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# Heart-brain medicine: Update 2008

Investigators involved in heart-brain medicine are dedicated to defining the physiology associated with interactions of the neurological and cardiovascular systems. In 2004 the Bakken Heart-Brain Institute was founded at Cleveland Clinic because we believed that furthering our understanding of this physiology could lead to a better understanding of chronic disease, define novel therapies, and improve patient outcomes.

The 2008 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. The opening session of the 2008 Summit focused on reviewing the evidence linking psychiatric disorders—specifically depression—to increased inflammation and plaque rupture associated with worsening outcomes in patients with atherosclerotic heart disease. These pathways linking psychiatric disorders to acute coronary syndrome were proposed after the 2007 Bakken Heart-Brain Summit (**Figure 1**)<sup>1</sup>:

- Depression leads to decreased vagal tone
- Decreased vagal tone leads to increased inflammation
- Increased inflammation leads to acute coronary syndrome.

Speakers at the 2008 Summit offered insights into the physiology, clinical measures, and molecular pathways involved in linking the heart and the brain, including:

- Measures of heart rate variability in depression
- The utility of heart rate variability and heart rate recovery in quantifying vagal tone and outcome in patients with and without coronary artery disease
- Pathways of inflammation involved in acute coronary syndrome.

## ■ MOUNTING CLINICAL EVIDENCE LINKING DEPRESSION WITH CARDIAC OUTCOMES

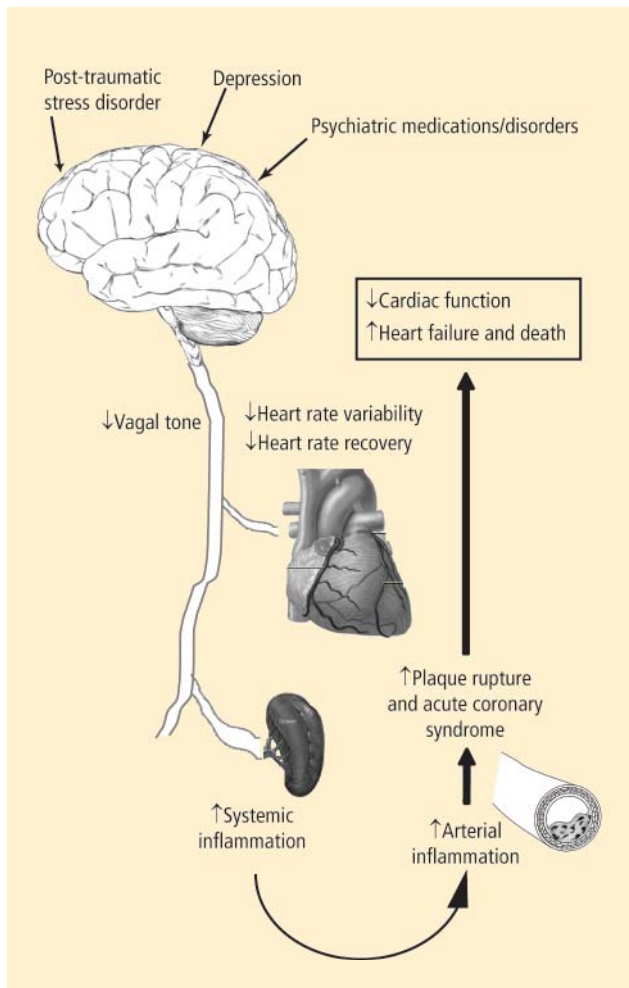
The 2007 and 2008 Summits highlighted the link between depression and outcomes in patients with atherosclerosis (2007)<sup>1</sup> and the potential associated

mechanisms (2008). Just as exciting are the developments since last June: numerous papers have been published demonstrating this link in clinical populations, and depression screening has been included in recommendations from the American Heart Association on the treatment of patients with coronary artery disease—recommendations that are endorsed by the American Psychiatric Association.<sup>2</sup>

The studies published since June 2008 demonstrate clear links between depression and morbidity and mortality from cardiovascular causes. A recent paper from the Nurses' Health Study showed that individuals with depression had a higher incidence of cardiovascular death.<sup>3</sup> Notably, subjects in the Nurses' Health Study had no clinical evidence of atherosclerotic heart disease at enrollment. In another recent study, depression was associated with worse outcomes in patients following coronary stenting.<sup>4</sup> Finally, and most interestingly, depression was recently associated with endothelial dysfunction in patients with atypical angina and angiographically normal coronary arteries.<sup>5</sup> Thus, regardless of the degree of underlying atherosclerosis, depression is associated with cardiovascular morbidity or mortality.

