

Leading Article

Neurothanatology – clinical significance of cerebrally induced cardiac changes

Stephen Oppenheimer

Robarts Research Institute, 100 Perth Drive, London, Ontario N6A 5K8, Canada

That cardiac changes occur following cerebral lesions is substantiated by over 40 years of clinical and experimental research. The initial observation was prompted by a victim of subarachnoid haemorrhage (SAH) who developed new electrocardiogram (ECG) changes suggestive of acute myocardial infarction.¹ Various reports followed.^{2–4} Burch found similar ECG changes in victims of SAH, intracerebral haemorrhage and ischaemic stroke in the first systematic study of neurogenic cardiac effects.⁵ Principally, cardiac repolarization changes were noted. None of these early reports addressed the possible contribution of concomitant ischaemic heart disease. As autopsy evidence accrued, it became clear that neurogenic ECG changes occurred even in patients with normal coronary arteries.^{3,6–8} Moreover, in the majority of cases where coronary atheroma was present, there was no evidence of acute cardiac ischaemic change. However, several hours are required for the development of observable pathology following myocardial infarction. Similarly, intracoronary thrombus may fragment prior to death.⁹ In patients who die rapidly therefore, such changes may not appear, although this does not explain the occurrence of ECG changes in those with no atheroma.

Goldstein⁷ lessened the effects of concomitant heart disease by comparing ictal ECGs with those obtained some 4 months prior to acute stroke. New ECG changes were identified in 74% of victims of strokes of all types, compared with 14% of the matched control population.

ECG repolarization abnormalities generally are more frequent following subarachnoid or intracerebral haemorrhage (66%) than after ischaemic stroke.^{4,5,7,10} The commonest alterations are: QT prolongation (32%), U wave alterations (13%), ST changes (21%), T wave inversion (15%).⁷ The similarity of such ECG changes to

those of hypokalaemia suggests this as the basis of the phenomenon.¹¹ No association has been found, however, between electrocardiographic changes and plasma potassium levels after SAH.^{12–14} Conversely, a correlation was demonstrated between total exchangeable body potassium after SAH, and ECG changes.⁵ These measurements were made at least one week after the event, the majority of values being only in the low-normal range. Thus, the significance of this study is questionable.

Repolarization changes indicate a propensity to arrhythmogenesis. The observed incidence of cardiac arrhythmias of all types is 98% after SAH, 71% after intracerebral haemorrhage and 39% after ischaemic stroke.^{7,16,17}

As yet, there is no definite clinical evidence identifying electrocardiographic effects with a specific neurological site. ECG changes are more frequent after hemispheric than brainstem infarction,^{18,19} and a weak association exists with haematomas of the left frontal lobe.¹⁷

Consideration of creatine kinase (CK) alterations following stroke yields further evidence for a primary association between cerebral lesions and myocardial changes. Elevation of the cardiac isoenzyme is seen in 10% of patients compared with 0% of matched controls.²⁰ A strong association with electrocardiographic events is evident. The enzyme change is slower, and the duration longer than that of myocardial infarction, implying a different aetiology.

Koskelo demonstrated subendocardial haemorrhages following SAH, which are absent in myocardial infarction.²¹ Greenhoot suggested a spectrum of changes exist, ranging from myocyte swelling and contraction bands, to myocyte disruption, inflammatory cell infiltration and haemorrhage.²² Such pathology has been reported in 15%–30% of stroke necropsies, and correlates with ECG change.^{21,23,24} Interestingly, Greenhoot noted that the abnormalities centred on intracardiac nerves, implying that the perpetrating agent was neurally derived.²²

Persuasive evidence indicates catecholamines as

the most likely instruments of myocardial damage. These are elevated following stroke.²⁵ The cardiac pathological effects of stroke are identical to those seen after noradrenaline or adrenaline treatment, or in phaeochromocytoma.²⁶ Similarly, such changes have been induced in animals by catecholamine infusion.²⁶⁻²⁸ Experimental administration of catecholamines into healthy young humans reproduces the ECG changes of stroke.²⁹ There is also a strong correlation between catecholamine and plasma CK levels.²⁰

Evidence for cardiac involvement in other neurological conditions is less abundant: T wave and ST segment alterations occur in 25% of spontaneous seizures of all types;³⁰ after temporal lobe seizures³¹ (when they accompany the aura and are not associated with movement); and in paralysed and ventilated epileptics whose generalized seizures were induced by pentylentetrazol.³²

Cardiac arrhythmias are common seizure accompaniments: simultaneous ambulatory EEG/ECG monitoring in temporal lobe epileptics identified arrhythmias in 52% of recordings. These most frequently comprised a marked beat to beat variation in the R-R interval.³³ Serious cardiac arrhythmias occur: 3 of 26 patients developed frequent ventricular ectopic beats during their fits, and one each either supraventricular tachycardia or 'considerable' bradycardia. Two cases of sinus arrest during a seizure have been reported.^{34,35} In one further case this was induced by photic stimulation.³⁶

Repolarization abnormalities have been recorded in 15% of cases of meningitis,¹¹ and QT prolongation in 13%.³⁷ In neither study was there evidence of pre-existing cardiac disease. No conclusive evidence for the presence of ECG changes in patients with intracerebral tumours has been forthcoming.¹¹ It would appear that cardiac effects are less frequent in chronic or subacute neurological conditions.

