</td>
<td>no</td>
</tr>
<tr>
<td>V-HeFT-II (17)</td>
<td>enalapril vs hydralazine + isosorbide dinitrate (Males)</td>
<td>804</td>
<td>II-III</td>
<td>24</td>
<td>18% vs 25% RR 28%, ( p = 0.016 )</td>
<td>yes</td>
</tr>
<tr>
<td>Hy-C (18)</td>
<td>captopril vs hydralazine</td>
<td>117</td>
<td>III-IV</td>
<td>12</td>
<td>19% vs 49% ( p = 0.05 )</td>
<td>yes</td>
</tr>
<tr>
<td>SOLVD-Treatment (19)</td>
<td>enalapril vs placebo</td>
<td>2,569</td>
<td>II-III</td>
<td>41</td>
<td>35% vs 40% RR 16%, ( p = 0.0036 )</td>
<td>no</td>
</tr>
<tr>
<td>SOLVD-Prevention (20)</td>
<td>enalapril vs placebo</td>
<td>4,228</td>
<td>no HF EF &lt;.35</td>
<td>37</td>
<td>RR 8% ( P = 0.3 )</td>
<td>no</td>
</tr>
<tr>
<td>SAVE (21)</td>
<td>captopril vs placebo</td>
<td>2,231</td>
<td>no HF EF &lt;.40</td>
<td>42</td>
<td>20% vs 25% RR 19%, ( p = 0.019 )</td>
<td>no</td>
</tr>
<tr>
<td>ISIS-4 (22)</td>
<td>captopril vs placebo</td>
<td>58,050</td>
<td>post MI &lt;24h</td>
<td>1.25</td>
<td>7.19% vs 7.69% ( p = 0.02 )</td>
<td>no</td>
</tr>
<tr>
<td>GISSI-3 (23)</td>
<td>lisinopril vs control</td>
<td>19,384</td>
<td>post MI &lt;24h</td>
<td>1.5</td>
<td>6.3% vs 7.1% RR 11%</td>
<td>no</td>
</tr>
<tr>
<td>AIRE (24)</td>
<td>ramipril vs placebo</td>
<td>2,006</td>
<td>post MI 2-9 Days</td>
<td>18</td>
<td>17% vs 18% RR 27%, ( p = 0.002 )</td>
<td>yes</td>
</tr>
<tr>
<td>CCS-I (25)</td>
<td>captopril vs placebo</td>
<td>13,634</td>
<td>post MI &lt;36h</td>
<td>1</td>
<td>9.05% vs 9.59% RR 5.3%, ( p = 0.2 )</td>
<td>no</td>
</tr>
<tr>
<td>SMILE (26)</td>
<td>zofenopril vs placebo</td>
<td>1,556</td>
<td>post MI &lt;24h</td>
<td>12</td>
<td>10% vs 14.1% RR 29%</td>
<td>no</td>
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patients with mild left ventricular dysfunction without overt heart failure and 2) improved survival in patients following myocardial infarction, as well as in patients with mild to advanced heart failure.

**How do ACEI improve survival in heart failure?**

We are able to glean some insights into the mechanisms of survival benefit of ACEI therapy by examining results from these large randomized trials. The benefits do not appear to be attributable to hemodynamic effects alone, because other vasodilators, titrated to similar hemodynamic responses, do not show the same survival benefit (18). Markers of neurohumoral activation were reported in several of these trials. In the CONSENSUS trial (16), enalapril was associated with a significant reduction in plasma norepinephrine by 6 weeks of therapy. Interestingly, enalapril was most effective in improving survival in the heart failure patients with the greatest elevation in neurohormones. In the SOLVD treatment trial (20), enalapril therapy was associated with a reduction in plasma norepinephrine levels compared to placebo.

In summary, ACEI reduce plasma norepinephrine levels which suggests that a beneficial effect on the sympathetic nervous system may contribute to its beneficial effects on survival.

**What are the mechanisms of ACEI interactions with the SNS?**

There are many potential mechanisms by which ACEI therapy modulates SNS activity; the specific ones which are responsible for the favorable effects of ACEI therapy in heart failure remain to be clarified (Fig. 6). ACEI act peripherally, as well as in the central nervous system, to reduce sympathetic nerve activity. ACEI increase the sensitivity of afferent baroreceptor nerves, thereby augmenting their tonic restraint on central sympathetic outflow. In the brain, ACEI reduce central angiotensin levels which normally contribute to increased central sympathetic outflow (28). Additionally, ACEI increase central bradykinin levels, which contribute to suppression of central sympathetic outflow (29). Finally, ACEI reduce angiotensin enhancement of ganglionic transmission, and angiotensin-induced facilitation of norepinephrine release from sympathetic nerve terminals.

