REVIEW ARTICLE

The Insular Cortex and the Pathophysiology of Stroke-Induced Cardiac Changes

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ABSTRACT: *Over the past fifty years considerable clinical evidence has accrued to demonstrate involvement of the* cerebral cortex in cardiac function. Hemispheric stroke is often associated with electrocardiographic (ECG) evidence of cardiac repolarisation abnormalities. In addition strokes of all types are associated with specific pathological changes in the ventricular myocardium (myocytolysis). These effects are not attributable to concomitant cardiac ischemic disease in the majority of cases. The insular cortex has recently been shown to contain a site of cardiac representation. Prolonged stimulation of this region in the rat produces ECG and cardiac pathological changes similar to those observed after human stroke. It is suggested that middle cerebral artery stroke in certain cases either directly or indirectly leads to insular disinhibition, and increased autonomic activity represented by cardiac changes which significantly influence prognosis.

RÉSUMÉ: Le cortex insulaire et la physiopathologie des modifications cardiaques induites par un accident cérébro-vasculaire. Au cours des cinquante dernières années, une quantité considérable de données cliniques ont été amassées démontrant une implication du cortex cérébral dans la fonction cardiaque. L'accident cérébro-vasculaire hémisphérique est souvent associé à l'observation d'anomalies de la repolarisation cardiaque à l'ECG. De plus, les accidents cérébro-vasculaires de tous genres sont associés à des changements pathologiques spécifiques dans le myocarde ventriculaire (myocytolyse). Ces effets ne sont pas attribuables à une maladie cardiaque ischémique concomitante dans la majorité des cas. On a démontré récemment que le cortex insulaire contient un site de représentation cardiaque. Une stimulation prolongée de cette région chez le rat produit des changements électrocardiographiques et anatomopathologiques semblables à ceux qui sont observés après un accident cérébro-vasculaire chez l'humain. Nous suggérons qu'un accident cérébro-vasculaire dans le territoire de l'artère cérébrale moyenne provoque dans certains cas, soit directement ou soit indirectement, une désinhibition insulaire et une augmentation de l'activité autonomique représentée par des changements cardiaques qui influencent significativement le pronostic.

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One of the oddities of medicine is that an important observation with no known mechanism can be accepted as axiomatic for a very long period of time without further question. Witness the nearly fifty years since the original observations in the Western literature that ECG changes can attend acute neurological lesions (especially stroke),[1,2] and that patients dying suddenly and unexpectedly during an otherwise unremarkable seizure, and who have no history of cardiac disease may develop cardiac muscle lesions.[3] These fascinating findings have, until recently, passed almost without comment.

In the earliest survey of this field, Burch and colleagues identified cardiac repolarisation changes as the chief cardiological concomitant of acute stroke whether ischemic or hemorrhagic.[4] It was noted that prolongation of the QT interval, abnormal T waves, ST segment changes and abnormal U waves were particularly frequent following acute stroke. In their small sample of 17 patients, these changes were thought to be more common after subarachnoid hemorrhage (SAH) than after intracerebral hemorrhage or ischemic stroke. Isolated reports of similar ECG changes after stroke have continued to appear sporadically confirming this impression. In general, ECG changes of the type identified by Burch and colleagues have been found in 61% of hemorrhages (whether intracerebral or subarachnoid) and in 5-17% of ischemic strokes.[4-8]

The similarity of the post-stroke ECG changes to those seen after acute myocardial infarction, originally was a source of considerable alarm to neurosurgeons. Cropp and Manning's[9] proband case was thought to have sustained an acute myocardial infarct along with her SAH. Operation was postponed and the patient rebled and died. To their consternation, no evidence of ischemic myocardial necrosis was discovered at autopsy. This prompted them to identify a further 29 patients admitted to the Victoria Hospital, London, Ontario with SAH and concomitant ECG changes. Autopsies were performed in 5 of the 8 patients

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who died, and significantly showed no evidence of acute ischemic cardiac lesions to explain the ECG findings. Other studies have confirmed these autopsy findings in ischemic stroke[5] and intracerebral hemorrhage.[8]

On the other hand, the risk factors of ischemic cerebral and cardiac disease and for intracerebral hemorrhage are not dissimilar. Could it not be that the ECG changes are to be accounted for by subtle myocardial ischemia? Not only does this seem unlikely on the basis of the autopsy findings already discussed, but several other studies have addressed this issue. Goldstein[8] compared the ECGs of 53 patients admitted with acute stroke (whether subarachnoid or intracerebral hemorrhage or ischemic stroke) with their ECGs taken on average 4 months prior to admission. New ECG changes not seen in the original recordings were observed in 74% of patients. A control group of age/sex matched patients admitted to the same hospital for non-cardiac or stroke-related causes showed such new changes in only 14%. This finding was highly statistically significant and suggested that the ECG abnormalities were primarily associated with the cerebral event and not with concomitant cardiac disease. A similar conclusion was attained by Lavy and colleagues[10] who showed that new ECG changes ("ischemia pattern" or arrhythmia) occurred in 44% of ischemic stroke patients with no evidence of previous cardiac disease and in 71% of similar intracerebral hemorrhage patients.

