Advances in Heart Failure

Mind-Body Medicine in Chronic Heart Failure
A Translational Science Challenge

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The connection between the mind and body has often been regarded by Western medicine as something ascribed to the mystical and a topic residing outside the scope of scientific thought. However, it has been a long-term integral tenet in the medical practice of many other cultures. It could be argued that the reliance of Western thought on the concept of dualism in which Plato, Aristotle, and other classical philosophers separated the body as a physical entity from the mind as a “spiritual” force has ultimately discouraged health care professionals from serious consideration of what has appeared to be a vague and even mysterious connection between the mind and body. Nevertheless, a growing body of research has progressively identified the mechanistic building blocks that demystify the reciprocal mind-body interaction and show that it is clearly a physical rather than mystical connection. Descriptions of neurovisceral changes in which readily demonstrated structural alterations in the brain, heart, and other organ systems arise in response to stress and a variety of emotional states provide further demonstration of the true organic mind-body connection. Perhaps the most abundant mechanistic data pertain to the brain-heart interaction under both conditions of health and a variety of cardiovascular disease states. The increasing body of evidence for these important interactions has in fact led to the call for dedicated integrated fields such as neurocardiology or behavioral cardiology.

It is therefore important to examine the current state of our understanding of mind-body interactions including the experimental evidence identifying the physiological basis for these interactions and their impact on clinical outcomes. As will be shown, there is a significant overlap between the pathophysiological mechanisms of congestive heart failure and the major effectors of mind-body connections. This provides the basis for potential new therapies that incorporate mind-body medicine. However, it must be determined whether our current understanding of the mechanisms governing mind-body interactions is sufficient to proceed with routine application of mind-body therapies in patients with heart failure. Further, are patients with heart failure amenable to interventions that act on the “heart-mind” axis in the same way as those without heart failure? This review will examine this understanding in an effort to determine whether current evidence justifies incorporation of mind-body medicine in the treatment of patients with congestive heart failure. Does the current value or future potential of heart/brain medicine in fact justify the creation of a new transdisciplinary and translational scientific field of study and realm of clinical practice?

The Mechanistic Building Blocks Governing Mind-Heart Interactions

The Autonomic Nervous System

The autonomic nervous system is probably the earliest and most closely studied effector limb of the mind-heart interaction. As early as 1915, Eppinger and Hess proposed that behaviors may differ between individuals because of a predominance of sympathetic or parasympathetic activity. This predominance determined the physiological as well as behavioral responses to environmental stimuli and could predispose individuals to disease states such as hypertension or asthma. As discussed in excellent reviews by Samuels,5,6 the impact of stress and intense emotion on cardiovascular function was submitted to credible scientific thought and investigation in 1942 by Walter Cannon in a report reviewing what has been called “Voodoo Death.” This report described episodes of sudden death recounted from a variety of cultures which were apparently secondary to profound fear or emotion often inspired by superstitious beliefs. Cannon speculated that death resulted from enhanced sympathetic nervous system and adrenal responses to intense emotional stress and a belief in a power over which the victim had no control. The events discussed in his article are in fact early descriptions of what has come to be known as sudden unexpected death, and a myriad of evidence has supported the major role of the sympathetic nervous system in mediating these episodes.

Foundation evidence for the role of the autonomic nervous system in stress-induced sudden cardiac death has been provided by a variety of animal models. A wide range of stressors have been shown to be associated with sudden death. In general, interventions that interrupt release of intracardiac but not circulating norepinephrine prevent stress-induced sudden death. Autonomically mediated mind-body interactions constitute one of the fundamental links between emotional states and cardiovascular disease in human beings. Perhaps the most...
dramatic example of this connection is in the so-called “broken heart syndrome” or Takotsubo cardiomyopathy. This syndrome of acute and generally reversible heart failure with a characteristic pattern of ventricular contraction abnormalities appears due in part to increased sympathetic activity producing either direct myocardial damage or contractile dysfunction resulting from diffuse coronary vasospasm. A variety of other stress and distress related conditions have been similarly shown to be characterized by significant abnormalities of the autonomic nervous system. Prominent among these is depression, which has been shown to be associated with sympathetic and parasympathetic imbalance and accordingly an environment that can promote coronary artery disease, congestive heart failure, and sudden death.

