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Heart-brain medicine: Update 2007

Heart-brain medicine is dedicated to furthering our understanding of the interaction between the body's neurologic and cardiovascular systems. As discussed previously,[1] the advent of subspecialization in health care delivery has led to significant advances in the care of patients with acute disease or acute exacerbations of chronic disease. While these advances have led to improved outcomes, we were reminded several times this past year how difficult it is to further improve outcomes using the "silo"-based, highly subspecialized approach that has yielded results in the past.

The 2007 Bakken Heart-Brain Summit, held last June in Cleveland, further demonstrated real progress in our understanding of the importance of heart-brain interactions in health and disease. A series of presentations—highlighted by the Bakken Lecture given by Peter Shapiro, MD, an investigator with the SADHART trial—reviewed the effect of psychiatric disorders on the incidence of cardiovascular disease and its consequences. These presentations by leaders in the field (many of which are summarized in the pages that follow) offer irrefutable evidence of the following:

- Patients with depression and heart disease have worse outcomes than patients with heart disease without depression[2]
- Patients with depression have decreased vagal tone[3]
- Patients with coronary artery disease (CAD) can be safely treated with and respond to antidepressants.[4]

These data were complemented by a keynote presentation by Kevin Tracey, MD, whose elegant work over the past many years has demonstrated a link between vagal tone and inflammation.[5] His most recent data have shown that the vagus has direct input into the inflammatory state of macrophages in the spleen. The effect is mediated via vagal innervation of the spleen and the α7 subunit of the nicotinic receptor expressed on the cell surface of the resident macrophages.[6,7] The relevance of vagally mediated modulation of systemic inflammation has been shown in sepsis and more recently by our group in left ventricular remodeling following acute myocardial infarction.

'RECONNECTING THE BODY' TO IMPROVE OUTCOMES

The continuing emergence of the link between psychiatric and neurocontrol of systemic inflammation offers an undeveloped strategy for further improving outcomes in patients with cardiovascular disease. One of our interests in pursuing heart-brain medicine is to reconnect the body and exploit the physiologic interplay between the heart and brain to improve patient outcomes.[1] Given the disappointments over the past year for new therapies like cholesteryl ester transfer protein inhibitors[8] and vascular cell adhesion molecule (VCAM) inhibitors, strategies that have a singular organ or cellular target focus, now may be the time for exploiting multisystem approaches for modulating disease states such as CAD, congestive heart failure, and arrhythmia.

Thus, the emerging data linking neuromodulation to systemic inflammation offers mechanistic insights into long-standing expressions such as "scared to death." For example, multiple studies have demonstrated that CAD patients exposed to terrorist events have an increased risk of myocardial infarction and death. Taking this observation one step further in the context of our discussion at this year's summit, patients with post-traumatic stress disorder (PTSD) have been shown to have low vagal tone[9]—and thus presumably to have increased systemic inflammation. Such a state has been shown by many to increase the risk of plaque rupture, acute coronary syndrome, and myocardial infarction. Thus, while the concept of being "scared to death" has been thought to relate more to arrhythmogenic sudden cardiac death, the scope of potential mechanistic mediators should clearly be broadened **(Figure 1)**.

The potential consequences of these pathways are profound and include the following:

- A physiologic mechanism for the increased incidence of myocardial infarction observed with medications that have anticholinergic properties and potentially decrease autonomic tone
- Worse outcomes in patients with CAD and depression
- An increased incidence of CAD in patients with

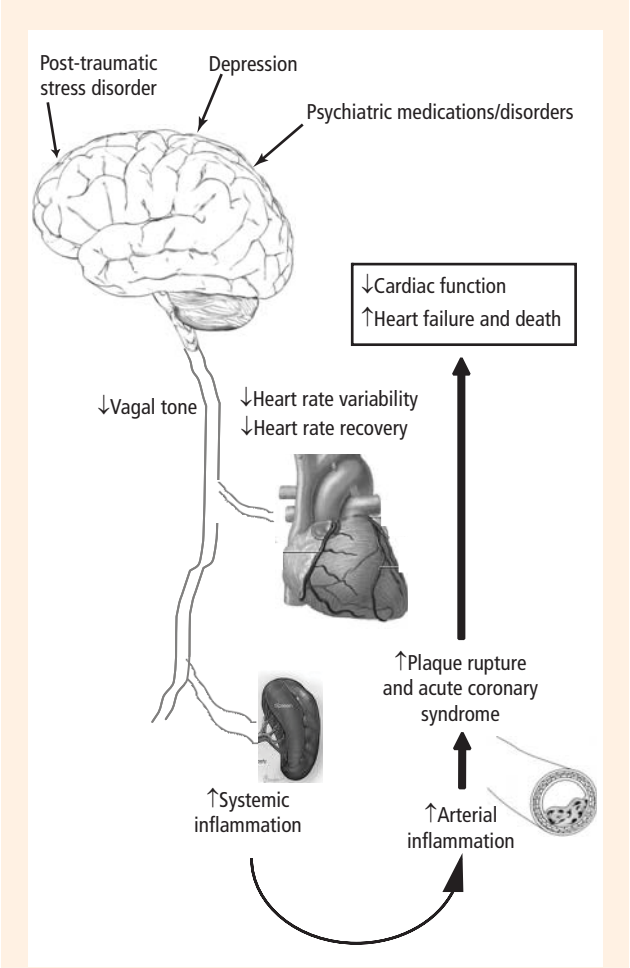

FIGURE 1. Proposed pathways involved in psychiatrically mediated states altering cardiovascular disease and outcomes.

psychiatric disorders that in themselves may be associated with decreased vagal tone, as well as in patients on long-term drug therapies that alter parasympathetic tone

- Increased incidences of CAD, myocardial infarction, and death in patients with PTSD.

AN URGENT NEED FOR CLINICAL TRANSLATION

Clearly the underlying science of heart-brain medicine is fascinating and needs to be pursued vigorously. While the science is ongoing, the need to translate what we know to the bedside has never been greater, given the prevalence of CAD, chronic heart failure, and psychiatric and mood disorders, as well as the likelihood of an increasing incidence of PTSD in light of the Iraq war and terrorist threats.

Multiple studies have been performed to position the field for a trial to test whether treating depression leads to improved outcomes in patients with CAD. We know that patients with depression have decreased vagal tone based on decreased heart rate variability; we know that CAD can be safely treated with selective serotonin reuptake inhibitors; and we know that this patient population is more effectively treated with medications. There was a clear sentiment among faculty and attendees of the 2006 Bakken Heart-Brain Summit that the next step in the clinical science of heart disease and neurologic state is in fact a clinical trial to test the efficacy of this approach. Unfortunately, funding for such a trial from the pharmaceutical industry or government agencies is lacking. The Bakken Heart-Brain Institute is working diligently to secure private financing of such a trial from those with personal interests in moving this field forward. We hope to be able to commence such a trial in the near future. We believe the successful initiation of a multicenter trial not only will demonstrate new avenues for improving outcomes in millions of patients but will validate the concept and usher in a new age of cooperative medicine among multiple disciplines.

As we discussed last year,[1] both the need for and the future of heart-brain medicine are great. The advances seen over the past year and those being pursued in basic and clinical science laboratories throughout the world are very exciting. We thank those colleagues who attended the 2007 Bakken Heart-Brain Summit, and we hope you can join us June 4–5, 2008, in Cleveland to continue this exciting pursuit.

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