Myocardial Damage from Acute Cerebral Lesions

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SUMMARY **Autopsy findings in 58 patients with intracranial lesions were compared with those in 50 control patients for myocardial damage, characterised by a change from a myofibrillar to a granular staining pattern, using a histochemical method for succinic dehydrogenase. Transmurally scattered foci of damaged myocardial fibres were significantly more common ($p<0.01$) in patients with intracranial lesions (62%) compared to controls (26%). No victims of sudden violent deaths showed these cardiac lesions.**

Focal myocardial damage required at least six hours to develop after onset of the acute neurological event and was not observed after the second week. It was associated with lesions producing a rapid increase in intracranial pressure and was usually absent in patients with slowly enlarging or small cerebral lesions. Similar myocardial changes were seen in patients in the control group dying from prolonged shock or other forms of acute circulatory or metabolic failure.

The postulated mechanism of cardiac damage in these patients is increased levels of plasma catecholamines secondary to rapidly increasing intracranial pressure, irrespective of the cerebral pathology.

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ELECTROCARDIOGRAPHIC (ECG) changes in patients with cerebral lesions were first described in 1938[1] and these findings were later confirmed by other workers.[2, 3] In acute stroke patients, evidence of myocardial damage was also found, including increased serum levels of cardiac enzymes,[4, 5] the occurrence of cardiac arrhythmias[6] and high levels of plasma catecholamines.[7] Focal myocytolysis was described at autopsy in 8–12% of patients dying from a variety of acute cerebral lesions.[8, 9] Since this secondary myocardial damage may indicate more widespread and subtle reversible cardiac changes, we undertook the present study using a more sensitive histochemical method to determine the frequency and extent of myocardial injury in stroke and other forms of acute cerebral lesions.

Materials and Methods

Consecutive complete autopsies supervised by the same pathologist in a general teaching hospital were performed within 36 hours of death. Death was due to an acute intracranial lesion in 58 patients and to non-cerebral causes, including a variety of heart diseases, in 45 patients. In five other patients, death was instant and due to a sudden violent cause, such as suicide.

The hearts were weighed, measured and transversely sliced through the ventricles. Transmural blocks of the left ventricular wall were obtained from the sites of attachment of the anterior and posterior papillary muscles and split horizontally for corresponding cryostat and paraffin blocks. If either of these sites was affected by necrosis or fibrosis, an additional transmural block was obtained from an apparently healthy segment of the ventricle. Cross-sections of the three major coronary artery trunks were collected for routine histology. Unfixed cryostat sections (8u) from each cardiac sample were stained with nitro-blue tetrazolium (NBT) to demonstrate succinic dehydrogenase (SDH) activity[10] and then microphotographed within three days of autopsy. Sections were stained in pairs to ensure uniformity and exclude artefacts, so avoiding false-positive results.

All muscle fibres in normal myocardium stain with the same intensity and pattern, irrespective of their location. Very fine granules of violet formazan of NBT are deposited between myofibrils, producing a 'myofibrillar' staining pattern[11] characteristic of normal myocardial fibres. Formazan granules in damaged fibres are coarse and irregularly distributed, producing a 'granular' staining pattern,[11] with a loss of outline of fine muscle fibre details (fig.1). Granular muscle fibres scattered individually or in groups through the central and external thirds of the left ventricular wall of both samples were considered to indicate transmural myocardial damage (TMD).

Corresponding halves of the blocks were fixed in neutral 10% formol, embedded in paraffin and stained with hematoxylin-eosin. Foci of myocytolysis, necrosis and small groups of mononuclears replacing dead muscle fibres were sought in these sections.

Brain was fixed in 10% neutral formol for at least 14 days and examined independently by a neuropathologist. The timing of the cerebral event was assessed clinically, and the pathological diagnoses, size and age of the lesion were correlated with myocardial findings. All cardiac sections were examined immediately and coded positive or negative for SDH changes without prior knowledge of the cerebral lesions. Student's t-test and X^2-test were used to compare groups for statistical significance.

Results

Multifocal transmural myocardial damage was significantly more frequent ($p < 0.01$) in patients with intracranial lesions than in the control group (table 1).