Although sustained increases in sympathetic activity are known to adversely affect cardiovascular function, inappropriately enhanced activity of the parasympathetic nervous system may be similarly damaging. ECG recordings obtained in some rat models of stress show that sudden death is mediated by profound bradycardia progressing to asystole. This suggests that extreme stress may produce an “autonomic storm” characterized by excessive activation of both the sympathetic and parasympathetic nervous systems. Such malignant parasympathetic activity has been shown to play a role in human disease. In a study by Luu et al., 62% of deaths in patients with advanced heart failure awaiting cardiac transplantation were due to profound bradycardia, suggesting malignant vagotonia as a cause of death.

The autonomic control of mind-body interactions has special relevance to patients with heart failure who characteristically have marked parasympathetic/sympathetic imbalance. Can stress produce autonomic imbalance that in fact leads to the occurrence or progression of ventricular failure? In turn, can the autonomic imbalance in heart failure that parallels that found in stress states in fact promote distress? The significant coincidence of congestive heart failure and depression and data indicating that depression may precede the appearance of congestive heart failure suggest that this may be the case. Mind-body interactions that interrupt this reciprocal autonomic dysfunction may therefore benefit both conditions.

How Are Emotions and Stress Connected to the Heart?

The autonomic nervous system is classically regarded as an “involuntary” system regulated by hypothalamic centers and thus beyond direct conscious control. Nevertheless, it appears that conscious effort can alter cardiovascular function acting through the so-called involuntary autonomic nervous system. However, the question remains how an involuntary nervous system may mediate the cardiovascular responses that characterize conscious mind-heart interactions and the physiological response to various mental states. Increasing understanding of the relationship of cortical function to autonomic control centers provides insight into possible mechanisms for volitional control of cardiovascular function.

Recognition of the role of cortical control of autonomic function dates to at least 1869 when John Hughlings Jackson observed significant cardiovascular changes during major motor seizure activity. He reasoned that cortical centers governed not only voluntary motor movements but vasomotion and visceral motor activity. Over the years, a variety of stimulation, ablation, and neuroanatomic studies have defined cortical regions that have projections to centers having direct control over sympathetic and parasympathetic activity. These cortical regions include the insular cortex, the somatic and motor sensory cortex, the medial prefrontal cortex, and the anterior cingulate cortex. As an example, the insular cortex has been shown to have a “representation of the autonomic nervous system” as well as “viscerotopic sensory inputs,” including those from the cardiovascular system. Studies in animal models using both insular cortex stimulation and localized destructive lesions and studies in humans who have had insular strokes suggest that the right posterior insular cortex modulates cardiovascular sympathetic control and the left posterior insular cortex modulates parasympathetic function. In these models and in human subjects, stimulation of the left insular cortex produced ST changes, widening of the QRS complex, complete heart block leading to asystolic death, and contraction band necrosis (see below). The cardiovascular regulatory capacity of the insular cortex suggests one pathway for volitional cardiovascular control that may be operative in mind-heart interactions. Similarly, the anterior cingulated cortex (ACC) has been shown to serve as an interface between cognitive and emotional inputs with projections to autonomic control centers. It therefore plays a critical role in adaptive responses to the internal and external environment and has been shown to mediate these responses through autonomic pathways. The ACC is functionally, anatomically, and histologically designed to integrate the emotional and cognitive activity of the mind with the physiological responses of the cardiovascular system as well as other organ systems.

Functional imaging studies in humans have demonstrated that cortical centers such as the ACC and prefrontal cortex constitute a network integrating emotional and cognitive components of the mind with autonomic cardiovascular control. Integrative body-mind training has been shown to increase parasympathetic activity, increase electroencephalographic theta waves originating from these regions, and increase blood flow to these central nervous system centers. Therefore, changes in cognitive and emotional state produce changes in autonomic cardiovascular control producing what some authors have called “brain-body harmony.” These functional changes can be accompanied by structural central nervous system changes as evidenced by destructive lesions in the ACC in patients with depression who have had a myocardial infarction.

