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Heart-brain medicine: Where we go from here and why

This past June, the Earl and Doris Bakken Heart-Brain Institute (BHBI) held the first annual Heart-Brain Summit at the Cleveland Clinic. The BHBI's goal is to investigate physiological and molecular relationships between the heart and the brain and to translate these findings into strategies to improve patient outcomes.

The need for this type of innovative approach for the development of novel therapies has never been greater. Modern medicine, through the development of early diagnostic imaging and endovascular approaches, has significantly reduced the morbidity and mortality of previously devastating acute conditions such as acute myocardial infarction and subarachnoid hemorrhage. In the case of acute myocardial infarction, 30-day mortality rates have declined from nearly 20% two decades ago to less than 5% in recent clinical trials using primary percutaneous intervention **(Figure 1)**.[1] This amazing achievement has unfortunately fostered a population of patients with chronic heart failure, which has a prevalence of greater than 5 million in the United States and affects more than 10% of the US population older than 65 years. While significant efforts have been put forth to improve outcomes in patients with chronic heart failure, mortality rates in clinical trials have not decreased significantly over the same span of time **(Figure 2)**.[1]

THE GOAL: THERAPIES BASED ON HOW THE ORGANS INTERRELATE

Thus, in an attempt to improve patient outcomes beyond the acute event, the BHBI aims to "put the body back together," or understand how different organ systems interrelate and, with this information in hand, develop therapeutic strategies to reduce morbidity and mortality.

Several lines of evidence suggest that in-depth investigation in the area of heart-brain medicine will yield significant results. Recent examples of the importance of heart-brain interactions in physiology and patient populations with chronic disease include the following:

- Studies showing that angina pectoris can be controlled by carotid stimulation
- Multiple studies that have demonstrated the link between depression and poor outcomes in patients with coronary artery disease
- Findings that cardiac arrhythmias and sudden cardiac death are frequent causes of death over the long term in patients who survive subarachnoid hemorrhage
- The observation that vagal stimulation is mechanistically linked to leukocyte activation and inflammation at the molecular level
- Evidence that chronic hypertension can be controlled by carotid body stimulation.

Each of these conditions represents a significant patient population, many of which are underserved by current strategies and techniques.

Beyond these examples there is a large literature, often discounted by modern science, that suggests that integrative lifestyle approaches improve patients' well-being and outcomes. The least controversial and best supported of these approaches is exercise. However, other approaches—including yoga, biofeedback, and mind-body stress-relieving techniques—have their supporters, and they warrant study to further determine their clinical benefit and what might be the mechanism responsible for such benefit.

A NEED FOR INTERDISCIPLINARY COLLABORATION

Whether the goal is to evaluate clinically based strategies like those listed above or integrative approaches, it is clear that collaboration among disciplines is required before any significant improvements in patient outcomes can be achieved.

For example, clearly the development of implantable cardiac pacemakers was one of the great advances of the 20th century. This innovation not only treated patients with bradycardia, it led the way to the development of internal cardiac defibrillators[2] and, more recently, biventricular cardiac resynchro-

