PAPERS AND ORIGINALS

Stroke after acute myocardial infarction: relation to infarct size

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Summary and conclusions

In a consecutive series of 783 patients with acute myocardial infarction, 13 (1.7%) suffered a stroke. In all but one case the strokes occurred among the 255 patients whose peak creatine kinase (CK) concentrations fell in the upper third of the range of values (over 1160 IU/l, about eight times the upper limit of normal); the exception was a patient with a pre-existing ventricular aneurysm. The incidence of stroke in the patients with CK over 1160 IU/l was 4.7%, 24 times the incidence when peak CK was below this value (0.2%). Higher peak serum enzyme concentrations were associated with an even higher incidence of stroke. Comparison of peak enzyme concentrations with cumulated CK showed a close correlation ($r=0.90$ with peak CK; $r=0.85$ with peak aspartate transaminase), suggesting that the peak enzyme values reflected infarct size.

Thus the risk of stroke after infarction was a function of the size of the myocardial infarct; two-thirds of the patients had negligible risk of stroke and did not need anticoagulant prophylaxis.

Introduction

Stroke complicating myocardial infarction may have disastrous and long-lasting effects. In controlled clinical trials short-term anticoagulants effectively reduced the incidence of this complication.^{1,2} Nevertheless, there is reluctance to expose every patient with infarction to the risk of anticoagulants to prevent a complication that has a relatively low incidence. It is therefore important to try to identify the patient most likely to benefit

from anticoagulants. Russek³ suggested that patients at high risk of thromboembolic complications could be identified from clinical indices of the severity of infarction. A recent report indicated that measurement of the plasma fibrinogen concentration would identify patients at high risk of developing thromboemboli including stroke.⁴ Measurement of plasma fibrinogen, however, entails a laboratory test that is not routine for patients with myocardial infarction.

The results of the following study indicate that routine daily serum enzyme estimations simply and reliably identify patients at high risk of having a stroke and suggest that stroke is a complication of large infarctions only.

Patients and methods

During January 1973 to December 1976, 783 patients with definite (WHO criteria⁵) acute myocardial infarction were admitted to the coronary care unit at this hospital. On admission each patient had data recorded on a standard form and filed in a digital computer; serum enzyme concentrations were recorded daily for three to five days after admission in each case. Patients were examined daily and complications noted as they occurred. Patients were managed in a single coronary care ward, progressing from standard intensive coronary care to early ambulation and rehabilitation and discharge on the 10th-14th day.

"Stroke" was recorded when there was an acute development of neurological signs that had not been present on admission. Episodes in which the signs disappeared or substantially improved within 48 hours were not included. Serum enzymes were measured on an AutoAnalyzer, the method of Siegel-Cohen⁶ being used for creatine kinase (CK) and that of Morgenstern *et al*⁷ for aspartate transaminase (serum AST; SGOT). The normal range for CK was 25-130 IU/l and for AST 6-40 IU/l.

Altogether 119 patients had cumulated CK measured in samples taken at two-hour intervals via a catheter inserted into the superior vena cava; cumulated CK was estimated from the Shell-Sobel formula,^{8,9} using an average kd value of 0.06/hour, and correlated with the peak of the daily serum enzyme estimations.

Results

Of the 783 patients, 13 suffered a stroke while in hospital (table I), 10 in the first week, two in the second week, and one in the third week; 7 (54%) died. Stroke was a major cause of delayed recovery

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after infarction, the six survivors having hospital stays of 22-254 days, occupying 432 bed-days—equivalent to the number of bed-days occupied by 30 patients with uncomplicated myocardial infarction. Three of the survivors were left with severe neurological defects. All but one of the 13 patients had transmural infarction with greatly increased serum enzyme concentrations, the exception (case 13) being a patient with a previous history of two myocardial infarctions and clinical evidence of ventricular aneurysm.

INCIDENCE OF STROKE AND PEAK ENZYME VALUES

Tables II and III show the incidences of stroke in relation to the peak CK concentrations. Figures are given separately for patients admitted before and after mid-1975, when routine selective anticoagulation (see below) was introduced, and for the whole four-year period.

Patients admitted before mid-1975—Among the 490 patients admitted before July 1975 the incidence of stroke was 1.8% (9 cases). When patients were ranked by their peak CK values the incidence was zero (0/320) in the lower two-thirds compared with 5.6% (9/160) in the upper third (table II). When patients were ranked by multiples of the upper limit of the normal range ($\times N$) of peak CK the incidence of stroke was zero (0/271) when peak CK was less than $8 \times N$ (< 1040 IU/l) compared with 4.3% (9/209) when peak CK was greater than $8 \times N$ (table III).

