Psychophysiologic Remodeling of the Failing Human Heart

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Autonomic imbalance is a therapeutic target in heart failure patients. Overactivation of the sympathetic branch of the autonomic nervous system has for years been treated with beta-adrenergic blocking drugs, although it cannot be long before invasive therapies such as renal sympathetic denervation, currently being tested for resistant hypertension, make their way to the heart failure arena. Insufficient parasympathetic input to the heart is already being augmented with implanted vagal nerve stimulators. It is our contention that biofeedback training could provide much of the same benefit as these more invasive therapies in improving autonomic imbalance, with the added advantage of increasing patient self-efficacy. This article describes a pilot study of biofeedback training in patients with end-stage heart failure awaiting heart transplantation. It was our goal to show not only that patients would appreciate this training and benefit from it but also that patient-controlled autonomic modulation could actually reverse the cellular and molecular markers of heart failure, or remodel the failing heart, similar to what we had previously shown for other types of heart failure therapy such as the left ventricular assist device. To our knowledge, this is the first study to demonstrate changes in the biology of the failing heart in response to a psychophysiologic intervention.

Introduction

Biofeedback training allows an individual to gain control of the autonomic nervous system (ANS), including both the sympathetic (SNS) and parasympathetic (PNS) branches. Physiologic parameters such as skin conductance, blood pressure, heart rate, and more recently heart rate variability (HRV) can be accurately measured, used for training, and interpreted as reflections of autonomic balance, the appropriate combination of input from the SNS and PNS to various organ systems of the body. Biofeedback has successfully been used to target the ANS in diseases such as hypertension and Raynaud’s disease, in which poor circulation results in cold hands and feet (Yucha & Montgomery, 2008).

The use of biofeedback to target SNS overarousal in patients with cardiovascular disease is not a new idea. Some of the earliest biofeedback studies targeting the heart showed that patients could successfully control their own heart rate and could reproducibly decrease the incidence of premature ventricular contractions (Benson, Alexander, & Feldman, 1975; Pickering & Gorham, 1975; Weiss & Engel, 1971). There are, however, several new pieces of information that caused us to revisit the idea of using biofeedback in cardiovascular disease and specifically led us in the direction of patients with end-stage heart failure (HF). One new and stimulating area for consideration comes from the work of Kevin Tracey and colleagues, showing that PNS activation can have an anti-inflammatory effect (Tracey, 2002, 2009). Although this has not yet been directly demonstrated in patients with HF, it has been clear for some time that HF involves an inflammatory response and that interfering with the inflammatory response has therapeutic potential (Gullestad & Aukrust, 2005; Levine, Kalman, Mayer, Fillit, & Packer, 1990; Mann, 2002). We have also learned over the past 20 years that, in addition to hyperactivity of the SNS, HF is also characterized by a lack of appropriate PNS input to the cardiovascular system through the vagus nerve, with important and limiting consequences for cardiac function.
resilience (Bivevski & Dunlap, 2001; Binkley, Nunziata, Haas, Nelson, & Cody, 1991). This fairly recent realization has led to the development of vagal nerve stimulators, currently being evaluated in the INOVATE trial (Hauptmann et al., 2012; Schwartz & DeFerrari, 2009), underscoring the importance of regulating both the SNS and PNS in HF.

Finally, the heart failure phenotype has been well described over the past 20 years and has also been shown to be reversible. That is, we now understand, better than any time in medical history, many of the cellular and molecular defects and aberrant signaling pathways that underlie the process of cardiac failure (Prasad et al., 2009; Tan et al., 2002; Yang et al., 2000). Not only have these abnormalities been defined, but many of them have also been shown to be reversible with fairly invasive therapies such as left ventricular assist devices (LVADs), some by our own group of clinicians and scientists (Aquila, McCarthy, Smedira, Young, & Moravec, 2004; Ogletree et al., 2010, Ogletree-Hughes et al., 2001). Now is certainly the time to ask whether biofeedback training in patients with advanced HF can be used to decrease the activity of the hyperactive SNS while at the same time increasing the contribution of the PNS to cardiac function through the vagus nerve. Because it changes autonomic balance, similar to other HF therapies, perhaps biofeedback will even produce the same reversal of HF biology that has been shown for treatments such as LVADs (see Figure 1). That was the starting point for our study of biofeedback training in end-stage HF patients.