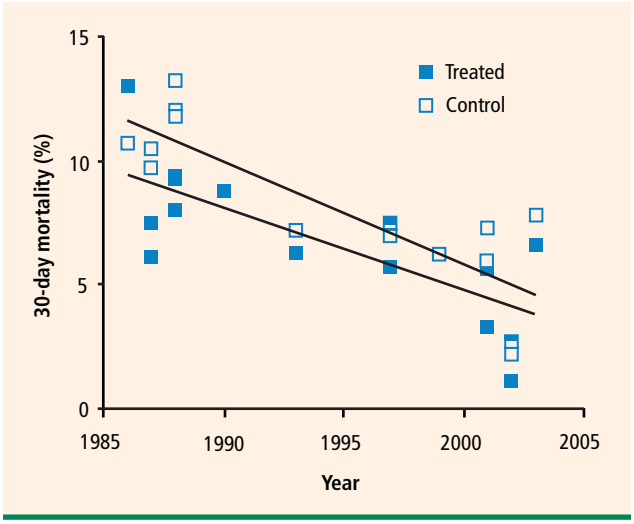

FIGURE 1. Reported mortality in treatment and control groups in studies of patients with acute myocardial infarction with ST elevation, including the GISSI, ISIS, GUSTO (I, IIb, III, and V), ASSENT-2, ADMIRAL, CADILLAC, and DANAMI-2 investigations. Adapted from Penn and Topol[1] with permission; copyright © 2007 Humana Press.

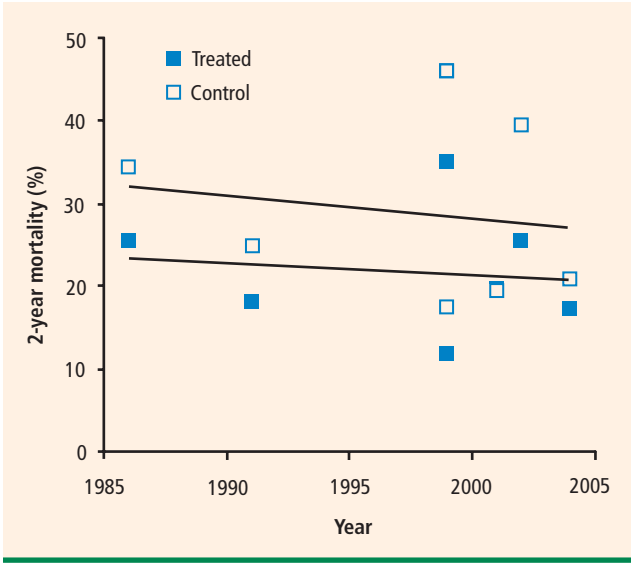

FIGURE 2. Reported mortality in treatment and control groups in chronic heart failure trials, including the V-HeFT, V-HeFT-2, Val-HeFT, RALES, CHARM, COPERNICUS, and CIBIS II investigations. Adapted from Penn and Topol[1] with permission; copyright © 2007 Humana Press.

nization therapy,[3] techniques that improve patients' well-being and reduce mortality.

Unfortunately, it took more than 40 years for similar technology to be applied to the other electrically active organ of the body, the brain. Just as cardiac pacing has revolutionized the cardiologist's approach to patients with rhythm abnormalities, deep brain stimulation is on the verge of revolutionizing the treatment of patients with depression, Parkinson disease, and many other psychiatric and movement disorders. However, before we can learn how to improve cardiac function through neurostimulation, improve the outcomes of patients with coronary artery disease by treating their depression, or improve outcomes in stroke and subarachnoid hemorrhage through rhythm management, we must be able to cross the often wide chasms between medical disciplines.

In reality, there are many similarities between the heart and the brain:

- As already mentioned, they are both electrically active organ systems.
- Each has its own form of electrical instability—seizures in the brain, and ventricular tachycardia and fibrillation in the heart. Interestingly, patients with either condition are at risk of dying of sudden cardiac death.[4,5] Electrical stimulation or conversion is a treatment in both organs.
- Chronic changes within each organ system lead to organ dysfunction—specifically, atherosclerosis in the heart and amyloid plaques in the brain. Studies have suggested that these two processes are linked at the molecular level.[6]
- Ischemic disease is the greatest cause of organ dysfunction in both systems—obviously, stroke in the brain and myocardial infarction in the heart. Restoration of blood flow is the optimal treatment of both, and improving organ-specific cell function is critical.
- A process known as ischemic preconditioning can significantly reduce the area of ischemic damage in both organs. Yet little focus has been directed at understanding the commonalities of the molecular pathways in the two systems.[7,8]

There have been previous and ongoing attempts at fostering heart-brain research. The ongoing collaborative network led by J. Andrew Armour, MD, PhD, Mike J.L. DeJongste, MD, PhD, and Robert D. Foreman, PhD, has performed important studies on the role of spinal cord stimulation for the control of myocardial ischemia.[9] The National Institute of Neurological Disorders and Stroke has its Clinical Neurocardiology Section, headed by David S. Goldstein, MD, PhD, which has similarly done revolutionary work in the field of neurological control of cardiac function.[10] We are thrilled that each of these investigators has joined us this year for the first Heart-Brain Summit.