Total series—The incidence of stroke during the whole four-year period was 1.7% (13/783). In the lower two-thirds of peak CK concentrations the incidence was 0.2% (1/512) compared with 4.7% (12/255) in the upper third (table II). When peak CK was less than

$8 \times N$ the incidence was 0.2% (1/475) compared with 4.1% (12/292) when peak CK was greater than $8 \times N$ (table III). All these differences were highly significant ($P < 0.001$). Similar differences in the incidence of stroke were noted in relation to the peak serum AST concentrations. For the whole four-year period the incidence was 0.4% (2/512) when the peak AST was in the lower two-thirds of values (≤ 220 IU/l) compared with 4.3% (11/255) when in the upper third (> 220 IU/l); and 0.4% (2/481) when peak AST was less than $5 \times N$ (< 200 IU/l) compared with 3.8% (11/286) when peak AST was greater than $5 \times N$. These differences were also highly significant ($P < 0.001$).

EFFECT OF SELECTIVE ROUTINE ANTICOAGULATION

After case 9 (mid-1975) routine anticoagulation with heparin and warfarin for every patient with peak CK exceeding 1000 IU/l was begun. Subsequently two strokes occurred in patients receiving anticoagulants—one (case 10) had a ventricular aneurysm as a result of a previous infarction, and one (case 11) had extensive infarction with cardiogenic shock and prolonged hypotension. In case 12 the patient was not anticoagulated because of an incorrect laboratory report. Case 13, the only patient to suffer a stroke when peak enzyme values indicated a small infarction, is described above.

NECROPSY FINDINGS

Postmortem examination was performed on five patients (cases 1, 4, 6, 8, and 10). Typical extensive recent transmural myocardial infarction was present in all. In four cases there was endocardial

TABLE I—Details of patients with stroke complicating myocardial infarction (MI)

Case No	Age (years)	No of previous MIs	ECG*		Peak CK (IU/l)	Peak AST (IU/l)	Day of stroke	Duration of hospital stay (days)	Outcome	Residual defect
			Location	Extent						
1	72	1	INF-LAT	TM	1200	185	6	10	Dead	None
2	68		INF-LAT	TM	3500	560	2	22	Alive	
3	68		BBB		3500	900	1	4	Dead	
4	71	2	ANT-LAT	TM	1900	370	3	14	Dead	None
5	72		INF	TM	2750	470	13	22	Alive	
6	53		ANT	TM	2550	275	6	8	Dead	
7	76	1	ANT-LAT	TM	1480	330	2	51	Alive	Aphasia, hemiplegia
8	37	1	ANT	TM	2490	540	5	5	Dead	
9	64		ANT	TM	1200	530	18	31	Dead	
10	68	1	ANT-LAT	TM	2000		5	20	Dead	None
11	53	1	ANT	TM	3450	400	4	41	Alive	
12	66		ANT-LAT	TM	2700	350	7	42	Alive	
13	72	2	ANT	NTM	280	70	3	254	Alive	Aphasia, hemiplegia

*INF = Inferior. ANT = Anterior. LAT = Lateral. BBB = Bundle-branch block. TM = Transmural. NTM = Non-transmural.

TABLE II—Incidences of stroke in patients with peak serum creatine kinase (CK) concentrations in lower, middle, and upper thirds

Peak CK by thirds	Jan 1973 to June 1975*		July 1975 to Dec 1976		All patients (Jan 1973 to Dec 1976)	
	No of patients	No (%) with stroke	No of patients	No (%) with stroke	No of patients	No (%) with stroke
Not estimated	10		6		16	
Lower third (80-470 IU/l)	160		96	1 (1.0)	256	1 (0.4)
Middle third (471-1160 IU/l)	160		96		256	
Upper third (1161-7800 IU/l)	160	9 (5.6)	95	3 (3.2)	255	12 (4.7)
Total	490	9 (1.8)	293	4 (1.4)	783	13 (1.7)

*Period before June 1975 was before selective routine anticoagulation was introduced.

TABLE III—Incidences of stroke in relation to peak serum creatine kinase (CK) concentrations expressed in multiples of upper limit of normal range

Peak CK by multiples of upper limit of normal (N) (range in IU/l)	Jan 1973 to June 1975*		July 1975 to Dec 1976		All patients (Jan 1973 to Dec 1976)	
	No of patients	No (%) with stroke	No of patients	No (%) with stroke	No of patients	No (%) with stroke
Not estimated	10		6		16	
$< 4 \times N$ (≤ 520)	182		138	1 (0.7)	320	1 (0.3)
$4-8 \times N$ (521-1040)	89		66		155	
$8-12 \times N$ (1041-1560)	93	3 (3.2)	42		135	3 (2.2)
$12-16 \times N$ (1561-2080)	51	1 (2.0)	22	1 (4.5)	73	2 (2.7)
$> 16 \times N$ (> 2080)	65	5 (7.7)	19	2 (10.5)	84	7 (8.3)
Total	490	9 (1.8)	293	4 (1.4)	783	13 (1.7)

*Period before June 1975 was before selective routine anticoagulation was introduced.

mural thrombosis; in three the cerebral artery obstruction was definitely embolic.