In the 38 stroke patients, the presence of TMD was apparently related to the size and duration of the lesion (table 2). In the 25 cerebral infarct cases, cerebral lesions were larger in the TMD-positive group than in the TMD-negative group but this difference was not significant. Since the size of the autopsy lesion does not include surrounding edema, more mass effect may have occurred than appeared. In 13 cerebral hemorrhage cases, where the size of the cerebral lesion is

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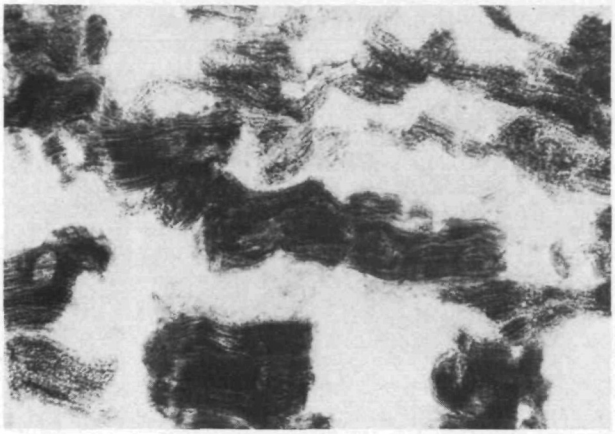

FIGURE 1. *Granular myocardial fibres seen mainly in upper third of picture; band of normal myocardium (myofibrillar staining) in centre. SDH method with nitro-blue tetrazolium, 600×.*

easier to determine, lesions were significantly larger ($p < 0.04$).

Patients die from cerebral infarction or hemorrhage within the first week mainly from the mass effect of cerebral edema or hematoma.[12, 13] This rapid manner of death (coning) may influence the presence of transmural cardiac lesions in the cerebral infarction group. Cardiac lesions were not seen in cerebral hemorrhage patients with brief (mean duration 9 hr) illnesses, presumably because they did not have time to develop cardiac damage.

All 14 non-stroke TMD-positive patients (table 1) also died from raised intracranial pressure, either acutely or as a terminal event in a chronic illness. In eight patients with subarachnoid hemorrhage and the one with acute purulent meningitis, death occurred from an acute intracranial complication, with a presumed increase in intracranial volume, such as hydrocephalus. In five TMD-positive patients with neoplasm, four died in coma, from a sudden increase in brain volume (hemorrhage into tumour in 3 cases and purulent encephalitis in the fourth) and the fifth died in status epilepticus. All five TMD-negative patients with neoplasm and the one patient with subarachnoid hemorrhage died of non-cerebral complications such as pneumonia.

In 13 TMD-positive controls (table 1), eleven had prolonged severe shock, one died of thyroid crisis and another of acute mitral incompetence. Six patients with significant heart disease, including hypertension and recent or healed myocardial infarction, had no evidence of TMD. Age, sex, heart weight, degree of coronary narrowing and presence of healed myocardial infarctions were unrelated to SDH changes.

Infrequent and inconspicuous dead muscle fibres were found in six patients with intracranial lesions (2 intracerebral hemorrhages, 1 astrocytoma, 3 subarachnoid hemorrhages) and in the patient dying of thyroid crisis. Histochemically demonstrated myocardial damage was more conspicuous and extensive than the few dead myocardial fibres found in the paraffin sections of these seven cases.

Discussion

Transmurally scattered foci of myocardial injury were found in patients dying from acute intracranial lesions large enough to produce acutely increased intracranial pressure, such as intracranial bleeding, meningitis or massive ischemic edema. These cardiac lesions were not seen in patients with slowly progressive intracranial tumours, unless additional factors such as

TABLE 1 *Incidence of Transmural Myocardial Damage (TMD) in Patients Dying of Brain Lesions, Compared to Control Groups*

	Brain lesion group						Control group		
TMD	SAH	ICH	Inf	Neo	AcM	Total	Hospital	Sudden death	Total
Positive	8	9	13	5	1	36	13	0	13
Negative	1	4	12	5	0	22	32	5	37
Total	9	13	25	10	1	58	45	5	50

SAH = subarachnoid hemorrhage; ICH = intracerebral hemorrhage; Inf = brain infarct; Neo = neoplasm; AcM = acute purulent meningitis.

TABLE 2 *Size of Lesion and Duration of Stroke in 38 Patients with (TMD+) and without (TMD−) Transmural Myocardial Damage*

	Patients (number)	Mean size of lesion (range)	Mean duration of stroke (range)
Cerebral infarction			
TMD+	13	6.5cm (3–10)	6 days† (0.3–11)
TMD−	12	4.1cm (1–10)	24 days (3–49)
Cerebral hemorrhage			
TMD+	9	8.6cm* (3–30)	20 hours (7–48)
TMD−	4	2.8cm (2–5)	9 hours (2–24)

*$p < 0.04$.
†$p < 0.004$.

hemorrhage into a tumour or inflammatory edema superimposed an acute rise in intracranial pressure (tables 3 & 4).