A GATHERING PLACE FOR HEART-BRAIN MEDICINE

Where have previous programs failed? In fact, it is not clear that they have. Rather, what has hindered

growth of this field has been the lack of a gathering place that inherently believes in the potential of heart-brain medicine, fosters collaboration among investigators and industry, encourages young investigators to enter the field, and works to obtain seed funding for interesting areas of research.

The acceleration of medical knowledge is staggering. Over the past 20 years, our colleagues have dramatically improved the outcomes of patients with acute neurological and cardiac events. Industry has miniaturized devices and has developed the technology to enable endovascular therapy. At the bench, the genome has been unraveled so that we now stand at the threshold of an abundance of insights and treatments to be derived from stem cells.

We could clearly continue in our organ-based silos and undoubtedly advance science and improve patient outcomes. However, so many disciplines—including neurology, cardiology, neurosurgery, neuroscience, psychiatry, cardiothoracic surgery, molecular cardiology, physiology, biomedical engineering, and psychology—have very real input and unique insights into our understanding and measurement of heart-brain interactions. For this reason, we believe that coming out of our silos will make possible significantly greater advances and that those advances will be more rapidly translated into improved patient outcomes.

We are deeply grateful to all of our colleagues who joined us in Cleveland this past June. What follows are brief summaries and transcripts of many of the lectures presented at this inaugural Heart-Brain Summit. It was an extraordinary collection of speakers and attendees from multiple disciplines, and the result was a stimulating and rewarding experience. We look forward to a similarly rewarding and enjoyable summit in Cleveland this June and for many Junes to come, and we hope you all can join us.

REFERENCES

1. **Penn MS, Topol E.** The challenge for stem cell therapy. In: Penn MS, ed. Stem Cells and Myocardial Regeneration. Totowa, NJ: Humana Press; 2007:1–8.
2. **Bardy GH, Lee KL, Mark DB, et al.** 2005. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005; 352:225–237.
3. **Young JB, Abraham WT, Smith AL, et al.** Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA 2003; 289:2685–2694.
4. **Beqqali A, Kloots J, Ward-van Oostwaard D, Mummery C, Passier R.** Genome-wide transcriptional profiling of human embryonic stem cells differentiating to cardiomyocytes. Stem Cells 2006; 24:1956–1967.
5. **Leung H, Kwan P, Elger CE.** Finding the missing link between ictal bradyarrhythmia, ictal asystole, and sudden unexpected death in epilepsy. Epilepsy Behav 2006; 9:19–30.
6. **Casserly I, Topol E.** Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. Lancet 2004; 363:1139–1146.
7. **Gidday JM.** Cerebral preconditioning and ischaemic tolerance. Nat Rev Neurosci 2006; 7:437–448.
8. **Kloner RA, Rezkalla SH.** Preconditioning, postconditioning and their application to clinical cardiology. Cardiovasc Res 2006; 70:297–307.
9. **Southerland EM, Milhorn DM, Foreman RD, et al.** Preemptive, but not reactive, spinal cord stimulation mitigates transient ischemia-induced myocardial infarction via cardiac adrenergic neurons. Am J Physiol Heart Circ Physiol 2007; 292:H311–H317.
10. **Goldstein DS, Eldadah B, Holmes C, Pechnik S, Moak J, Sharabi Y.** Neurocirculatory abnormalities in chronic orthostatic intolerance. Circulation 2005; 111:839–845.

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