The Heart of the Matter

Stephen Oppenheimer

PharmaNet, Inc., Princeton, N.J., USA

In 1913, Levy [1] identified a neural cause for the unexpected deaths occurring during chloroform anesthesia. The lethal ventricular tachyarrhythmias invoked were abolished by cardiac sympathectomy, and reproduced by reflex sympathetic activation. A few years later, Beattie et al. [2] showed that these arrhythmogenic effects of chloroform were abolished by transection in a plane extending between the superior colliculus and hypothalamus. Thus began in earnest the realization that the central nervous system (especially sympathetic pathways) play a role in the induction and maintenance of cardiac arrhythmias.

It is nearly 70 years since diseases of the nervous system were independently associated with cardiac changes. Neuberger [3] described scattered subendocardial hemorrhages in the hearts of patients who died during epileptic seizures. These individuals lacked other cardiac pathology and were innocent of cardiac symptoms. Five years later, Aschenbrenner and Bodechtel [4] showed that young patients with tumors in the region of the third ventricle, in the diencephalon and parietal lobe developed significant and lethal ventricular arrhythmias. Autopsy again revealed no significant cardiac findings.

These things remained virtually forgotten until 1960 when Cropp and Manning [5] reported on patients who developed ECG repolarization changes indicative of cardiac ischemia, in the context of subarachnoid hemorrhage. In many cases surgery was postponed, and fatal rebleeding occurred. Autopsy did not reveal coronary artery disease, but subendocardial hemorrhages as reported earlier by Neuberger [3]. A few years later, Greenhoot and Reichenbach [6] showed that similar cases were

associated with an expanded cardiac pathology, termed myocytolysis, in which scattered areas of ventricular muscle hemorrhage, monocytic infiltration and myocardial necrosis were seen. Intriguingly, these areas centered on nerves and not on blood vessels, further underlining a neural, rather than a humoral, basis for these cardiac changes. More recently, Kono et al. [7] showed that patients who developed ST elevation during the course of a subarachnoid hemorrhage had reduced cardiac contractility but normal coronary arteries.

It therefore seems highly likely that in the context of subarachnoid hemorrhage, cardiac structural, functional and electrophysiological abnormalities are independent of preexisting cardiac pathology. This conclusion is supported for subarachnoid hemorrhage alone by the data presented by Khechinashvili and Asplund in this volume [14]. Why then, has it been so difficult to identify similar cardiac associations with ischemic stroke? In their meta-analysis, Khechinashvili et al. identified a similar incidence of ECG repolarization changes (75%) in both unselected stroke patients (ischemic stroke and intracerebral hemorrhage) and in those without known cardiac disease. Their conclusion was that these changes were not specific for stroke, and were therefore likely related to concomitant cardiac disorders. Indeed the high incidence of ECG changes in studies from which symptomatic patients have been removed may relate to the high incidence of asymptomatic coronary artery disease in such patients. And herein lies the rub: the risk factors for stroke (ischemic and hemorrhagic) are similar to those for coronary artery disease. Additionally, there is only a limited range of

KARGER

Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2002 S. Karger AG, Basel
1015–9770/02/0142–0065\$18.50/0

Accessible online at:
www.karger.com/journals/ced

Stephen Oppenheimer, MD
PharmaNet Inc.
504 Carnegie Center
Princeton, NJ 08540 (USA)

Tel. +1 609 951 6632, Fax +1 609 520 8105, E-Mail soppenheimer@pharmanet.com

organ response to an insult: diverse etiologies may give rise to very similar expression (in this case ECG changes) so distinction between neurogenic and intrinsic cardiac causes may be difficult.

In the face of much evidence that brain damage can induce cardiac abnormalities how might this problem be best addressed? Firstly, look for sequences of ECG abnormalities evolving over time. The problem inherent in studies forming the basis of the metaanalysis reported by Khechinashvili et al. is that ECG data were obtained at various times after stroke onset and generally only on one occasion. Trends and patterns were not sought by the individual investigators. Next, continuous monitoring is likely to be more revealing than isolated ECG recordings obtained as they are from only a few minutes of data during a 24-hour period: significant abnormalities prejudicing survival will be underestimated. Indeed, it is cardiac arrhythmias, presaged by ECG repolarization changes and QT interval prolongation which prejudice survival. These were not reported in the current communication, and their examination may reveal differences between stroke patients with and without concomitant cardiac disease. Also, it is most likely the interaction between cerebral and preexisting cardiac pathology that will prove the most significant predictor of cardiac outcome; so studies must be structured to explore this.