Experimental evidence supports the role of several of these mechanisms in heart failure patients. In a trial of acute ACEI therapy in humans with heart failure, Dibner-Dunlap and colleagues (30) found that intravenous enalaprilat improved arterial and cardiopulmonary baroreflex control of sympathetic nerve activity. These findings have been extended by Grassi and colleagues (31) who studied the effects of chronic ACEI on...
sympathetic nerve activity and baroreflex activity in patients with heart failure. Following 2 months of ACEI therapy with benazepril, resting sympathetic nerve activity was markedly reduced. Baroreflex restraint of muscle sympathetic nerve activity and heart rate was markedly enhanced. These findings support the concept that blunted baroreflex control underlies the sympathetic excitation in heart failure, and that therapy with ACEI restores baroreflex control towards normal in heart failure patients.

Takeishi and colleagues (32) used $^{125}$I-MIBG to measure cardiac sympathetic nerve activity in heart failure patients treated with enalapril compared to placebo. Cardiac sympathetic nerve activity, like muscle sympathetic nerve activity, is governed by baroreflexes. Patients were studied before and after treatment for a mean of nine months. Cardiac sympathetic nerve activity was significantly reduced in the enalapril group but not the control group. Thus, sympathetic influences on the heart are decreased on enalapril therapy.

In summary, evidence is accumulating that ACEI modulate the SNS though baroreflex pathways. There is also evidence that ACEI may act to reduce sympathetic drive through a reduction in angiotensin levels in crucial brain centers involved in sympathetic regulation.

Do ACEI and angiotensin II receptor antagonists have similar efficacy in heart failure?

A new class of drugs has recently become available for the treatment of humans with heart failure – the angiotensin II receptor blockers (AT receptor blockers). The AT receptor blockers that have been introduced into clinical practice block AT-1 receptors and spare AT-2 receptors. Most of the detrimental effects of angiotensin are mediated through AT-1 receptors. The physiological significance of AT-2 receptor activation is unknown, but beneficial effects have been suggested.

In what ways do AT-1 receptor blockers and ACEI differ? ACEI increase bradykinin in addition to decreasing angiotensin II. In contrast, the AT-1 receptor blockers do not alter bradykinin levels or actions. ACEI do not interrupt formation of angiotensin through alternative (non ACE dependent) synthetic pathways. In contrast, the AT-1 receptor antagonists block the actions of angiotensin formed through both ACE and non-ACE dependent pathways. As mentioned previously the AT-1 receptor blockers spare effects of angiotensin on AT-2 receptors whereas ACEI would reduce angiotensin stimulation of both AT-1 and AT-2 receptors. Thus, although both AT-1 receptor blockers and ACEI act to modulate angiotensin actions, there are potentially important differences in these two classes of drugs.

At this time, it is unclear if functional and survival benefits of ACEI will be shared by the AT-1 receptor blockers. Preliminary studies with AT-1 receptor blockers appear promising. In a study of heart failure produced by coronary ligation in rats, survival was equivalent with the AT-1 receptor antagonist, losartan, compared to captopril (an ACEI) (33). There has been one randomized study of AT-1 receptor blockers in humans with heart failure (34). In this study called the Evaluation of Losartan in the Elderly Study (ELITE), heart failure patients ≥65 years were randomized to losartan or captopril with the primary endpoint being renal function, and the secondary endpoint being survival (34). There was no difference in the incidence of renal insufficiency (10.5% in both groups). Unexpectedly, however, at 48 weeks survival was better in the losartan group (34). Larger trials are now in progress to confirm these intriguing preliminary findings.

What is the role of beta-adrenergic blockade?

