STEPHEN OPPENHEIMER, MD, PhD*†
Sentient Medical Systems
Cockeysville, MD

Cortical control of the heart

Neuraxial organization of cardiac control can be considered as a series of hierarchically organized oscillatory networks. Some of the oscillatory activity is determined by intrinsic characteristics of the cells themselves, but it may also be related to neural networks that are either situated inside or distributed between specific brain nuclei. The functional rationale for such hierarchical organization is unclear, but this probably permits integration between cardiac neural regulatory elements and extraceptive and intraceptive perceptions, allowing for contextually appropriate response patterning.

The anatomic locations involved in cardiac regulation extend from the spinal cord to the cortex itself. At the cortical level, the insula has received the most recent attention and this will be the major focus of this article.

INVESTIGATING THE ROLE OF THE INSULAR CORTEX

For many years, the role of the insular cortex was unclear. Recently, viscerotopicity has been demonstrated and chemosensation, taste, and respiratory representation have been shown.[1]

The insular cortex is also of interest because neuroanatomic tracing experiments have shown efferent and afferent connectivity with several diencephalic and brainstem structures known to be involved with cardiovascular representation.[1]

Stimulus choice

One problem with investigating cardiac representation is the difficulty in obtaining specific cardiac effects (ie, changes in heart rate or rhythm) without concomitant changes in blood pressure and respiration. When these occur, uncertainty arises as to whether the resultant cardiac effects are primary or secondary. Overcoming this problem required a different stimulus, which we accomplished by discriminating the R wave of the electrocardiogram (ECG) and using it to trigger a microstimulus delayed by approximately 120 msec (the estimated cortical cardiac time delay from neural transfer between the insular cortex and the sinoatrial node), which reached the heart just prior to the P wave. In this way, cardiac responses could be obtained without changes in the respiratory rate or blood pressure. In chloralose-anesthetized rats, microstimulation of the posterior insular cortex in phase with the ECG R wave produced significant increases in heart rate and bradycardia without concomitant detectable autonomic changes.[2]

Potential arrhythmogenesis

With success in obtaining changes in heart rhythm in these rats, we were next interested in whether or not ventricular arrhythmias could be provoked by phasic microstimulation of the insular cortex. Stimuli were arranged so as not to change heart rate, by generating the neural activity reaching the heart during the early part of the T wave. This was done in hopes of increasing cardiac sympathetic drive at a time when the ventricle might be most vulnerable to destabilizing neural influences.

Results obtained with microstimulation of the left insular cortex were compared with those obtained with peri-insular stimulation in the parietal region, which served as a control.

Prolonged stimulation in parietal locations over approximately 8 hours produced little change in the ECG pattern. In contrast, stimulation within the left insular cortex produced ST-segment depression followed by QT prolongation, broadening of the QRS complex, and increasing degrees of heart block leading to complete heart block and culminating in death in asystole. These changes were associated with myocytolysis, a form of cardiac muscle damage characterized by scattered areas of necrosis with monocytic infiltration and subendocardial hemorrhage adjacent to the left ventricle. This was accompanied by a significant increase in levels of plasma norepinephrine, which, in the rat, is indicative of a neurally mediated mechanism rather than adrenal activation.[3]

These findings suggest that stimulation within the insular cortex mimics the repolarization and structur-

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al changes that occur with catecholamine-induced cardiomyopathy seen under certain clinical circumstances, including death following extreme and prolonged stress, and that these effects are likely associated with neural activation within the ventricular myocardium.

Investigation of patients in the acute phase of insular stroke revealed significant increases in the corrected QT interval and in ventricular arrhythmias, indicating that insular damage may produce effects on cardiac repolarization, extending the experimental observations into a relevant clinical context.[4]

LATERALIZATION OF CARDIOVASCULAR CHANGES

In an attempt to demonstrate lateralization, a series of single localized lesions was placed in either the left or right posterior insula, the left or right anterior insula, and in adjacent peri-insular regions. We found no changes in basal cardiovascular state except with lesions placed in the right posterior insular cortex, which produced elevations in mean arterial pressure and basal heart rate and, interestingly, no change in baroreceptor gain. In contrast, left posterior insular lesions significantly increased baroreceptor gain. These findings suggest a differential effect, with the right posterior insula involved in cardiovascular sympathetic control and the left posterior insula involved in the regulation of cardiac parasympathoregulatory function.[5]

Following these observations, spectral analysis of heart rate variability in the rat was used to explore the effects of microstimulation within the right insular cortex since the previous findings indicate a role specific to sympathoregulatory cardiovascular mechanisms in this location. This appeared to upregulate sympathetic neural activity significantly without changing heart rate or blood pressure, and was associated with a decrease in baroreceptor reflex gain.[6]