Data for more than a century have confirmed that cortical centers integrating emotional responses and cognitive states, which constitute in part what is regarded as the “mind,” have a direct connection to autonomic function. Autonomic control is not simply based on reflex responses but is tightly linked to cortical function. It would therefore be surprising if positive and negative emotional and cognitive states did not have an impact on cardiovascular function and the evolution of cardiovascular diseases. The cortical influence over auto-
nomic centers supports the belief that cardiovascular function and disease risk can be altered through conscious efforts.

**Inflammatory and Neuroimmune Pathways**

Both cardiovascular disease and mental distress are associated with activation of proinflammatory mechanisms. The commonality of these mechanisms identifies inflammatory pathways as a major mediator of reciprocal mind-heart interactions. In addition, inflammation and autonomic activity are closely tied promoting states of neuroimmune activation that are operative in governing both psychological and cardiovascular function.

Although the end-organ effects of proinflammatory cytokines are well recognized, the immune system also serves as a communication network between the central nervous system and other organ systems. Cytokines produced and released in the periphery can diffuse into the central nervous system, where they in many ways function as neurotransmitters. Importantly, proinflammatory cytokines, either from the periphery or produced within the central nervous system, can stimulate the production of norepinephrine and sympathetic activity. However, beyond the role of circulating cytokines which must diffuse through the blood-brain barrier to the central nervous system, Tracey and other have shown that proinflammatory cytokines convey signals through the peripheral nervous system constituting a system of rapid communication from the periphery to the central nervous system. It is apparent that cytokine signaling via the Vagus nerve can occur with cytokine concentrations that fall well below the circulating levels required to cross the blood-brain barrier.

In response to peripheral signaling by cytokines, the autonomic nervous system can in turn activate both proinflammatory and antiinflammatory mechanisms. Stress-induced increases in catecholamines and cortisol rapidly increase NF-κB expression in peripheral blood monocytes that subsequently increase cytokine production. Further, NF-κB production could be inhibited by α- and β-adrenergic blockade demonstrating the role of sympathetic activation in triggering proinflammatory states.

The description of a “cholinergic antiinflammatory reflex” exemplifies the orchestration of the mind-body communication network integrating inflammation and autonomic function. Studies by Tracey et al. have shown that stimulation of the efferent Vagus nerve reduces both cytokine production and release by cells of the reticuloendothelial system. The inflammatory reflex consists of stimulation of vagal afferent fibers by cytokines, as discussed above, resulting in an augmentation of central parasympathetic outflow via the Vagus nerve and consequent reduction of cytokine production and release. This system constitutes a servocontrol mechanism that keeps inflammation in check preventing the deleterious effects of excessive proinflammatory stimulation. Conversely, reduced parasympathetic activity, as occurs in disease states such as congestive heart failure, can result in a failure to inhibit proinflammatory cytokine production enhancing the risk of end-organ inflammatory damage and has been shown to be a possible cause of increased proinflammatory cytokines in human subjects.

The evidence is clear that unrestrained proinflammatory stimulation is associated with cognitive and mood changes. A variety of animal models have shown that acute or chronic stress results in increased proinflammatory cytokine production accompanied by behavioral changes and cognitive impairment. These studies parallel investigations in human subjects that show a significant association between distress and depression and immune activation. Similar to animal studies, administration of cytokines to human subjects, such as interferon-α, or stimulation of the immune system through vaccination results in depressed mood and activation of the central nervous system in regions known to affect cognitive function and mood.

Studies by Kiecolt-Glaser and Glaser exemplify the connection between chronic stress conditions in human subjects and increases in proinflammatory cytokines. Aging caregivers of patients with dementia were followed over a 6-year period with measurement of circulating concentrations of interleukin-6 (IL-6). Progressive increases in IL-6 concentrations were seen in all patients over time, but the rate of increase was significantly higher in members of the care giver cohort, who were under increased stress. Similar increases in IL-6 were seen in other stress states such as marital discord. These and similar studies demonstrate one pathway by which acute or chronic stress can lead to immune system activation with resultant inflammatory cardiovascular damage. Especially considering the apparent role of inflammation in the pathogenesis of congestive heart failure, these data suggest an intriguing link between stress and the evolution of ventricular dysfunction. Preliminary data from Ferketich et al. support this link in a study in which patients with symptomatic reduction in ventricular systolic function were screened for symptoms of depression using the Beck Depression Inventory (BDI). In these patients, there was a significant linear correlation between BDI score and concentration of tumor necrosis factor-α. It can be safely said that the coincidence of depression and heart failure likely creates a proinflammatory environment that can promote the progression of both disorders.

