Biofeedback training can be used to reduce activation of the sympathetic nervous system (SNS) and increase activation of the parasympathetic nervous system (PNS). It is well established that hyperactivation of the SNS contributes to disease progression in chronic heart failure. It has been postulated that underactivation of the PNS may also play a role in heart failure pathophysiology. In addition to autonomic imbalance, a chronic inflammatory process is now recognized as being involved in heart failure progression, and recent work has established that activation of the inflammatory process may be attenuated by vagal nerve stimulation. By interfering with both autonomic imbalance and the inflammatory process, biofeedback-assisted stress management may be an effective treatment for patients with heart failure by improving clinical status and quality of life. Recent studies have suggested that biofeedback and stress management have a positive impact in patients with chronic heart failure, and patients with higher perceived control over their disease have been shown to have better quality of life. Our ongoing study of biofeedback-assisted stress management in the treatment of end-stage heart failure will also examine biologic end points in treated patients at the time of heart transplant, in order to assess the effects of biofeedback training on the cellular and molecular components of the failing heart. We hypothesize that the effects of biofeedback training will extend to remodeling the failing human heart, in addition to improving quality of life.

**ABSTRACT**

Biofeedback training can be used to reduce activation of the sympathetic nervous system (SNS) and increase activation of the parasympathetic nervous system (PNS). It is well established that hyperactivation of the SNS contributes to disease progression in chronic heart failure. It has been postulated that underactivation of the PNS may also play a role in heart failure pathophysiology. In addition to autonomic imbalance, a chronic inflammatory process is now recognized as being involved in heart failure progression, and recent work has established that activation of the inflammatory process may be attenuated by vagal nerve stimulation. By interfering with both autonomic imbalance and the inflammatory process, biofeedback-assisted stress management may be an effective treatment for patients with heart failure by improving clinical status and quality of life. Recent studies have suggested that biofeedback and stress management have a positive impact in patients with chronic heart failure, and patients with higher perceived control over their disease have been shown to have better quality of life. Our ongoing study of biofeedback-assisted stress management in the treatment of end-stage heart failure will also examine biologic end points in treated patients at the time of heart transplant, in order to assess the effects of biofeedback training on the cellular and molecular components of the failing heart. We hypothesize that the effects of biofeedback training will extend to remodeling the failing human heart, in addition to improving quality of life.

**BIOFEEDBACK: AN OVERVIEW**

Biofeedback is a self-regulation therapy that aims to teach individuals the skills that will allow them to change their physiology in healthy directions. Biofeedback involves a client, a trained biofeedback coach, and appropriate instrumentation. Sensors are connected to the client, and various physiologic parameters (such as heart rate, blood pressure, and digital peripheral temperature) are displayed on a computer screen. The client is guided through a brief mental stress test and a relaxation exercise to learn to recognize differences between hyperarousal and a more relaxed physiology. Biofeedback training involves a series of sessions in which the goal is to help the client gain control of his or her own physiology by learning relaxation techniques such as deep breathing, progressive muscle relaxation, and guided imagery. Although biofeedback can be used solely as operant conditioning, it is more commonly and more effectively combined with techniques of stress management.

Biofeedback training is commonly (although not exclusively) used to decrease activation of the sympathetic branch of the autonomic nervous system (the “fight or flight” response). The reduction in sympathetic nervous system (SNS) activity is manifest as an increase in digital peripheral temperature and decreases in skin conductance, heart rate, and blood pressure, as well as changes in the frequency distribution of heart rate variability. While the SNS is becoming less activated, the parasympathetic portion of the autonomic nervous system (“rest and digest”) is becoming more involved in regulating body functions. More parasympathetic nervous system (PNS) activation and less SNS activation produces a healthier physiologic state, and thus biofeedback can be used to move the body in the direction of health and wellness.

**HEART FAILURE: BIOLOGIC MECHANISMS OF INJURY**

Heart failure is the end result of most untreated cardiovascular diseases. Heart failure involves inadequate cardiac pump function, such that appropriate perfusion of end organs does not occur. The process of developing heart failure is a gradual one that begins with compensatory processes. In response to an injury or insult, such as chronic high blood pressure or long-standing coronary artery blockage, the heart compensates by activating various neurohormonal pathways in an attempt to preserve cardiac function and end-organ perfusion. When these pathways are activated, they initially help the heart to compensate for the ongoing challenge of increased pressure or decreased tissue oxygenation and allow the cardiovascular system to pump sufficient blood. Over time, however, these compensatory processes become maladaptive. Cellular signaling pathways, which were activated in order to help the heart compensate, actually become as much of a problem as the decreased cardiac function.
Hyperactivation of the SNS
Chief among these pathways is the SNS, which is the most powerful means by which cardiac function can be augmented. In response to decreased cardiac function, cardiac sympathetic nerves are activated, releasing norepinephrine locally, and both norepinephrine and epinephrine increase in the circulating blood. Beta-adrenergic receptors on cardiac myocytes and on vascular smooth muscle cells are stimulated, and the resulting augmentation of cardiac contraction helps the heart to overcome an immediate challenge. If the insult or injury to the heart is acute and time-limited, this system compensates and the situation is resolved. However, chronic activation of the SNS creates more problems than it solves for the failing heart, including:
- Myocardial cells are challenged by the need for increased energy production to support the chronic stimulation
- Oxidative stress ensues
- Receptors are downregulated
- Pathways that result in necrosis and apoptosis are activated
- Myofilament proteins respond to chronically elevated intracellular calcium.