The finding of cardiac changes following stroke is of prognostic significance. After intracerebral haemorrhage or ischaemic stroke, mortalities of 80% and 63% respectively occurred in patients with new ECG changes, compared with 0% in either group showing no ECG change.¹⁸ Similarly, the mortality following stroke was 43% in patients with CK elevation, compared to 0% in the group with none.⁷ ECG changes following SAH predict the presence of vasospasm and a poor prognosis.³⁸

Of acute stroke unit admissions, 6% die suddenly without necropsy-identifiable cause. Such death is unrelated to clinical state and occurs at any time during the first month.³⁹ It is likely to be caused by a cardiac arrhythmia; as already noted, these are common following stroke. Prolonged QT intervals are frequent in these circumstances, and

suggest the possibility of associated torsade de pointes; 4% of SAH patients develop this malignant arrhythmia which directly correlates with their QT length.⁴⁰ Consequently, vigilance must be observed in stroke victims manifesting electrocardiographic abnormalities as there is an appreciable risk of arrhythmia-induced hypotensive episodes (extending stroke size), or sudden death. The duration of cardiac monitoring is unclear; certainly stroke-derived ECG changes persist for several weeks;^{2,5} the risk of sudden death continues for at least one month.³⁹ Cardiac monitoring should probably continue for as long as evolving ECG abnormalities are present. Concomitant ischaemic heart disease may be a synergistic factor, summing with the cardiac effects of stroke; thus patients with known ischaemic heart disease could form a subgroup worthy of especially close surveillance.

Sudden unexpected epileptic death occurs in young patients whose seizures are well-controlled and infrequent. They die during an otherwise unremarkable fit; there is no post-mortem evidence of an identifiable cause of death.⁴¹⁻⁴³ Anticonvulsant levels are often subtherapeutic and the patients poorly compliant. The incidence varies between 0.5 and 2 per 1000.⁴¹ In view of the frequency with which ECG changes are observed during seizures, death is probably due to a cardiac arrhythmia. The site of origin or spread of seizure discharge coupled with a sudden decrease in plasma anticonvulsant levels may result in heightened cardiac excitability. Until more is known, attempts must be made to impress upon patients the necessity for punctilious drug compliance.

Occasionally, patients investigated for a cardiac arrhythmia are found to have underlying epilepsy. Walsh⁴⁴ reported a patient presenting with recurrent supraventricular tachycardia, whose ECG demonstrated generalized spike and wave discharges statistically associated with shortening of the R-R interval, leading to the arrhythmia. Two further cases have been reported,^{45,46} in each, extensive investigation failed to identify an intrinsic cardiac cause for the arrhythmia. In both a temporal lobe focus was present. All three patients did not respond to conventional antiarrhythmic medication; however, control was achieved with antiepileptic drugs, an unusual finding. The possibility exists of an underestimation of epileptic discharge as a mechanism of cardiac arrhythmogenesis. A cerebral focus should be sought in situations where an intrinsic cardiac aetiology is lacking, and where there is no response to conventional antiarrhythmic drugs.

The risk factors for sudden death and myocardial infarction are identical, as is the extent of coronary artery disease.⁴⁷⁻⁴⁹ Often, those presenting as sudden death do not have a symptomatic

cardiac history nor pathological evidence of myocardial infarction.⁴⁷⁻⁴⁸ It is suggested that emotional factors generating abnormal cardiac sympathetic drive may interact with an ischaemic myocardium and be strongly arrhythmogenic, resulting in sudden death. Myocardial infarction without arrhythmogenesis may arise following a different combination of factors. Evidence exists to support this contention; ventricular ectopics may be generated by emotional stress in both the normal and the ischaemic heart.^{50,51} These effects may be abolished by meditation or by beta-blockade. Their presence may correlate with plasma noradrenaline levels. It is possible to significantly raise plasma noradrenaline levels and to generate lethal cardiac

arrhythmias by stimulating the rat insular cortex; this area is acknowledged to be involved in the integration of emotional and autonomic control.⁵²

In conclusion, acute neurological lesions have been demonstrated to produce cardiac effects. This may result in sudden unexpected death under a variety of circumstances, or contribute to the morbidity of stroke.

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