A variety of effectors of both the proinflammatory cascade and autonomic nervous system likely play a role in patients with congestive heart failure. As an example, nitric oxide, which is dysregulated in congestive heart failure, plays a role in modulating autonomic function and in mediating inflammation. Reduction in nitric oxide production in congestive heart failure has been associated with abnormalities in autonomic balance. Recent studies of a loss of function polymorphism of the promoter for nitric oxide synthase demonstrate that it is indeed tightly linked to autonomic function in patients with congestive heart failure. Therefore, nitric oxide exemplifies a family of mediators of both inflammatory and autonomic pathways that regulates mind-body interactions and that is especially relevant in patients with congestive heart failure.

**Environmental Factors Contributing to Mind-Heart Interactions**

Although mind-body interactions are often considered a self-contained, closed-loop process, there is evidence that
external factors, such as infectious agents, may play a role in governing these interactions. A progression of studies has shown a role for Epstein-Barr virus (EBV) infection in mediating altered mood through cytokine stimulation. An early viral protein, dUTPase, produced even during incomplete replication of EBV, has been shown to stimulate peripheral blood mononuclear cells to produce IL-6 and other cytokines. A strong association between the titer of dUTPase antibody and concentration of circulating IL-6 was found in the above noted study of caregiver stress. Therefore, reactivation of EBV, which is a common latent infection, appears to result in stimulation of production of IL-6 and other proinflammatory cytokines that can mediate both depression and cardiovascular injury. This provides a model by which an external infectious agent may modulate mind-body interactions through promotion and even initiation of the inflammatory “network of communication.”

**Neurovisceral Regulation: Anatomic Consequences of Mind-Heart Interactions**

Anatomic and structural changes in the heart and the brain accompany states of mental stress as well as different states of concentration and meditation. These anatomic changes solidify the physical connection between the mind and body further demonstrating the reality of these interactions.

In the myocardium, psychological stress has been demonstrated to produce classic changes of contraction band necrosis. Studies of hypothalamic stimulation in animal models demonstrated ECG changes resembling those seen in humans with central nervous system hemorrhage or infarction followed by arrhythmic death. Examination of the myocardium in these animals demonstrated what may be interpreted as contraction band necrosis resembling the lesions seen in ischemic infarction. Similar lesions have been produced without central nervous stimulation but with psychic stress. Studies in human subjects have reported these myocardial lesions in patients with psychiatric illness or subarachnoid hemorrhage. The finding of increased troponin levels in patients with intracerebral hemorrhage and the demonstration of wall motion abnormalities in patients without coronary artery disease who have had an insular stroke further speak to the structural myocardial damage that can be mediated by the central nervous system.

Conversely, structural changes in the central nervous system have been shown to accompany differing psychological states. Chronic depression has been associated with decreased hippocampal volume, which is related to the duration of depression. In contrast to the damage and volume loss that may accompany stress, practitioners of various forms of meditation have increased cortical thickening, especially in centers involved with attention and sensory processing including the prefrontal cortex and the right insular cortex. Corresponding to these observations, functional magnetic resonance studies have shown increased activity in specific regions of the brain in subjects who have practiced meditation for differing periods of time as compared with control subjects.

Associated with these anatomic changes is evidence for a remodeling of mind-body interactions, which evolves with repeated or sustained stress. This remodeling may “prime” the systems governing mind-body interactions to produce an exaggerated response to stressful stimuli. The existence of this remodeling process is supported by studies showing that subjects with early life trauma have significant increases in baseline and stress-induced neuroimmune activation. A variety of investigations have shown that episodes of depression are not isolated but demonstrate a pattern of repetition suggesting evolution of pathways that progres-
sively facilitate depressed mood. Indeed, many of the same mediators of mind-heart and mind-body interactions are operative in central nervous system structural remodeling. Chief among them are cytokines that are known to act as neural trophic factors but which can over time mediate apoptosis and reduction of tissue volume.