Recognition of the detrimental effects of sympathetic activation in heart failure has led to interest in beta-adrenergic blockade for the treatment of heart failure. Initial studies, although small and lacking adequate controls, reported clinical improvement and prolonged survival with beta-blockade in heart failure (35–37). In larger, controlled trials with beta-blockers, an improvement in left ventricular ejection fraction on beta-blockers has been demonstrated, but not an improvement in survival (38, 39). In the Metoprolol in Dilated Cardiomyopathy study, 383 New York Heart Association (NYHA) Class II and III heart failure patients with idiopathic dilated cardiomyopathy were randomized to placebo or metoprolol, a beta-1 selective antagonist (38). Left ventricular ejection fraction was significantly improved on therapy, but survival was not. In the Cardiac Insufficiency Bisoprolol Study (39), 641 NYHA Class III heart failure patients with ischemic and idiopathic etiologies were randomized to bisoprolol, a beta-1 selective antagonist, or placebo. Bisoprolol therapy was associated with improved functional class and fewer hospitalizations for heart failure, but no improvement in survival. Several studies of a third generation beta-blocker, carvedilol, have reported an improvement in functional class, ejection fraction and survival (40–43), although the improved survival has been questioned in an editorial commentary (44). It should be noted that carvedilol has alpha-1-adrenergic blocking, antioxidative and antiproliferative properties in addition to beta blocking properties, and some of its benefit could accrue from these other actions. Larger studies of beta-blockers in heart failure, empowered to determine more definitively a survival benefit, are currently ongoing.

In each of these trials, beta-blockers were carefully titrated, and have been well tolerated with <4% patients withdrawn early due to heart failure exacerbation. However, at this time, due to their potentially catastrophic acute effects, the use of beta-adrenergic blockers in heart failure should remain in the domain of the cardiologist with expertise in heart failure.

Beta-blockers antagonize the SNS at the beta-receptor level, but not equivalently. Metoprolol is a beta-1 selective antagonist, and is associated with upregulation of the beta-1 receptor (45). In contrast, carvedilol is a nonselective beta-blocker which interacts with G proteins leading to downregulation of beta-1 and beta-2 receptors (46).

In addition to their benefits at the receptor level, there is intriguing data to suggest a beneficial effect of beta-blockers on central SNS outflow. Chronic carvedilol therapy in heart failure patients has been associated with a fall in plasma norepinephrine levels. In patients with hypertension, chronic beta-
blockade reduces central SNS outflow (47). In a small study of metoprolol therapy in patients with heart failure, a marked reduction of muscle sympathetic nerve activity was reported after a mean follow-up of 20 months (48). The mechanism of the reduction in central SNS outflow associated with beta-blockers is unknown.

In summary, beta-blocker therapy in heart failure is associated with an improvement in ejection fraction. Somewhat surprisingly, in addition to decreasing beta receptor influences on the heart, chronic beta receptor blockade may reduce sympathetic activity to other tissues and organs. The benefits of beta-blockers on survival remain controversial. At this time, because of potential acute catastrophic effects, the use of beta blockers in heart failure should remain in the domain of a cardiologist with expertise in heart failure.

Is there still a role for digoxin in heart failure?

For decades, digitalis was the mainstay of the treatment of heart failure despite the absence of controlled clinical trials of its efficacy and safety. Digitalis was initially used for its positive inotropic properties, but the inotropic effect of digitalis is modest, and the value and safety of inotropic agents in heart failure have been challenged. Further, digitalis has a relatively narrow therapeutic range before toxicity. Therefore, the role of digitalis in heart failure was questioned. However, recently several small, short-term controlled studies in heart failure patients already treated with ACEI demonstrated that withdrawal of digoxin is associated with heart failure exacerbation and worsening functional capacity (49, 50). In the Digitalis Investigation Group (DIG) trial, empowered to demonstrate mortality effects, digitalis compared to placebo was not associated with improvement (or reduction) in survival in heart failure patients already treated with ACEI (51). The DIG study did, however, confirm that digitalis reduced heart failure exacerbation episodes requiring hospitalization.

The beneficial effect of digitalis in heart failure is likely not attributable to its inotropic effects (which are modest), but to its neurohumoral effects. In animals, digitalis sensitizes baroreceptors, thereby inhibiting sympathetic nerve activity (52). These baroreceptor actions that produce sympathetic inhibition are more pronounced in dogs with heart failure than in normal dogs. Digitalis also has neuromodulatory effects in humans. Acute digitalis administration in humans with heart failure inhibits sympathetic nerve activity, measured by microneurography (Fig. 7) (53) and by cardiac norepinephrine spillover (54). This effect is independent of hemodynamic responses. Chronic digitalis administration has similarly favorable neurohumoral effects. In dogs, chronic digitalis administration produces sustained sensitization of cardiac baroreceptors (55). In humans, chronic digitalis is associated with a reduction in plasma norepinephrine levels (56).