Of course, the presence of ECG changes per se may be nothing more than a curiosity. However, these abnormalities primarily affect the repolarisation phase. This is known to lead to cardiac electrical instability and the possibility of cardiac arrhythmias.[11,12] Accordingly, there is an appreciable incidence of new-onset cardiac arrhythmias after SAH (98%)[13] intracerebral hemorrhage (77%)[10] or ischemic stroke (22%).[10]

Several studies have indicated an increased mortality in patients demonstrating ECG changes after stroke compared to those without these changes.[8,10,14] Indeed there is an appreciable sudden death rate within the first month of stroke unanticipated by the patient's status.[15] This has been attributed to cardiac rhythm irregularities although there has as yet been no confirmation by direct recording.

The pathological basis of the ECG changes is not entirely clear, but as has been already mentioned it does not appear to relate to acute ischemic myocardial necrosis. On the other hand, some cardiac damage does seem to occur as evidenced by changes in plasma CPK and CPK-MB (the cardiac isoenzyme) after stroke.[7,8,16] Interestingly, the time course of these elevations after stroke differs from that seen after acute myocardial infarction, peaking at approximately 4 days.[16] This suggests a different mechanism of cardiac damage in the two conditions.

Pathologically, the hearts of patients who have died shortly after their acute stroke are frequently abnormal. Scattered foci of individual myofibrillary necrosis may be seen often accompanied by monocytic infiltration (termed myocytolysis). These foci are not centered around blood vessels, but around intracardiac nerves on electron microscopic examination suggesting a neural etiology rather than a cardiac vascular or humoral cause.[17] Frequently, hemorrhages may be observed in subendocardial locations, oftentimes scattered around the conducting system.[18]

The similarity of the pathological changes observed after acute stroke to those induced by cathecholamine infusions in animals and humans[19,20] has led to an hypothesis that these are related in some way to sympathetic overactivity. There is indeed some evidence for this after acute stroke; Myers and colleagues[21] demonstrated increases in plasma norepinephrine and to a lesser extent epinephrine after intracerebral hemorrhage or infarction. This was not accompanied by a rise in plasma cortisol and therefore implied an extra-adrenal probably neural source.

Clinical evidence points to hemispheric strokes as being more likely to produce cardiac arrhythmias than brainstem events.[22] On the other hand, physiological data have suggested the converse: that it is exceptionally difficult to induce changes in heart rate and rhythm by cortical stimulation.[23,24] This contrasts with the ease with which such changes may be elicited on diencephalic and brainstem stimulation.

Over the past few years, some of the mysteries of neurocardiology have started to unravel, and the rest of this lecture will consider how these findings may apply to the changes observed in the heart after acute stroke.

The Insular Cortex

Until recently, this area of the brain (which in humans lies buried beneath the superior temporal and the frontoparietal opercula) represented an island of mystery. No specific function could be ascribed to it and lesions of the region produced few if any symptoms.[25] Over the past few years, the insula has become the object of some attention by neurophysiologists and neuroanatomists. Anatomical tracing methods in the rat have demonstrated profuse reciprocal connectivity between the insular cortex and the limbic system, as well as with other areas of the brain involved in autonomic control such as the hypothalamus, the dorsal motor nucleus of the vagus and the nucleus of the solitary tract.[26,27] Stimulation experiments using currents in the microampere range demonstrated that changes in blood pressure, heart rate and respiration could be elicited in combination from the insula.[26,27] Moreover, stimulation of baroceptor afferents was shown to change the firing pattern of neurons within the insula.[28] These observations strongly suggested that the insular cortex was involved in cardiovascular control and might contain a site of specific cardiac representation. Up to this time, no such specific representation for the heart had been shown for any cortical site.