It may be speculated that remodeling of mind-heart interactions results in an increasing magnitude of stress responses that lead to permanent detrimental end organ damage. As an example, if repeated stress produces even small areas of contraction band necrosis over time, could this ultimately result in ventricular systolic dysfunction and dilation? Further, would such remodeling of mind-heart interactions make patients less susceptible to the potential beneficial effects of interventions such as biofeedback, meditation, or other mind-body therapies?

**Interventions Targeting Mind-Heart Interactions**

A rich mechanistic foundation for mind-body and mind-heart interactions has now been established. This then raises the question as to whether there are volitional modifications of these interactions that can prevent and treat disease states. There is now a wealth of clinical, mechanistic and outcome trials that attempt to address this issue although the quality of these investigations is highly variable. Relatively few of these specifically address prevention or treatment of congestive heart failure, although many have addressed risk factors for cardiovascular diseases in general, and may lead to further observations in the setting of ventricular failure. The mind-body interventions that have been explored include biofeedback methods, meditation techniques, and relaxation therapies.

**Biofeedback**

Biofeedback interventions can be broadly defined as those in which the subject learns to consciously regulate a given physiological “target” variable. Often, the ability to regulate this specific variable is accompanied by modification of other elements of the mind-heart interaction.

One of the most detailed studies of biofeedback is an investigation by Moser et al performed in patients with advanced congestive heart failure. Participants were randomized to either biofeedback intervention or to control conditions. The biofeedback cohort successfully increased skin temperature, and compared with control subjects, significantly increased cardiac output, reduced systemic vascular resistance, and decreased respiratory frequency. The mechanism by which the biofeedback intervention produced these changes in hemodynamic variables is not certain but may have resulted from biofeedback associated alterations in autonomic vascular control.

Similarly, short-term studies of slow breathing in patients with congestive heart failure have shown immediate changes in baroreflex sensitivity measured by the interaction of heart rate and blood pressure variability. For the congestive heart failure group as a whole, there was a decrease in systolic and diastolic blood pressure during slow breathing. This and other studies suggest that there is the capacity to consciously regulate autonomically governed mind-heart interactions through alteration of baroreflex function.

**Meditation and Relaxation Techniques**

Meditation and relaxation techniques have been investigated as other methods to beneficially alter mind-body interactions. Meditation techniques may be broadly classified in three categories. First are those techniques that require concentration on a specific external object or internal sensation (such as breathing) in preparation for focused reflection, exclusion of unwanted thoughts, or a quiet state of awareness. Transcendental meditation may be the most commonly recognized form of this category of meditation. Second are those that rely on increased awareness or mindfulness of the external and internal environment and exclusion of conscious interpretations or evaluations of events and sensations in these environments. Third is compassion mediation which incorporates stages of the above practices with the ultimate goal of eliminating negative evaluations and fostering positive attitudes toward the self and progressively to others in one’s surroundings. All of these require self-monitoring and progressive practice to achieve a desired state of awareness.

Other techniques rely on eliciting the relaxation response, which shares many features of the above meditation techniques. In essence, relaxation techniques consist of focused attention, a passive nonevaluative approach to thoughts, relaxation of muscle tone, and a nondistracting environment. The hallmark of the relaxation response is a reduction in sympathetic nervous system activity.

Only a relatively small number of outcome studies have examined the above or related mind-body interventions in patients with congestive heart failure. However, a number of studies have investigated both cardiovascular and clinical outcomes following programs of meditation or relaxation techniques. For example, it is estimated that there have been more than 600 studies published examining the impact of transcendental meditation on cardiovascular disease. A review of selected studies of these techniques in patients without heart failure provides proof of concept that they may be effective in altering mind-heart interactions in patients with ventricular failure.