OTHER THROMBOEMBOLIC EVENTS

During the four years there were five cases of clinically evident deep vein thrombosis and two of systemic non-cerebral embolism; all showed peak CK greater than eight times normal (>1040 IU/l) and all occurred before routine selective anticoagulation was begun. In view of the difficulties in diagnosing pulmonary embolism in the presence of acute myocardial infarction figures are not available for the frequency of this complication.

PEAK ENZYME VALUES AND CUMULATED CK ("INFARCT SIZE")

In the 119 patients whose peak serum enzyme concentrations were correlated with the cumulated CK estimated from two-hourly samples the coefficient of correlation was 0.90 ($P < 0.001$) with peak CK and 0.85 ($P < 0.001$) with peak AST.

Discussion

In this series stroke complicating myocardial infarction was confined almost exclusively to the one-third of patients with the highest serum enzyme concentrations and transmural infarction. An association between high serum enzyme concentrations and thromboembolism after myocardial infarction has been noted before, a strong association being found with AST² and, more recently,⁴ an association being reported with peak CK. We have presented additional evidence that the reason for this association is that high serum enzyme concentrations reflect extensive myocardial necrosis. The estimate of total CK release, which reflects infarct size in animals⁸ and patients dying of myocardial infarction,¹⁰ correlated remarkably well with the peak daily serum enzyme concentrations, indicating that these are clinically useful for estimating infarct size despite the theoretical disadvantage of the peak value⁹ and the wide sampling error in daily estimations.

The mechanism of the relation between extensive infarction and the risk of stroke is speculative. Clearly extensive endocardial damage in a transmural infarction increases the risk of thrombus formation with subsequent embolisation, but this mechanism was proved in only three of our cases. It is equally likely that the generalised disturbances of coagulation that accompany infarction are worse with major infarctions; indeed, we found that the five cases of unequivocal deep vein thrombosis were confined to patients with high serum enzyme concentrations. Fulton and Duckett⁴ found that the abnormalities of plasma fibrinogen after infarction paralleled the serum enzyme

values. They showed that the plasma fibrinogen concentration was an accurate indicator of the risk of thromboembolism and suggested that it be used clinically for this purpose. Our study shows that the peak serum enzyme concentrations, which are measured routinely in most hospital-treated patients with acute myocardial infarction, serve the same purpose without the need for an additional laboratory test. The data on the results of routine heparin and warfarin administration are presented not as evidence that the risk of stroke may be reduced by anticoagulants but as an example of a logical policy of prophylaxis for high-risk patients; convincing evidence that short-term anticoagulants reduce the incidence of stroke after myocardial infarction is available from at least two large-scale controlled trials.^{1,2} It may be concluded that stroke after myocardial infarction is a function of infarct size, being a complication almost exclusively of major infarction; infarct size may be estimated from the peak serum enzyme concentrations, and the number of patients requiring anticoagulants aimed at preventing stroke may be reduced by two-thirds.

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ONE HUNDRED YEARS AGO A highly educated and very sensible lady, well known to me, having for many years been a governess in a family in the midland counties on whose regard she had acquired a very strong hold, becoming the subject of severe occasional pains in the hip-joint, was coddled and petted in every possible way. The pains in time became so constant, that she passed her days almost entirely on the sofa, and never went out of doors except in a carriage. She and her friends were strongly under the impression that she was the subject of serious disease of the hip-joint; but she shrank from any surgical examination of it. Month after month passed without any decided change, either for the better or worse; and at last she yielded to my urgent representation that she should come up to town, on the promise that I would get for her a first-rate surgical opinion, in which she might place the most implicit confidence. That opinion was exactly what I expected. She was assured that there was nothing serious the matter; that she was not to mind the pain, but take moderate exercise, and do everything she could for the re-invigoration of her general health; and that in no very long time she would be "all right" again—which soon came to pass.—Again, one of my earliest friends came to town a few years ago for the removal of a scirrhus breast by Sir James Paget. She

was domiciled in her brother's house; and her sister-in-law, a lady of most excellent sense, but of a delicate, sensitive temperament, nursed her with the most sympathising care. On going to inquire after my old friend, I was consulted by her sister-in-law about herself. "I have been lately suffering," she said, "from pains in the same part, which made me so seriously uneasy, that I spoke to Paget; and he, finding that you were intimate with us, referred me to you." At once divining from this reference what Sir James meant, I explained to her that her pains simply proceeded—according to a well-known law of our constitution—from the very natural direction of her attention to the part; and that if she would dismiss from her mind all anxiety about them, they would soon cease to trouble her. This, also, speedily came to pass. Now if, instead of speaking out her trouble, my friend had gone on brooding over it in secret, I have very little doubt that some local disorder would have shown itself; for the truth of Sir Henry Holland's remark, that the strong and continued direction of the attention to a part, in all probability affects either its innervation or its circulation, or both, has been abundantly proved by the results of Mr Braid's experiments. Of that influence, the vasomotor system of nerves appears to me the most probable channel. (*British Medical Journal*, 1878.)