The Insular Cortex and the Heart

In previous attempts to investigate cerebral involvement in cardiac function physiologists used non-phasic stimulation of the brain usually with 50 Hz stimuli. Often, this produced no effects whatsoever on the heart rate. In the case of the insular cortex, microstimulation at this frequency did change heart rate, but altered blood pressure to a much greater extent.[26,27] It was unclear whether the observed cardiac effects were therefore primary or secondary to the other autonomic changes; this consideration also applies when insular stimulation engenders heart rate changes associated with changes in respiratory rate and depth.[29]

In order to circumvent these unwanted changes in non-cardiac autonomic variables, a novel form of phasic microstimulation was devised. The full details of the methodology have been published elsewhere.[30,31] To parallel a more physiological situ-

ation, the R wave of the ECG recorded in the lead II configuration served as the triggering stimulus. A glass microelectrode of internal diameter 10-20 nm and filled with 3 M saline served as the stimulating electrode and was placed in the left insular cortex of male Wistar rats. Using two stimulators in series, it was possible to stimulate the insular cortex at any point within the ECG cycle, and with any cycle multiple. In practice, pure changes in heart rate unaccompanied by any alterations in blood pressure or respiration occurred when the insula was stimulated 80-100 ms before the P wave, once with either each cycle or every fourth cardiac cycle.[30] The delay accounted for putative conduction time between the insular cortex and the cardiac nerves.[32] Optimal current strength was 500 μA with a pulse duration of 2 ms; the duration of stimulation was 45-90 s. By advancing the microelectrode in a rostro-caudal direction at 500 μm steps and by 200 μm in the dorsoventral plane, a cardiac chronotropic map of the insular cortex was assembled. This demonstrated that tachycardia sites were situated rostrally within the posterior insular cortex, and that bradycardia sites were caudally situated to these with some overlap.[30] The nature of the responses and their distribution were not dependent on the choice of the anesthetic agent. This represented the first demonstration of a cortical site of specific cardiac representation.

Having established a chronotropic map for the rat left insular cortex, the next investigation was designed to identify whether or not cardiac arrhythmias could be produced by phasic stimulation of this site. In this case, the stimulation parameters were changed. A train of three pulses, each of 5 ms duration and of 1500 μA was delivered to the insular cortex with each cardiac cycle, 80-100 ms before the T wave. At this phase of the cardiac electrical cycle, the ventricular myocardium is at its most unstable.[11] The stimulation parameters no longer could be considered within the microstimulation range; however, the object was to determine not from where within the insula arrhythmias could be generated, but whether stimulation could have this effect at all. The stimulation parameters would likely excite 1 mm of tissue[33] roughly encompassing the entire cardioactive region of the insular cortex. After a mean stimulation period of 5 hours under urethane anesthesia, the animals demonstrated a stereotyped series of changes: progressive atrioventricular block leading to complete heart block; interventricular block; QT interval prolongation; ST segment depression; ventricular ectopy and finally death in asystole.[31] Stimulation in the adjacent piriform or frontoparietal cortices was without effect on the ECG. Similar cardiac changes were elictable in both ventilated and unventilated rats. These effects were unlikely to be due to seizure activity or kindling: no overt seizure activity was observed; urethane at the concentration used in this study protects against kindling and seizure generation;[34] no change in pulse rate or in blood pressure or respiration occurred at a time when there were profuse electrocardiographic effects. This latter would be difficult to explain on the basis of seizure activity alone.

Changes in the ECG were directly correlated with the presence of myocytolysis in the stimulated rats (assessed blindly by a cardiac pathologist) and with the demonstration of hemorrhages adjacent to the conducting system at the origin of the left branch of the bundle of His. Such effects were not seen in the animals stimulated in the adjacent frontoparietal or piriform cortices. The presence of these changes also correlated with a significant elevation in plasma norepinephrine, but not epinephrine signifying an extra-adrenal, neural source.

Insular Cardiac Sites – Significance for Stroke-Induced Cardiac Changes

The ECG and cardiac pathological changes evoked by prolonged phasic insular stimulation to some extent mimic those seen after acute stroke. Moreover, as already discussed, available clinical evidence implies the involvement of a hemispheric rather than a brainstem site in these neurocardiological effects of stroke. It is possible that ablation of a site adjacent to the left insular cortex, such as part of the frontoparietal cortex may disinhibit the insula allowing for unbridled cardiac autonomic activity. There is some evidence for this as stimulation within the frontoparietal cortex actually decreases plasma catecholamine levels (Oppenheimer, SM: unpublished observations). The frontoparietal cortex is often involved in middle cerebral artery infarction, and this mechanism could go some way to explain the neurocardiological effects of such a stroke. On the other hand, it may be that there is a degree of laterality in the cerebral representation of the heart. The right insular cortex may have a more stabilizing effect on heart rate and rhythm than that shown for the left insula. Certainly such laterality has been demonstrated at lower levels of the neuraxis.[12] Consequently, cerebral infarction involving the right hemisphere might achieve an imbalance resulting in excessive autonomic activity and the reported cardiac effects. In this fashion, ablative lesions may produce similar changes to those induced by insular stimulation. Of course, there is as yet no evidence for a similar role of the insular cortex in the primate or human brain. However, considerable homology of connectivity exists between the regions investigated in these studies and the anterior insula of the primate.[35,36] It is therefore not without the bounds of possibility that cardiac chronotropic representation occurs in this region of the human brain, and that acute stroke may weave its cardiac web through insular involvement.

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