Barnes et al examined blood pressure and noninvasively measured cardiac output in adults without known cardiovascular disease who practiced transcendental meditation. Compared with a control group using relaxation methods, those practicing transcendental meditation had decreases in systolic and diastolic blood pressures, increases in cardiac output, and decreases in systemic vascular resistance during meditation. Similar results have been reported in adolescents with blood pressures in the upper percentiles of normal. The capacity to alter vascular tone and blood pressure may extend to perhaps all forms of meditation. A 6-week trial of yoga and meditation demonstrated significant reductions in heart rate and blood pressure and evidence for endothelium-dependent vasodilation in the intervention group.

It is probable that meditation exerts its effect on vascular control through autonomic mechanisms. This has been specifically examined by measurement of heart rate variability and noninvasive measures of the preejection period (a surrogate for sympathetic activity) in a study of mindfulness meditation. In subjects practicing this form of meditation, there was coactivation of the sympathetic and parasympa-
thetic nervous systems, a relative unusual event. This demonstrates the profound effect of this form of meditation on autonomic function which has been suggested in other studies and for other forms of meditation.49,120,121

In addition to their influence on autonomic function, meditation and related techniques appear to influence the immune component of mind-body interactions. In a recent study, investigators measured markers of immune function in healthy women stratified by their expertise in the practice of hatha yoga122 and found that experienced practitioners had lower levels of IL-6 and that novices had a greater odds of having detectable C-reactive protein. Similar results have been reported in a study of compassion meditation, in which expert practitioners were found to have lower social stress-induced levels of IL-6.110

These representative studies demonstrate that the various elements governing mind-body and mind-heart interactions can be consciously influenced by practices such as meditation. Even the immune system, which may appear to be far beyond the influence of conscious thought, can be regulated through conscious effort and meditative practices. The studies that have targeted patients with congestive heart failure suggest that this may be the case in at least selected patients with ventricular dysfunction.

Can Mind-Body Interventions Alter the Course of Congestive Heart Failure?

Does the fact that meditation and relaxation techniques modify mind-body interactions in non–heart failure populations imply that these techniques can serve as effective complementary therapies in patients with ventricular dysfunction? As the severity of ventricular dysfunction progresses, is the remodeling of mind-body interactions advanced to the degree that they are irreversible? In severely ill patients, including those with heart failure, heart rate and blood pressure do not correlate with the severity of anxiety.123 This implies that the underlying disease process of congestive heart failure may have already established a fixed autonomic set point which is not readily altered by meditation or relaxation therapies.

Among the relatively small studies that have specifically addressed patients with heart failure, Jayadevappa et al111 examined 23 African American subjects hospitalized for heart failure who were randomly assigned to a program of transcendental meditation or health education. After 6 months, the transcendental mediation group had a significant reduction in hospitalizations over the 6-month study period. Yeh et al124,125 used Tai Chi as a specific meditative style in heart failure patients in 2 different studies and found significant improvement in 6-minute walk distances, improved quality of life, and reduction of brain natriuretic peptide. A prospective study of body scan mediation in patients with heart failure demonstrated improved quality-of-life scores, improved measures of exercise performance, and reduction in plasma norepinephrine.126

Related to meditation techniques are stress management therapies designed to provoke the relaxation response. In a study of patients with New York Heart Association class II and III symptoms, cognitive therapy and stress management improved exercise stress duration as well depression scores and were associated with significant weight loss.127 Guided imagery offers another approach to elicit the relaxation response and has been examined in a small uncontrolled pilot study of patients with heart failure but only demonstrated trends to improved quality-of-life measures and no change in exercise capacity.128 Other relatively small studies ranging from 14 to 83 participants have examined a variety of relaxation therapies in patients with congestive heart failure and have found only changes in subjective measures of perceived wellness but not more objective physiological measures.129–132

The recently published SEARCH trial enrolled a comparatively large number of patients with relatively severe left ventricular dysfunction.133 Participants in the treatment arm were enrolled in a program of instruction in mindfulness-based stress reduction, coping skills, and participation in expressive support group discussions. At 12 months, the participants in the intervention program reported a perception of symptomatic improvement and had improved scores on anxiety, depression, and quality-of-life scales. This study represents one of the strongest demonstrations that mind-body interventions can produce a positive impact in at least a subset of patients with congestive heart failure and provides a foundation for future investigations (Table).