The granular staining pattern characterising damaged myocardial fibres requires several hours to develop under experimental conditions and then slowly dis-

TABLE 3. *Transmural Myocardial Damage in Patients with Cerebral Infarcts and Hemorrhages*

Patient No.	Age	Size of lesion	Duration of symptoms	Transmural myocardial damage	Notes
Infarcts					
1	68	multiple cortical	4 days	positive	septic shock
2	83	6cm	2 days	positive	
3	88	6cm	44 hours	positive	
4	75	multiple cortical	8 hours	positive	septic shock
5	88	5cm	16 days	positive	fresh hemorrhage into infarction
6	92	3cm multiple	24 hours	positive	
7	92	3.5cm	8 days	positive	old MI
8	78	6cm	5 days	positive	
9	62	multiple cortical	24 hours	positive	septic shock
10	69	5.5cm	11 days	positive	
11	74	7cm	10 days, 44 hours	positive	recent extension
12	88	2.5cm 1.5cm	5 days	positive	
13	55	3cm 5cm	17 days	positive	larger infarct more recent
14	77	5cm 2cm	32 days 6 days	negative	
15	71	6cm	47 days	negative	old MI
16	53	1cm	10 days	negative	
17	89	multiple cortical	49 days	negative	old MI
18	79	1.5cm	3 days	negative	old MI
19	65	1cm	35 days	negative	old MI
20	84	multiple 0.5mm	13 days	negative	old MI
21	87	3×2cm	25 days	negative	old MI
22	68	1.5cm	18 days	negative	
23	80	extensive cortical	16 days	negative	old MI
24	80	1.5cm	12 days	negative	
25	84	6cm	27 days	negative	
Hemorrhages					
1	72	multiple 5cm	17 hours	positive	
2	72	1.5×2cm	14 hours	positive	
3	75	4.5cm	9 hours	positive	
4	65	3cm	48 hours	positive	
5	80	5cm	12 days	positive	two stages
6	60	5×6cm	20 hours	positive	
7	92	5cm	7 hours	positive	
8	29	7cm	20 hours	positive	
9	23	5cm	23 hours	positive	
10	62	0.3×0.5cm	6 hours	negative	
11	61	2cm	2 hours	negative	
12	82	4cm	3 hours	negative	bilateral lesions
13	80	5cm	24 hours	negative	

TABLE 4. *Transmural Myocardial Damage in Patients with Intracranial Tumours*

Patient No.	Age	Neuropathological findings	Clinical progress	Transmural myocardial damage
1	68	multiple acute hemorrhages into secondary Ca	sudden coma	positive
2	21	astrocytoma purulent encephalitis	sudden coma	positive
3	70	astrocytoma massive hemorrhage	sudden coma	positive
4	62	multiple myeloma	status epilepticus	positive
5	59	astrocytoma	severe hypoglycemic attacks	positive
6	77	astrocytoma	slow	negative
7	50	astrocytoma	slow	negative
8	79	secondary carcinoma	slow	negative
9	59	secondary carcinoma	slow	negative
10	30	histiocytosis X	slow	negative

appears[14] but the exact timing and evolution of the cerebral lesions and its effect on the myocardium is more difficult to determine clinically. The cardiac lesions were not seen earlier than six hours after the acute cerebral event, nor later than two weeks, unless a new event occurred. They appear to be transient, and are not found if the patient survives longer than two weeks, though some may progress to myocytolysis. The size of the cerebral lesion was also important, since lesions smaller than 2cm did not produce myocardial lesions unless systemic shock was also present.

Myocardial damage was absent in victims of sudden violent death and in the majority of hospital control patients, including those with left ventricular hypertrophy or severe coronary heart disease. Neither hypertrophic myocardium nor heart muscle in the vicinity of scars and fresh infarction contained these lesions unless there were complicating factors, such as prolonged metabolic or circulatory failure.

Compared to the rarity of myocardial myocytolysis[8] and fuchsinophilia,[9] TMD appears to be more extensive and may constitute the morphological basis of the functional cardiac abnormalities observed in stroke. While myocytolysis implies destruction of myocardial fibres, TMD may represent reversible myocardial damage.[14] As the mechanism of this change depends on the accumulation of minute quantities of neutral fat in the muscle fibres, and not on mitochondrial or enzyme destruction, it could serve as 'a very sensitive index of myocardial alteration.'[11] Permanent changes are probably rare since most affected fibres appear to recover.

Increased levels of plasma catecholamines could be the common factor producing these myocardial effects in patients with acutely raised intracranial pressure or systemic shock.[15, 16] Experimentally, elevation of intracranial pressure produces a surge of plasma catecholamines.[16] In both experimental and clinical observations catecholamines may produce cardiac necrosis or histochemical changes similar to those described in this series.[14, 17–20] Increased levels of plasma catecholamines have been demonstrated in patients with acute stroke,[7] and cardiac damage in experimental intracerebral hemorrhage can be prevented by prior adrenalectomy or beta-adrenergic blockade.[21, 22]

These myocardial changes may represent a harmless epiphenomenon of acute intracranial lesions though there is evidence[23] to suggest that serious myocardial dysfunction may result.

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