**HF and the Autonomic Nervous System**

The heart is a terminally differentiated organ, which means that in response to stress, injury, or disease, the heart is not able to repair itself by increasing the number of cells available to do the work of pumping blood to the body’s organs. The heart relies on other compensatory mechanisms to preserve end-organ perfusion, and one of the early survival mechanisms is activation of the SNS. In response to SNS activation, the heart is able to pump harder and faster by regulating both the strength of cardiac muscle contraction and the heart rate. Like many of the body’s stress reactions, this activation of the SNS is acutely adaptive and chronically maladaptive. In the short term, elevation of plasma catecholamines, including norepinephrine (NE) and epinephrine (E), results in the binding of these neurohormones to beta-adrenergic receptor proteins on the surface of heart cells and at the level of the conduction system. This binding causes cardiac muscle to contract harder and the heart to beat faster. For a short time, the heart is able to cope with the increased demands of the body.

There are, however, two problems with the compensatory function of the SNS over the long term. One problem is that both the stimulation of increased muscle contraction and an increased heart rate are processes requiring the expenditure of additional cellular energy, which is also compromised by the disease process. Thus, the process of stimulating the heart to contract harder and faster is limited by decreased energy reserves. The second problem is that chronic stimulation of the beta-adrenergic receptor proteins on heart cells, using too much energy with every beat, leads to down-regulation, or decreased number, of the receptor proteins, because the cell internalizes them in an attempt to protect energy reserves. This is an adaptive response on the part of the cell, seeking to conserve energy and prevent overstimulation. However, for overall cardiac function, this limits the value of SNS activation in the long term for HF patients. The increased circulating hormones, NE and E, are no longer able to produce increases in contractile function of the heart muscle or in the heart rate. In the laboratory, if we take muscle from a failing heart and study its response to stimulation with NE, for example, we will observe that the response is diminished as compared with muscle from a normal human heart (see Figure 2). We can further measure the receptor proteins on the surface of the heart muscle cell that are responsible for the NE response and show that those are also diminished in failing hearts (see Figure 2). This was initially shown by Bristow and colleagues more than 30 years ago (Bristow et al., 1982) but has since been replicated by many groups, including our own (Ogletree-Hughes et al., 2001). The finding is robust enough that a decreased contractile response to NE and a decreased number of beta-adrenergic receptor proteins on the cell surface can actually be used as markers of HF and

![Image](image.jpg)

**Figure 1.** Schematic diagram showing the progression from a normal heart to a failing heart and including our previous demonstration that support of the failing heart with a left ventricular assist device (LVAD) results in cellular and molecular remodeling, which leaves the failing heart somewhere between the states of failing and normal. Finally, the possibility that biofeedback may produce some of the same changes as the LVAD is suggested.
can be assessed for their reversal potential (Ogletree-Hughes et al., 2001).

Thus, in HF, the SNS is overactivated in an attempt to compensate for injury to the muscle, which it does initially but not long term, because of the down-regulation of the entire process and the limitations of cellular energy reserves. At the same time, work over the past 20 years has established that the PNS, which normally plays a greater role in regulating baseline cardiac function than the SNS, has a diminished role in patients with HF. Studies in both animal models and human HF have shown that PNS or vagal control of the heart is abnormal in HF and that the abnormality occurs early during the progression of left ventricular dysfunction (Bibevsky & Dunlap, 2011; Binkley et al., 1991; Porter et al., 1990). Data further show that diminished vagal control is a poor prognostic marker in HF and that the location of the defect is likely the ganglia. Muscarinic receptors, the proteins that cause PNS effects in cardiac muscle cells, have been shown to be increased in HF (Dunlap, Bibevski, Rosenberry, & Ernsberger, 2003), perhaps as a compensatory mechanism to account for decreased vagal tone or decreased beta-adrenergic receptors. Overall, physicians and scientists have been concerned for years about the role of SNS down-regulation in HF. More recently, the additional problem of vagal withdrawal has been added, and the scientific community has come to recognize that the problem may actually be the balance between the two systems, which confers resilience in the cardiovascular system and which is lost in HF. Renewed therapeutic efforts are thus appropriate to reverse this autonomic imbalance.