Summary and Conclusions

Evidence shows that there is a genuine physical and reciprocal connection between the mind and the body defined by physiological pathways and organic structural remodeling of the elements of these interactions. Further, interventions and practices such as biofeedback, relaxation therapies, and meditation clearly alter at least acutely if not chronically the effector systems governing mind-body and mind-heart interactions. Less clear is the role these interventions may play in the immediate or future management of patients with ventricular failure. There is at this time a paucity of studies that directly address these questions in patients with congestive heart failure. Is it possible that mind-heart intervention techniques can reverse the remodeling of many of these pathways, including the known aberrations of autonomic balance that evolve early in the course of ventricular failure and that may contribute to the progression of the disease process?225 Can mind-body and mind-heart interactions address the significant depression and anxiety that are prevalent in patients with congestive heart failure and reverse the neuroimmune activation operative in both conditions?9,11,13,27,28,55,69,80

The evidence-based medicine to address these questions is lacking. As can be seen from the literature discussed in this review, the clinical studies of mind-heart interventions are often uncontrolled and underpowered owing to small sample sizes. This has been recognized as a major limitation faced by a large number of studies investigating mind-body interventions.103,134 In an era of translational investigation, this appears to be a field ideally suited to the evolving scientific
methods that connect fundamental scientific discovery to clinical practice.

It is possible that these interventions will constitute important therapies complementary to current standard care. As an example, a population-based study examining the impact of spirituality on autonomic function and cardiovascular disease found that an increase in the aggregate score of spirituality measures highly correlated with autonomic control.3 This is relevant to patients with congestive heart failure, who, with progressive severity of disease, lose diurnal variation of parasympathetic/sympathetic balance, which in effect represents a lack of what has been defined as autonomic control.135–138 Therefore, is it possible that mind-body interventions can restore normal autonomic control in patients with congestive heart failure? Could these interventions increase responsiveness to pharmacological treatment?

The role that mind-heart interventions will play in the future treatment of patients with congestive heart failure is yet to be defined. Although there is the clear indication that the field of behavioral cardiology is one that is likely to continue its evolution and play a significant role in the advancement of patient care, it is also clear that this must be preceded by further studies confirming benefit and defining this field of practice.134 Further, although complementary and alternative therapies are embraced by many patients, they require commitment of time and to lifestyle change.139 Nevertheless, the reality of the mind-heart connection cannot be ignored, and cardiovascular specialists must continue to engage in the understanding, translational research, and application of this field.

Translational science must now meet the challenge to build on the intriguing studies that have established the mechanistic