Less clear is the relationship between depression and inflammation as measured by surrogate inflammatory markers. An analysis of the Canadian Nova Scotia Health Survey [NSHS95] Prospective Population Study suggested that increased inflammatory markers accounted for only a small portion of the risk of coronary heart disease associated with depression.<sup>6</sup> Conversely, a recent analysis of patients with stable coronary artery disease demonstrated a strong correlation between major depressive disorders and high-sensitivity C-reactive protein.<sup>7</sup>

Clearly, significant work has yet to be done to fully elucidate the molecular pathways that link depression and adverse outcomes in patients at risk for coronary artery disease. That said, it is very encouraging that professional societies are beginning to recognize the value and importance of heart-brain medicine in identifying novel strategies for improving patient outcomes.



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

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**■ STILL ELUSIVE: EVIDENCE THAT DEPRESSION THERAPY IMPROVES CARDIAC OUTCOMES**

At the 2008 Summit there was clear enthusiasm among attendees and faculty for advances in our understanding of the pathways discussed above. Since then, as reviewed above, significant publications have furthered the link between heart and brain in the setting of atherosclerotic heart disease. That said, the missing piece—the demonstration that treating depression leads to improved outcomes in patients with coronary artery disease—remains missing.

Some advances in this regard have been made. A recent study from the Enhancing Recovery In Coronary Heart Disease (ENRICH) clinical trial demonstrated that major depression in any patient who survived myocardial infarction decreased survival

over 2.5 years.<sup>8</sup> Interestingly, and perhaps critical for an event-driven treatment trial in the future, this analysis showed an even worse outcome in patients who experienced their initial episode of major depression after their myocardial infarction.<sup>8</sup> The need, ethics, and design of clinical trials to determine whether treatment of depression leads to improved outcomes in patients with coronary artery disease will be a major topic of the 4th Annual Heart-Brain Summit, to be held in Chicago on October 15–16, 2009.

**■ OTHER HIGHLIGHTS, INCLUDING ROLE OF THE HEALING ENVIRONMENT**

While much of the early focus of the 2008 Heart-Brain Summit was on the interaction of depression, inflammation, and outcomes in patients with coronary artery disease, a significant portion of the Summit identified other disease states and opportunities. The disease states discussed can be divided into primary cardiac, primary psychiatric, and primary neurologic. Cardiac topics under continued investigation include the role of vagal tone on the inflammatory response that regulates left ventricular remodeling following acute myocardial infarction<sup>9</sup> as well as the role of spinal stimulation for treatment of refractory myocardial ischemia. Psychiatric disorders of interest that have been shown to modulate vagal tone include post-traumatic stress disorder,<sup>10</sup> which has also been shown to increase the risk for coronary heart disease.<sup>11,12</sup> Neurologically, advances concerning the polyvagal theory of autonomic nervous system control and cardiac control were discussed.<sup>13,14</sup>

On the Summit’s final day, the discussions of neuropathways, inflammation, and cardiac control gave way to presentations on the role of the healing environment. Following discussions of how depression can have significant ramifications on systemic inflammation and acute coronary syndrome, it was interesting to review data on how the presence of family and the patient environment can improve patient outcomes.

Many of the topics touched on above are discussed in greater detail in the following pages of this proceedings of the 2008 Bakken Heart-Brain Summit. We are gratified to see the advancements in the field of heart-brain medicine over the past 5 years, and especially to see the recognition the discipline is receiving in our attempt to improve patient outcomes.

**■ FAR MORE QUESTIONS REMAIN**

Without a doubt there are more questions than answers at this time. That said, by continuing the rigorous multidisciplinary approach that has served this

field well to date, many questions will be answered. We hope you will join us in Chicago on October 15–16, 2009, for the 4th Annual Heart-Brain Summit, which will be jointly hosted by the Society of Heart-Brain Medicine and the Bakken Heart-Brain Institute.

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