Cardiac representation in humans

Whether or not similar lateralizability exists within the human insular cortex was explored in human epileptic patients. In five patients undergoing temporal lobectomy for intractable seizures, exposure of the antero-inferior insular cortex allowed for study of the effects of intraoperative insular stimulation. The caveat here is that prolonged seizures may change synaptic relationships in the brain, and therefore the findings may not necessarily be applicable to normal individuals. Nevertheless, left anterior insular stimulation produced bradycardia in 93% of the stimulations. Stimulation of the right anterior insula produced tachycardia or an increase in diastolic blood pressure. Therefore, we demonstrated that cardiovascular changes could be elicited with human insular cortex stimulation, as well as lateralization of responses for a cortical site. As in the rat, right-sided dominance was demonstrated for sympathetic effects.[7]

Patients with stroke lateralized to the left insular cortex were then compared with age-matched controls. Using spectral analysis, we found a reduction of sympathovagal balance and a decrease in the randomness of heart rate variability. Further, one third of the stroke patients developed sinus tachycardia within 24 hours of admission in the absence of significant coronary artery disease. This implies that ablation of the left insular cortex, where it is believed that parasympathetic regulatory cardiac function is represented, predisposes to the development of adverse cardiac outcomes.[8]

Left insular stroke and adverse cardiac outcomes

To investigate whether or not left insular stroke contributes to adverse cardiac outcomes, we followed patients with left insular stroke and another group with noninsular cortical stroke or transient ischemic attack, and assessed adverse cardiac outcomes over 1 year. Using multiple regression analysis, left insular stroke was found to increase an aggregate measure of adverse cardiac outcomes that included sudden cardiac death, new-onset angina, myocardial infarction, and new-onset left ventricular failure. The association between left insular stroke and adverse cardiac outcomes was extremely significant when the analysis was restricted to patients without symptomatic coronary artery disease.[9] Exclusion of patients with symptomatic coronary disease reduced the likelihood of beta-blocker therapy in the remaining subjects, and we believe that beta-blocker therapy may confound the association between left insular stroke and adverse cardiac outcome by effectively attenuating insula-related cardiac sympathetic upregulation.

CONCLUSION

There is evidence for lateralization and specialization of cardioregulatory function within the insular cortex from both laboratory and clinical observations. The right insular cortex is primarily concerned with sympathoregulatory activity. The left insular cortex is more likely involved with parasympathoregulatory function. State-dependent inhibitory and excitatory pathways descend from these insular regions to other subcortical areas involved in cardiovascular regulation. Lesions that involve primarily the left insular

cortex are associated with destabilization of sympathoregulatory balance, exposing the heart to increased risk of arrhythmia and adverse cardiac outcomes through myocytolysis and other mechanisms.

REFERENCES

1. **Cechetto DF, Saper CB.** Evidence for a viscerotopic sensory representation in the cortex and thalamus in the rat. J Comp Neurol 1987; 262:27–45.
2. **Oppenheimer SM, Cechetto DF.** Cardiac chronotropic organization of the rat insular cortex. Brain Res 1990; 533:66–72.
3. **Oppenheimer SM, Wilson JX, Guiraudon C, Cechetto DF.** Insular cortex stimulation produces lethal cardiac arrhythmias: a mechanism of sudden death? Brain Res 1991; 550:115–121.
4. **Sander D, Klingelhofer J.** Changes of circadian blood pressure patterns after hemodynamic and thromboembolic brain infarction. Stroke 1994; 25:1730–1737.
5. **Zhang ZH, Rashba S, Oppenheimer SM.** Insular cortex lesions alter baroreceptor sensitivity in the urethene-anesthestized rat. Brain Res 1998; 813:73–81.
6. **Oppenheimer SM, Zhang ZH, Boekholdt M.** Electrical stimulation of the right posterior insular cortex increases cardiac sympathetic tone in the rat. Soc Neurosci Abstracts 1998; 24:1134.
7. **Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC.** Cardiovascular effects of human insular cortex stimulation. Neurology 1992; 42:1727–1732.
8. **Oppenheimer SM, Kedem G, Martin WM.** Left-insular cortex lesions perturb cardiac autonomic tone in humans. Clin Auton Res 1996; 6:131–140.
9. **Laowattana S, Zeger SL, Lima JAC, Goodman SN, Wittstein IS, Oppenheimer SM.** Left insular stroke is associated with adverse cardiac outcome. Neurology 2006; 66:477–483.

Address: *Stephen Oppenheimer, MD, PhD, Sentient Medical Systems, 10151 York Road, Cockeysville, MD 21030; soppenh@hotmail.com.*