<p>| Table. Representative Studies Examining Mind-Body Interventions in Congestive Heart Failure |
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<table>
<thead>
<tr>
<th>Intervention</th>
<th>Author and Reference No.</th>
<th>Type</th>
<th>n (Treatment Arm) Follow-Up</th>
<th>Outcomes With Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biofeedback</td>
<td>Moser et al105</td>
<td>Prospective Randomized controlled</td>
<td>40 (20) Immediate</td>
<td>Increased cardiac output and decreased systemic vascular resistance No changes in catecholamine levels or O2 consumption</td>
</tr>
<tr>
<td>Biofeedback</td>
<td>Swanson et al109</td>
<td>Prospective Randomized controlled</td>
<td>29 (15) 6 weeks</td>
<td>Improved 6MWD subgroup with ejection fraction &gt;30% (n=9 vs 8) No significant change in HRV or QoL</td>
</tr>
<tr>
<td>Slow breathing</td>
<td>Bernardi et al106</td>
<td>Prospective NR Self-matched and controlled</td>
<td>102 (81) Immediate</td>
<td>Increased baroreflex sensitivity and BP decrease in heart failure patients pre intervention vs postintervention (self-matched) No significant difference between heart failure and control populations</td>
</tr>
<tr>
<td>Transcendental Meditation</td>
<td>Jayadevappa et al111</td>
<td>Prospective Randomized controlled</td>
<td>23 (13) 6 mo</td>
<td>Improved 6MWD, depression scores, and QoL</td>
</tr>
<tr>
<td>Meditation</td>
<td>Curiati et al126</td>
<td>Prospective Randomized controlled</td>
<td>19 (10) 14 wk</td>
<td>Reduced NE levels and improved QoL Left ventricular ejection fraction not significantly changed</td>
</tr>
<tr>
<td>Tai Chi</td>
<td>Yeh et al24,125</td>
<td>Prospective Randomized controlled</td>
<td>30 (15) 12 wk</td>
<td>Improved QoL, 6MWD, decreased brain natriuretic peptide</td>
</tr>
<tr>
<td>Stress management</td>
<td>Kostis et al127</td>
<td>Prospective Randomized controlled</td>
<td>19 (7) 12 wk</td>
<td>Improved exercise time, QoL, depression, and weight loss 6MWD not statistically improved</td>
</tr>
<tr>
<td>Stress management</td>
<td>Luskin et al132</td>
<td>Prospective Incomplete Randomization controlled</td>
<td>33 (14) 10 wk</td>
<td>Improved 6MWD, depression, perceived stress, and emotional distress HRV not statistically improved</td>
</tr>
<tr>
<td>Mindfulness-based stress reduction</td>
<td>Sullivan et al (SEARCH Trial)133</td>
<td>Prospective NR</td>
<td>217 (117) 12 mo</td>
<td>Improved symptoms, anxiety, depression, and QoL No differences in death and rehospitalization</td>
</tr>
<tr>
<td>Guided imagery</td>
<td>Klaus et al128</td>
<td>Prospective NR Self-matched</td>
<td>8 6 wk</td>
<td>No statistically significant improvements in exercise or dyspnea measures QoL measures trended towards but not significant for improvement</td>
</tr>
<tr>
<td>Progressive muscle relaxation training</td>
<td>Yu et al129</td>
<td>Prospective Randomized controlled</td>
<td>121 (59) 14 wk</td>
<td>Trend toward symptom improvement</td>
</tr>
<tr>
<td>Relaxation response</td>
<td>Chang et al130</td>
<td>Prospective Randomized controlled</td>
<td>83 (33) Approx 4 mo</td>
<td>Improved spiritual QoL Trend toward improved emotional QoL Physical QoL and exercise capacity not improved by relaxation response</td>
</tr>
</tbody>
</table>

NR indicates nonrandomized; 6MWD, 6-minute walk distance; QoL, quality of life; HRV, heart rate variability; and NE, norepinephrine.
basis for mind-heart interactions. There are a wide variety of investigations that must follow:

- Investigate the capacity of mind-heart interactions to increase susceptibility to pharmacological therapy and to cardiac resynchronization therapy.
- Test whether the response to drug administration coordinated with mind-heart interventions is augmented compared with standard dosing regimens.
- Test the capacity of mind-heart interventions to alleviate comorbid conditions such as sleep disorders that commonly accompany ventricular failure are themselves influenced by states of stress and anxiety.
- Evaluate the capacity of mind-heart interventions to improve ventricular function through interruption of the cascade of autonomic and proinflammatory pathways activated by depression and stress.
- Investigate the response to mind-body interventions in the context of different genetic backgrounds similar to the pharmacogenetic impact on drug response. Conversely, evaluate the impact of mind-heart interventions on gene function based on preliminary studies showing the plausibility of “mind/gene” interactions.

These constitute just a few of the exciting possibilities for translational research in mind-heart medicine and adapting this field to the overall clinical and investigative approach to patients with congestive heart failure. It is hoped that the field of translational cardiovascular medicine will explore research questions such as these and others to allow mind-heart interventions to take a place in the growing armamentarium of heart failure therapies.

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Disclosures

None.

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4. Penn MS, Bakken EE. Heart-brain medicine: where we go from here and investigations that must follow. The authors suggest a few:
5. Evaluate the capacity of mind-heart interventions to im-
6. Test the capacity of mind-heart interventions to alleviate 
7. Investigate the capacity of mind-heart interactions to in-
8. Investigate the response to mind-body interventions in the context of different genetic backgrounds similar to the pharmacogenetic impact on drug response. Conversely, evaluate the impact of mind-heart interventions on gene function based on preliminary studies showing the plausibility of “mind/gene” interactions.
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