

The Insula and Cerebrogenic Sudden Death

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Sudden death is an “electrical accident” caused by fatal cardiac arrhythmias. While brain-heart control has physiological advantages, cerebrogenic sudden death and nonfatal cardiovascular disturbances can complicate stroke of all types, seizures and epilepsy, head injury, other neurological conditions, neurosurgical procedures, and intense emotional states. Cerebrogenic cardiovascular and autonomic disturbances include electrocardiographic changes, elevation of cardiac enzymes, cardiac arrhythmias, disturbances of blood pressure regulation, and cerebrogenic pulmonary edema. Evidence from experimental studies and clinical observations indicates a crucial role of the insula in cerebrogenic cardiovascular disturbances and sudden death. Future studies should focus on identification of at-risk patients, confirmation of a vulnerable period of cerebrogenic sudden death in those with different neurological conditions and intense emotional states, and clarification of the neurochemical mediators. *Arch Neurol.* 2000;57:1685-1688

An apparently healthy person may have nonaccidental sudden death within an hour or at most, a few hours of symptom onset. Sudden death, also known as sudden unexpected death or sudden cardiac death, accounts for 50% of all cardiovascular death or 25% of all fatalities.¹ Although sudden death shares the same risk factors as ischemic heart disease, some persons do not have postmortem evidence of coronary atherosclerosis, coronary thrombosis, or recent myocardial infarction; many do not have previous symptoms of ischemic heart disease. Sudden death is an “electrical accident” caused by fatal cardiac arrhythmias.

Cerebral regulation of cardiovascular and autonomic functions via the autonomic nervous system and endocrine-humoral mechanisms has evolutionary advantages. The brain-heart interactions enable second-to-second regulation of our cardiac activity and vasomotor tone in response to physical activity, threats, stresses, and changes in emotional states.² Never-

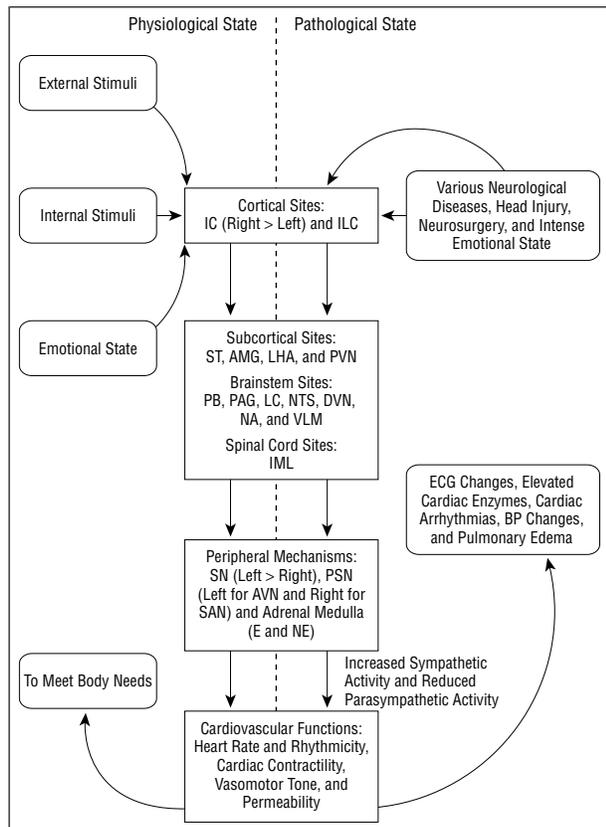
theless, abnormal neurological conditions and emotional states can produce cardiovascular and autonomic disturbances (**Figure**); cerebrogenic sudden death is the most serious consequence.