Current and Future Therapies for ANS Dysregulation

Over the past 25 years, it has become a mainstay of clinical cardiology practice to interrupt SNS overactivation in HF patients by treating them with beta-adrenergic blocking drugs if tolerated. The beta-adrenergic blocking drugs interfere with the down-regulation of beta-adrenergic receptors, conserve cellular energy stores, decrease cardiac remodeling, and have a positive effect on morbidity and mortality. Other drugs used to treat HF patients, such as angiotensin-converting enzyme inhibitors, also have a favorable impact on SNS overactivity. Treatment of the SNS problem in HF has largely been pharmacologic, which is convenient if also accompanied by the inevitable side effects, difficult for some patients to tolerate. Pharmacologic regulation of the PNS, however, is not as readily achieved, and thus newer therapies designed to augment vagal nerve control of the cardiovascular system have evolved based on devices used to treat certain types of epilepsy and treatment-resistant depression. Vagal nerve stimulators are small electrical generators that are implanted below the collar bone, with leads that connect to vagal nerve fibers in the neck (Schwartz & DeFerrari, 2009). The goal is to achieve increased vagal control of the heart in patients with HF, and the first multicenter randomized clinical trial, INOVATE, is currently under way (Hauptman et al., 2012). The goal of the INOVATE trial is to assess the safety and efficacy of this new therapy in 650 patients from 80 international sites, obviously indicating that vagal nerve stimulation is believed by many to be promising for HF and perhaps even the wave of the future. Along with spinal nerve stimulators targeting the T1–4 regions, carotid baroreflex stimulators, phrenic nerve stimulators for sleep apnea, and renal sympathetic denervation for resistant hypertension, vagal nerve stimulation for HF suggests that cardiovascular therapeutics are moving in the direction of devices that regulate or help to control autonomic balance.
If improving autonomic balance is advantageous to patients with HF, we hypothesize that biofeedback training could accomplish the same goals without an invasive procedure and would give patients an increased sense of control over their disease. Biofeedback training should allow the patients to decrease activation of their SNS while enhancing the contribution of the PNS. This not only should be helpful for symptom control and clinical status but also should help reverse some of the cellular and molecular changes observed in the failing heart, such as the receptor down-regulation and inability to respond to NE shown in Figure 2. We thus set out to test our hypotheses in a small pilot study.

Our Pilot Study

Our goal in this pilot study was not only to offer biofeedback-mediated stress management to patients with end-stage HF but also to test the hypothesis that the intervention could reverse some of the cardiac remodeling that results in HF at a cellular and molecular level, similar to what we had previously shown with LVAD therapy (see Figure 1). For this reason, we decided to enroll only patients who were listed for heart transplantation. For a number of years, one of us (C.S.M.) has been studying the explanted hearts of cardiac transplant recipients, trying to better understand the pathophysiology of HF and to determine which changes can be reversed. Thus, it was a natural extension of these studies to enroll patients on the heart transplant waiting list in our biofeedback study, asking them if we could study their hearts when they came to transplant. One of the things we found out in conducting this study was that end-stage HF patients awaiting transplantation are a difficult group to study; this was perhaps the most difficult study we will ever undertake, with some of the sickest patients we will ever meet. Many of them are incapacitated by their disease and are awaiting transplant either in the hospital or at home but are unable to get around by themselves. We decided to study both inpatients and outpatients, and we tried very hard to schedule outpatients for their biofeedback training on the days they were at the hospital for medical appointments because they frequently had to be driven everywhere by working spouses. The inpatients were somewhat easier to study because they were easily accessible, but they frequently did not want to participate in biofeedback training if they had an unexpected visitor to their hospital room or were not feeling as well as they would have liked. These difficulties in scheduling were minor but did result in some patient dropout and some patients taking much longer to finish the study than we had imagined. In addition, some of our patients received their new hearts and some died while we were early in the biofeedback training process, both obviously lost to our investigation. Some finished biofeedback training and were fortunate to receive a heart within a few weeks of finishing our study, and this was obviously the group we wanted to study. Others finished our study more than a year ago and are still waiting for a heart. We should also note, though, that during the course of our study, two patients who participated in our training protocol were actually removed from the transplant waiting list because they were “too well.” Unfortunately, absence of a matched control group prevents us from concluding that this improvement was due to our biofeedback training; this happens occasionally on transplant waiting lists and may not be related to our study at all. But we are optimistic in concluding that we might have helped, and we look forward to future studies that will certainly include a control group to definitively answer this question!

All in all, we screened 111 patients, invited 71 to participate in the study, enrolled 36, and had 20 who actually finished the entire training protocol. Of those 20, 12 have come to heart transplant, and we have been able to study their explanted hearts to address our biological hypotheses. The remaining 8 are either still waiting or have since died. Among the 20 who finished the protocol, most patients commented freely that they loved the training and thought it was beneficial. Some of our cardiology colleagues were so impressed with the positive feedback from the patients that they called and asked us to enroll their patients, and one psychiatrist wrote a note in a patient’s chart about how much her attitude and coping skills had improved with biofeedback. Anecdotally, the training was a success for the patients who completed it.