There may be specific stroke locations which, embedded in the stroke group as a whole, are particularly prone to induce cardiac changes. Recent evidence points to the involvement of the insular cortex in cardiac regulation [8–12]. Indeed lateralization of cardiac autonomic regulation

has been shown in many species including man, with cardiac sympathetic tone predominantly regulated by right insular regions, and parasympathetic cardiac mechanisms regulated by the left insula [8, 9]. Several groups have indicated that insular involvement after stroke may be associated with cardiac arrhythmias in comparison with strokes in other locations [10–12].

The evidence therefore is strongly in favor of a direct effect of brain injury on cardiac physiology and structure. This is primarily evident in the case of subarachnoid hemorrhage, where patients are younger, less likely to have preexisting cardiac disease and there is multifocal damage to the central nervous system. In the case of ischemic stroke, dissection of changes due to cerebral injury from those due to preexisting disease is difficult since patients are older and the coincidence of cardiac pathology is high. There is likely to be an interactive effect between cardiac disease and lesions involving specific regions of the brain concerned with autonomic regulation, one such being the insula. Identification of these patients and the mechanisms involved in these cardiac irregularities is important: the commonest cause of death and new morbidity after stroke is from cardiac disease and may be unrelated to the severity of the event [13]. Therefore therapeutic intervention will be important and could improve functional morbidity and mortality outcomes. What we now need to know is not whether there are cardiac abnormalities occurring after ischemic stroke, but what stroke locations and what cardiac profiles particularly predispose to the risk of adverse outcome.

References

- 1 Levy AG: The exciting causes of ventricular fibrillation in animals under chloroform anaesthesia. *Heart* 1912;4:319–378.
- 2 Beattie J, Brow GR, Long CNH: Physiological and anatomical evidence for the existence of nerve tracts connecting the hypothalamus with spinal sympathetic centres. *Proc R Soc Lond (Biol)* 1930;106:253–275.
- 3 Neuberger K: Ueber die Herzmuskelveränderungen bei Epileptikern und ihre Beziehungen zur Angina pectoris. *Frankfurt Z Pathol* 1933; 46:14–19.
- 4 Aschenbrenner R, Bodechtel G: Ueber EKG Veränderungen bei Hirntumorkranken. *Klin Wochenschr* 1938;17:298–302.
- 5 Cropp GJ, Manning GW: Electrocardiographic changes simulating myocardial ischemia and infarction associated with spontaneous intracranial hemorrhage. *Circulation* 1960;22:25–38.
- 6 Greenhoot JH, Reichenbach DD: Cardiac injury and subarachnoid hemorrhage: A clinical, pathological, and physiological correlation. *J Neurosurg* 1969;30:521–531.
- 7 Kono T, Morita H, Kuroiwa T, Onaka H, Takatsuka H, Fujiwara A: Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: Neurogenic stunned myocardium. *J Am Coll Cardiol* 1994;24:636–640.
- 8 Oppenheimer SM, Gelb AW, Girvin JP, Hachinski VC: Cardiovascular effects of human insular stimulation. *Neurology* 1992;42:1727–1732.
- 9 Zhang ZH, Rashba S, Oppenheimer SM: Insular cortex lesions alter baroreceptor sensitivity in the urethane-anesthetized rat. *Brain Res* 1998;813:73–81.
- 10 Vingerhoets F, Bogousslavsky J, Regli F, Van Melle G: Atrial fibrillation after stroke. *Stroke* 1993;24:26–30.
- 11 Sander D, Klinghoffer J: Changes of circadian blood pressure patterns after hemodynamic and thromboembolic brain infarction. *Stroke* 1994;25:1730–1737.
- 12 Oppenheimer SM, Kedem G, Martin WM: Left-insular cortex lesions perturb cardiac autonomic tone. *Clin Auton Res* 1996;6:131–140.
- 13 North American Symptomatic Carotid Endarterectomy Trial Collaborators: Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade stenosis. *N Engl J Med* 1991;325:445–453.
- 14 Khechinashvili G, Asplund K: Electrocardiographic changes in patients with acute stroke: A systematic review. *Cerebrovasc Dis* 2002;14: 67–76.