Some electrocardiographic (ECG) changes are associated with a higher risk of sudden death. These are QT prolongation, late ventricular potentials, frequent ectopic ventricular beats, polymorphic ectopic ventricular beats, R-on-T phenomenon, and runs of ventricular tachycardia. In addition, abnormal heart rate variability is a sensitive predictor of sudden death. Heart rate variability can be measured by variation in the R-R intervals or power spectral analysis.³⁻⁷

CLINICAL EVIDENCE OF CEREBROGENIC CARDIOVASCULAR AND AUTONOMIC DISTURBANCES

Electrocardiographic changes without acute coronary events have been reported in patients with subarachnoid hemorrhage (40%-70%), intracerebral hemorrhage (60%-70%), and ischemic stroke (15%-40%).^{1,2} Similar ECG changes can be found in patients with head injury, brain

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A schematic drawing of the sites involved in the brain-heart control under physiological and pathological states. IC indicates insular cortex; ILC, infralimbic cortex; ST, stria terminalis; AMG, amygdala; LHA, lateral hypothalamic area; PVN, paraventricular nucleus; PB, parabrachial nucleus; PAG, periaqueductal gray; LC, locus ceruleus; NTS, nucleus tractus solitarius; DVN, dorsal vagal nucleus; NA, nucleus ambiguus; VLM, ventrolateral medulla; IML, intermedialateral column; ECG, electrocardiographic; BP, blood pressure; SN, sympathetic nerve; PSN, parasympathetic nerve; AVN, atrioventricular node; SAN, sinoatrial node; E, epinephrine; and NE, norepinephrine.

tumors, meningitis, multiple sclerosis, spinal cord lesions, and hydrocephalus and during neurosurgical procedures. The reported ECG changes include prolonged QT intervals; depressed ST segments; flat or inverted T waves; U waves; tall, peaked T waves; notched T waves; elevated ST segments; peaked P waves; Q waves; and increased QRS amplitudes. These changes usually evolve for several days and disappear within 2 weeks; QT prolongation and U waves may be permanent.

The cardiospecific isoenzyme creatine kinase myocardial band is often increased in patients with cerebrogenic ECG changes but is undetectable in those without these changes.² Elevation of this cardiospecific isoenzyme correlates with the presence of ECG changes, cardiac arrhythmias, or both in patients with acute stroke. In contrast to acute myocardial infarction, the level of this isoenzyme increases gradually during the first 4 days of stroke.

Various neurological diseases may mimic acute coronary events. Postmortem examination reveals focal myocytolysis; myofibrillar degeneration; subendocardial congestion, hemorrhages, or both; lipofuscin pigment deposition in the myofibrils; and histiocytic infiltration with no evidence of acute myocardial infarction or coronary thrombosis.^{1,2} These pathologi-

cal changes can be reproduced experimentally by increasing the sympathetic nervous activity or infusing catecholamines.

Cardiac arrhythmias have been reported in patients with all types of stroke; these arrhythmias include bradycardia, supraventricular tachycardias, atrial flutter, atrial fibrillation, ectopic ventricular beats, multifocal ventricular tachycardias, torsade de pointes, ventricular flutter, and ventricular fibrillation.^{1,2} In addition, cardiac arrhythmias can complicate seizures, neurosurgical procedures, head injury, and cerebral tumors.

Acute severe hypertension due to sympathoadrenal hyperactivity is seen in ischemic, hemorrhagic, degenerative, or neoplastic lesions of the hypothalamus, medulla oblongata, or posterior fossa.² In patients with stroke or seizures, mild to moderate hypertension can be due to preexisting hypertension, stress, a cerebral lesion, and/or abnormal neurological activities.

Cerebrogenic pulmonary edema is caused by a transient increase in pulmonary intravascular pressure, more prolonged pulmonary capillary leakage, or both.² Cerebrogenic pulmonary edema has been described in patients with subarachnoid hemorrhage, generalized seizures, head injury, increased intracranial pressure, focal lesions or neurosurgical manipulation of the hypothalamus or brainstem, and bulbar poliomyelitis.

The peripheral mechanisms of cerebrogenic cardiovascular disturbances include increased sympathetic nervous discharge, enhanced secretion of adrenomedullary catecholamines, and reduced parasympathetic nervous activity.^{1,2} Recent evidence indicates the importance of asymmetric innervation of the heart and imbalance between sympathetic and parasympathetic components in cerebrogenic sudden death. The predominant influence on the sinoatrial and atrioventricular nodes comes from the parasympathetic innervation, whereas the ventricular muscle is affected more by the sympathetic innervation.² The right vagus nerve has more effect on the sinoatrial node, whereas the left vagus nerve has more influence on the atrioventricular node. In addition, the left cervicothoracic ganglion or the left-sided sympathetic activity has greater arrhythmogenic potential than the right cardiac sympathetic innervation.