So, what did we learn, and was the training able to reverse any of the biologic remodeling of the failing heart? From our biofeedback data, recorded over an initial stress assessment, six training sessions with a biofeedback-certified health psychology postdoctoral fellow, and a final stress assessment, we learned that patients with end-stage HF, all of whom have left ventricular ejection fractions less than 20% (critically ill and symptom limited, with no relief in sight but a transplant), can learn to regulate their breathing. Most patients started at about 15–16 breaths per minute and were able to decrease the rate of breathing to 8–9 breaths per minute after training, although some actually got to 6 breaths per minute. Most patients reported that this felt better to them, and most were breathing at this reduced rate at the start of the next session, not just during the
training periods. We learned that finger temperature biofeedback\(^1\) is not a great modality to use with end-stage HF patients, many of whom are taking significant vasodilators and thus walk in the door with high finger temperatures. Patients were willing to try, but starting at a finger temperature of 90°F to 92°F does not leave much room for improvement! We learned that some of our patients were able to regulate skin conducance and some were able to regulate muscle tension, but these modalities were difficult to use with all patients for various practical reasons, and thus our data set is not robust enough to draw conclusions about those two variables. We monitored heart rate and HRV, and although we did not use HRV biofeedback, we noted that the standard deviation of the normalized interbeat interval (SDNN; the time between heart beats in milliseconds) went up in most patients from the first training session to the last, with the average beginning in the unhealthy range of 0–50 ms and getting close to the moderately impaired range of 50–100 ms by the end of the session. These SDNN values were calculated based on 5-minute samples of heart rate. Several patients moved from the range of 30–39 into the range of 70–79 in SDNN by the end of training. Kimberly Swanson, Richard Gevirtz, and coworkers have shown that patients with HF are able to participate in HRV biofeedback training and that those with higher ejection fractions (greater than 30%) were able to use the training to clinical advantage, increasing their exercise tolerance (Swanson et al., 2009). Our patients were sicker than those in the Gevirtz population (all less than 20% ejection fraction and all needing a new heart), and we did not try HRV biofeedback, but we will next time. The fact that SDNN improved in most of the patients indicates that some cardiovascular resilience remains and is capable of being recovered.

Although clinical course and quality-of-life measures could be systematically collected in only some patients and indicated a variable degree of improvement, we were able to study the hearts at explant in all 12 patients who received a heart transplant after biofeedback training. To have valid controls for this part of the study, we included hearts from patients without HF (normal), those with HF who had not had biofeedback training (failing), and those who had waited for a heart with the aid of an LVAD (failing + LVAD), which we had previously shown to result in remodeling of the failing heart (Aquila et al., 2004; Ogletree et al., 2010; Ogletree-Hughes et al., 2001). Although we had previously studied these groups in detail, we included new groups who had come to transplant at the same time as the biofeedback patients. Amazingly, data from this study suggest that biofeedback training causes some of the same remodeling that was caused by the LVAD in our earlier studies (Ogletree-Hughes et al., 2001). That is, patients who have had biofeedback training, when compared at transplant with those who have not had training, show some remodeling of the beta-adrenergic receptor proteins on the surface of the cardiac muscle cell and also show improvement in the response to stimulation of those receptor proteins, designed to increase muscle contraction. This indicates some reversal of the cellular and molecular changes accompanying HF after patients have been treated with a program of biofeedback training. The changes were not present in all patients, and we noted that there was more variability in the biofeedback-treated patients than there had been in the LVAD-treated patients. Nonetheless, 8 of 12 patients treated with biofeedback showed some degree of recovery of the functional alterations in heart cells and muscles after biofeedback. We are currently statistically analyzing the variability within the biofeedback-treated group, testing the hypothesis that those who were better able to learn self-regulation showed more remodeling of the heart.

**Conclusions**

We tested the hypothesis that a program of biofeedback-mediated stress management in patients with end-stage HF awaiting transplantation would cause some reversal of the cellular and molecular changes that accompany the progression to HF. We had previously shown that such remodeling occurred when patients were treated with an implanted LVAD. In this study, we used the LVAD group as a positive control for the amount of remodeling possible, and we also compared both groups to a population of patients coming to heart transplant without any biofeedback training and to a population of normal hearts. Although this was a pilot study, there were numerous experimental problems encountered, and we did not use a randomized control group. Results of this early study are encouraging in suggesting that patients with later stages of HF are able to learn to control their own physiology. Results further suggest that such control results in positive biologic remodeling of the heart. These preliminary results must be confirmed in a randomized controlled study, but at this point they suggest that biofeedback training can be used in patients with cardiovascular disease, even those with end-stage HF severe enough that they are awaiting a heart transplant, to gain control of autonomic imbalance and possibly to cause some biologic reversal.

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\(^1\) Thermal biofeedback trains the individual to warm the hands, via a combination of relaxation and imagery procedures with direct feedback of moment-to-moment changes in peripheral temperature. Peripheral temperature generally reflects arteriole diameter.
References


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