As a result, the heart begins to spiral more quickly into a decompensated state. The toxicity of SNS overactivation is the reason for the success of beta-adrenergic blocking drugs in treating heart failure, but this situation is complicated further by adrenergic receptor polymorphisms and nonhomogeneous responses to beta-blocking agents. It is safe to say that the goal of much heart failure therapy is inactivation of the once-compensatory SNS and its resulting biologic effects.

Hypoactivation of the PNS
In addition to hyperactivation of the SNS, heart failure is also accompanied by a decrease in the role of the PNS. Under normal resting conditions, the human heart is governed more by the PNS than the SNS, with the SNS becoming a major source of cardiac control only during periods of decreased cardiac function. In heart failure, however, this relationship is reversed, with the SNS taking over the governing role and PNS input becoming less significant. Studies have suggested that the lack of contribution of the PNS to cardiac regulation in heart failure may be as deleterious as overactivation of the SNS. Most recently, stimulation of the vagal nerve has been shown to be beneficial in both animal models and humans with heart failure, confirming that augmenting PNS activity may be as important as inhibiting SNS activity. Although vagal nerve stimulation may be the first heart failure therapy aimed specifically at the PNS, it is likely that the future will hold more therapies with this goal.

PNS as regulator of inflammation of the failing heart?
It has recently been suggested that beyond its role in regulating cardiac function under baseline conditions, the PNS may participate in regulating the inflammatory state of the failing heart. It has been established since the observations of Packer and colleagues in the early 1990s that proinflammatory cytokines such as tumor necrosis factor-alpha, interleukin-6, and interleukin-1 are elevated in the circulation of heart failure patients, that these cytokines are correlated with clinical prognosis, and that they play a role in the activation of deleterious cardiac signaling pathways. Trials of anti-inflammatory therapies in heart failure have been less than successful, but this may be because the complexity of the activation has been underestimated. In elegant work reported several years ago, Kevin Tracey’s group showed that stimulation of the vagus nerve could inhibit inflammatory processes associated with sepsis. Since that time, the reflex activation and inactivation of inflammatory processes by the PNS have become more widely accepted. Although it has not yet been directly demonstrated, it is possible that part of the benefit of vagal nerve stimulation in heart failure will prove to be due to its ability to reduce the chronic inflammatory state of the failing heart.

BIOFEEDBACK IN HEART FAILURE: RATIONALE
The failing heart is characterized by autonomic imbalance (hyperactivation of the SNS and hypoactivation of the PNS) and by a chronic inflammatory state. It has been hypothesized both directly and indirectly that these two major pathophysiologic processes may be intertwined. Biofeedback-assisted stress management is a therapy that has the potential to interfere with both processes. If the patient with heart failure can be trained to reduce activation of the SNS and to increase control by the PNS, it is likely that the negative consequences of autonomic imbalance will be decreased or possibly even reversed. Whether these effects are limited to quality of life and clinical status, or whether they extend to an effect on myocardial remodeling processes, remains to be established. Since the chronic inflammatory state can also be affected by increasing PNS control of the cardiovascular system, we further hypothesize that biofeedback training may have a direct effect on the inflammatory processes involved in the downward spiral of heart failure.

BIOFEEDBACK IN HEART FAILURE: STUDIES
We are certainly not the first group to hypothesize that self-regulation may have a role in the treatment of cardiovascular diseases in general or heart failure in particular. It has been shown that patients with heart failure manage their disease better and experience less emo-
tional distress when they have a greater sense of control over their condition. In addition to giving patients a greater sense of control, some mind-body therapies have been shown to be beneficial in those with heart failure. Pischke et al showed as part of the Multicenter Lifestyle Demonstration Project that patients with left ventricular ejection fractions in the range associated with heart failure (≤ 40%) were able to learn and benefit from stress management techniques equally as well as those with more normal cardiac function. Both relaxation training and meditation have been shown to improve quality of life in heart failure patients, but meditation also reduced circulating norepinephrine, a marker of SNS activation. Mindfulness training improved clinical symptoms of heart failure and also reduced both anxiety and depression in patients with heart failure. Training heart failure patients to breathe more slowly is an intervention that is normally part of biofeedback training, but even when used alone it has resulted in decreased dyspnea, increased oxygen saturation, and improved exercise tolerance.

To our knowledge, three studies to date have specifically used biofeedback training in patients with documented heart failure. As early as 1997, Moser and colleagues showed that heart failure patients were able to raise their finger temperature in spite of disease-related vascular changes, and that a single session of finger temperature biofeedback resulted in meaningful clinical improvement. Luskin et al randomized 33 heart failure patients to either biofeedback-assisted stress management or a control group, and showed improvement with the intervention in perceived stress, emotional distress, exercise tolerance, and depression. Most recently, Swanson and colleagues demonstrated improved exercise tolerance after cardiorespiratory biofeedback in patients with higher left ventricular ejection fractions (≥ 31%), although improvement could not be accomplished in those with ejection fractions below 30%.

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