Cerebrogenic cardiovascular disturbances can be long lasting. Abnormal heart rate variability was observed in the immediate phase and persisted up to 6 months after hemispheric infarction.⁵ Nevertheless, the circadian variation of heart rate variability was reversibly abolished in the immediate phase of ischemic stroke and recovered within the subsequent 6 months.⁶

EXPERIMENTAL EVIDENCE IMPLICATING THE INSULA IN GENERATING CEREBROGENIC CARDIOVASCULAR AND AUTONOMIC DISTURBANCES

There is a viscerotopic sensory representation in the rat insula. The insula receives taste, gastrointestinal stimuli, respiratory afferents, chemoreceptor, and cardiovascular inputs; it has reciprocal connections with the parabrachial nucleus, the contralateral insula, adjacent cortical regions, the infralimbic cortex, the thalamus, the

lateral hypothalamic area, and the amygdala.⁸ Pressor responses were elicited by stimulation of the rostral half of the posterior part of the dysgranular and agranular insula, whereas depressor sites were located in the caudal part of the dysgranular and agranular insula. The connections of the pressor and depressor sites have been defined. The viscerotopic sensory representation in the insula and its input and output connections enable the insula to play a key role in the brain-heart interactions.

Electrical stimulation of the insula produces changes in arterial pressure, heart rate, respiration, piloerection, pupillary dilation, gastric motility, peristaltic activity, salivation, and adrenaline secretion in rats, cats, dogs, monkeys, and humans.⁹ An isolated increase in arterial pressure and heart rate was reported in patients with epilepsy when the insula was stimulated.¹⁰ Using phasic microstimulation triggered by the R wave, changes in heart rate were achieved without concomitant changes in arterial pressure or respiratory effects.⁹ A cardiac chronotropic map of the insula was derived: tachycardiac sites were in the rostral posterior insula, and bradycardiac sites were in the caudal posterior insula.⁹

The role of the insula in cerebrogenic cardiovascular and autonomic disturbances was first implicated in a transorbital left-sided middle cerebral artery occlusion stroke model in the cat. The role of the insula in stroke-induced cardiovascular and autonomic disturbances was confirmed in the rat¹¹; the disturbances were more profound in older rats and in rats with right-sided cerebral infarction.^{12,13}

RECENT CLINICAL OBSERVATIONS

There is clinical evidence of lateralization in neurocardiac control. The heart rate increased with left hemispheric inactivation by intracarotid amobarbital but decreased with right hemispheric inactivation.¹⁴ By measuring heart rate variability before and after intracarotid amobarbital injection, the right cerebral hemisphere was shown to predominantly modulate sympathetic activity.¹⁵ Lateralization of sympathetic cardiovascular effects to the right insula was also seen in patients with epilepsy during intraoperative stimulation.¹⁰ In a small study,¹⁶ supraventricular tachycardia was seen in 4 of 19 patients with right hemispheric infarction but not in the 19 patients with left hemispheric infarction, suggesting a reduction of parasympathetic cardiac innervation in patients with right hemispheric infarction. When the heart rate variability was measured in 20 patients with right hemispheric infarction and in 20 patients with left hemispheric infarction, results indicated a reduction in the total cardiac autonomic innervation after infarction of either hemisphere.³ In addition, reduction in the cardiac parasympathetic innervation was greater in patients with right hemispheric infarction, suggesting an unbalanced cardiac autonomic activity favoring the sympathetic system and arrhythmogenesis.³ A reduced respiratory component of the heart rate variability was seen in 13 patients with a right-sided cerebral infarct when compared with 10 patients with a left-sided infarct, suggesting reduced cardiac parasympathetic activity in patients with right-sided ischemic stroke.⁴