In summary, digitalis therapy has favorable neurohumoral effects in heart failure, including a sustained decrease in sympathetic activity. It is associated with a reduction in heart failure exacerbations, but not with improved survival.

What should we tell our patients with heart failure about exercise?

Exercise intolerance is a hallmark of congestive heart failure. Because of this and a concern about safety, endurance exercise training has not commonly been recommended for patients with heart failure. Surprisingly, there is strong rationale for exercise training in patients with heart failure (57). The reduction in exercise capacity in patients with heart failure is related more to abnormalities in the peripheral circulation and skeletal muscle than to the magnitude of ventricular dysfunction. Heart failure is accompanied by skeletal muscle atrophy and abnormalities in skeletal muscle that resemble deconditioning (58). These patients also have impairment in skeletal muscle blood flow during exercise that results, in part, from increased neurohumoral activation (59). Heart failure is also characterized by an increased ratio of sympathetic to parasympathetic activity, which may increase the risk of sudden cardiac death. Endurance exercise training acts to reverse many of these abnormalities in skeletal muscle, the peripheral circulation and the autonomic nervous system. Exercise training does not improve ventricular function, but as discussed previously this may not be essential for effective treatment of heart failure.

Figure 7. Direct intraneural recordings of muscle sympathetic nerve activity from a patient with heart failure showing a substantial decrease in sympathetic activity 20 minutes after intravenous administration of the cedilanid, a cardiac glycoside (adapted from Ferguson, et al (53)).
heart failure.

There are several controlled clinical trials of endurance exercise training in patients with chronic heart failure and severe left ventricular dysfunction. These trials range from 3 to 24 weeks (60–63); there are uncontrolled trials extending for 19 months (64). Virtually uniformly, these studies demonstrate an increase in exercise duration and peak oxygen consumption. This benefit is related to peripheral neurohumoral and circulatory adaptations and not to improvement in ventricular function. Exercise training promotes a reduction in resting sympathetic activity and enhances vagal tone in patients with heart failure (60, 64–67). A transient sympathetic modulating effect has even been observed after a single bout of endurance exercise in patients with heart failure (68). In addition, exercise training enhances skeletal muscle blood flow and the ability of skeletal muscle to extract and utilize oxygen during exercise.

In summary, endurance exercise training increases exercise tolerance and peak oxygen consumption in patients with heart failure. This effect results from favorable neurohumoral and peripheral circulation adaptations. It is not known if exercise training improves survival, but a long term (12 month) controlled clinical trial of the effects of exercise training on functional capacity and quality of life is reported underway. In the meantime, there is sufficient rationale and evidence to support the benefit and safety of endurance exercise training as an adjunct to established pharmacological therapy in heart failure.

Summary

Heart failure is characterized by neurohumoral activation. The heart failure patients with the greatest activation of the sympathetic nervous system have the poorest survival. Sympathetic neural activation contributes to the progression of left ventricular dysfunction, renal sodium retention, the development of clinical heart failure, and susceptibility to malignant ventricular arrhythmias. The mechanisms underlying activation of the sympathetic nervous system are not entirely clear, but evidence supports a major role for impaired baroreflex function. Normally, baroreflexes tonically restrain sympathetic nerve activity; in heart failure patients, this restraint is attenuated. Angiotensin converting enzyme inhibitors impede the progression of heart failure, and improve survival in heart failure patients. These beneficial effects are largely due to the neurohumoral actions of ACEI, including interactions with the sympathetic nervous system. Therapy with ACEI diminishes sympathetic nervous activation in heart failure. It is not known if angiotensin II receptor antagonists (AT-1 receptor antagonists) will have similar beneficial effects in heart failure, but early reports appear promising. In patients with heart failure already treated with ACEI, addition of beta-blocker therapy is associated with an improvement in ejection fraction. Carvedilol, a third generation beta receptor blocking drug with additional properties, has been reported to improve survival, but this finding has been challenged, and studies empowered to determine impact of beta blockers on survival are ongoing. Digitalis added to ACEI therapy is safe, improves exercise tolerance and decreases the incidence of heart failure exacerbation requiring hospitalization. The beneficial effects of digitalis are likely due to its neurohumoral, and not inotropic, effects. Digitalis does not improve survival. Exercise training in patients with heart failure is surprisingly well tolerated and is associated with improved exercise tolerance and oxygen consumption and modulation of neurohumoral activation, but survival benefits are unknown.

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