When repeated 24-hour blood pressure recordings were made in 45 patients with cerebral infarction, circa-

dian blood pressure variation was significantly increased after hemodynamic infarction but decreased after thromboembolic infarction.¹⁷ Involvement of the insula was associated with a nocturnal increase of blood pressure, a higher norepinephrine level, QT prolongation, and cardiac arrhythmias. The role of the insula in stroke-associated pathological sympathetic activation was confirmed in another study¹⁸ of 52 patients with thromboembolic cerebral infarction: inclusion of the insula in the cerebral infarct was more important than the infarct size. In a prospective study,¹⁹ recent-onset atrial fibrillation was found to be related to intracerebral hemorrhage and infarctions involving the insula or the brainstem, supporting the role of the insula in cerebrogenic arrhythmogenesis.

Most recently, 62 patients with ischemic stroke and 62 control subjects were studied to determine the effect of stroke location on cerebrogenic cardiac disturbances.⁷ All patients had reduced heart rate variability; those with infarctions involving the right insula had significantly lower sympathetic and parasympathetic activities than the other patients. In addition, 5 patients with right insular infarction experienced sudden death compared with 2 sudden deaths in patients with left insular infarction.

RECENT EXPERIMENTAL EVIDENCE

A modified technique of phasic microstimulation of the insula created an R-on-T scenario in the rat and produced increasing degrees of heart block, leading to escape rhythms, ectopic ventricular beats, and eventually death due to asystole.²⁰ These ECG changes were associated with elevated plasma norepinephrine levels, cardiac myocytolysis, and subendocardial hemorrhages.

Neuroanatomical and electrophysiological studies⁸ show direct and reciprocal ipsilateral connections between the insula and the amygdala. The amygdala, an important central cardiovascular control center within the limbic system, plays a crucial role in producing the cardiovascular responses to stressful stimuli.²¹ Increased immunostaining of neuropeptide Y, leucine-enkephalin, dynorphin, and neurotensin was seen in the amygdala on the side of damage after the insular involvement by ischemic stroke or excitotoxic injury.²²⁻²⁴ The neurochemical change in the amygdala, which was greatest at 3 days after ischemic stroke and had subsided by 10 days,²³ may mediate the cerebrogenic cardiovascular disturbances originating from the insula.

The cardiovascular responses to intermittent and continuous noise and air-jet stimulation were examined in male Wistar rats from day 2 to 10 after right-sided ischemic stroke or sham stroke.²¹ Compared with the control rats, intermittent noise elicited significant tachycardiac responses on days 5 and 7 after stroke. Air-jet stimulation also elicited a significant tachycardiac response on day 5 of ischemic stroke, whereas continuous noise produced significant tachycardiac and pressor responses on days 5 and 7, respectively, when compared with the control rats.²¹ Analyses on the heart rate variability revealed significant increases in the sympathetic reactivity on day 7 for intermittent noise and air-jet stimulation.²¹ The results indicate a course of exaggerated cardiovascular responses to stress and suggest a poststroke state of susceptibility to cardiac perturbations in rats.

IMPLICATIONS AND FUTURE DIRECTION

Sudden death can be a lethal form of cerebrogenic cardiovascular disturbances. Previous reports have documented and characterized these disturbances in patients with various neurological conditions and intense emotional states. We have compelling evidence to shift our attention from the hypothalamus, brainstem cardiovascular centers, and spinal autonomic outflows to the cortical and subcortical regions, such as the insula and amygdala, regarding the site of origin of cerebrogenic sudden death. Researchers and clinicians can readily identify patients at risk of sudden death through detection of ECG signs and analysis of heart rate variability. The addition of acoustic stimulus or simple tests of cardiovascular reflexes such as passive postural change, the Valsalva maneuver, and the cold face test may be helpful. Involvement of the right insula, advancing age, concomitant hypertensive and ischemic heart diseases, and the presence of intense emotional stress are the risk factors for cerebrogenic cardiovascular disturbances and probably for sudden death. Confirmation of a vulnerable period of sudden death in patients with different neurological conditions and intense emotional states awaits further studies. Finally, more work on the neurochemical mediators of cerebrogenic cardiovascular disturbances is needed before potentially effective pharmacological therapy can be tested in randomized clinical trials.

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