Commentary

Intracerebral haemorrhage revisited

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Summary

Much evidence suggests that acute intracerebral haemorrhage usually starts to appear an hour or two after a thromboembolic brain infarct. Intravenous thrombolytic treatment is accepted treatment for acute ischaemic stroke; but all neurologists concur that brain imaging should be performed first, so that thrombolysis can be avoided if bleeding has already started. This article calls into question the current guidelines for the use of thrombolytic treatment in acute stroke. Are they too restrictive?

Introduction

Many physicians assume that acute bleeding into the substance of the brain—intracerebral haemorrhage (ICH)—occurs because arterial hypertension has overstretched and ruptured previously normal blood vessels. But in 1926, Lampert and Müller reported that at necropsy, they could not rupture normal human cerebral arteries of any size by increasing intravascular pressure.1 Arteries were usually forced off the cannula rather than splitting, unless they were already obviously diseased. Although so-called ‘Charcot-Bouchard’ microaneurysms have been thought to cause acute ICH in man, an electron micrographic study only identified two microaneurysms amongst 61 hypertensive patients with ICH.2 Most apparent microaneurysms have been identified as injection artifacts caused by arteriolar coils and twists. These can only be seen clearly when thick brain sections are examined by special endothelial staining techniques.3

Fifty years ago I was driven to think about the cause of ICH by some unexpected but intriguing results thrown up by a human necropsy study. In the post-mortem room of the Middlesex Hospital, Drew Thomson and I tried to find whether stenotic disease of the main cerebral arteries might be the cause of ‘essential’ hypertension. We suspected that the long course of the vertebral and internal carotid arteries in the neck could contribute a significant resistance to blood flow, especially when diseased. This would require a rise of systemic arterial pressure to preserve normal flow to the brain.

In 94 cadavers, we cannulated the origins of these four arteries and cut the arteries across at their terminations within the skull. After relaxing all post-mortem arterial spasm with 5% aqueous ammonia, we perfused with water the full lengths of both vertebral and both internal carotid arteries. We recorded (with a stopwatch and measuring jug) the maximal flow rates obtainable from each main artery, perfused from a high reservoir supplying a constant 140 mmHg pressure at each artery’s origin. Water flowed freely out of the cut ends of each artery, at atmospheric pressure. By adding together the maximal flow rates obtained from each of the four cerebral arteries, we arrived at a value that was a crude estimate of the total fluid-carrying capacity of these vessels in their course through the neck and skull base of each subject. Individual values ranged between 21.0 and 111.9 ml/s in our system. The lowest flow rates were in arteries with extensive atheromatous stenoses of the neck vessels.

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I do not apologise for revisiting this old study. It would be impossible to repeat or extend today, being done at a time when adequate necropsies were routinely and regularly carried out in teaching hospitals. Drew and I were able to publish full tables of all our raw data, which included the dimensions of each cannula used, the individual flow rates obtained for each artery and relevant clinical details of all subjects. Our data also included values for ante-mortem blood pressure, independently obtained from the hospital notes, of people who were not, at that time, receiving hypotensive drugs.

Atheromatous lesions of the neck arteries must have substantially increased blood flow resistance during life. In our crude measuring system, the mean±SEM summated flow rate for the four cerebral arteries of 30 previously normotensive individuals with macroscopically normal brains was 25.2±2.7 ml/s (range 61.3–113.8). In 17 former patients with uncomplicated ‘benign essential’ hypertension (blood pressure > 1.50/90 mmHg) it was much lower: 68.1±2.5 ml/s (range 44–91.5). Our summated flow rates, measured after death, obviously could not relate directly to blood flow or vascular resistance during life, but they were highly significantly (inversely) related to ante-mortem blood pressure readings, previously and independently recorded in the hospital notes. The investigation was compatible with our hypothesis that the cause of ‘essential’ hypertension could be neurogenic—an adaptation by the brain to overcome increased large cerebral artery resistance. I developed this idea later, in two monographs 25 years apart. It has not so far been disproved.

**Necropsy observations on strokes**

In 28 of our cadavers, there was unequivocal macroscopic evidence of cerebral infarction (CI), with no obvious precipitating cause other than thrombo-embolic or stenotic arterial disease. The mean±SEM sum of the flow rates for the main cerebral arteries of these subjects was 50.5±2.9 ml/s (range 21–77.5). We also made measurements in 16 cadavers with macroscopically visible intracerebral haemorrhage, in whom there was no evident cause other than benign phase hypertension and arterial disease. The mean±SEM summated flow rate in these subjects was 47.8±1.9 ml/s (range 34–68.1). The effective fluid-carrying capacity of both groups was much less than that of non-stroke patients, but there was no significant difference between the two groups of stroke patients (0.5 < p < 0.6). (I have omitted consideration of cases in our series with manifestly different and specific causes of cerebral haemorrhage: two with subarachnoid haemorrhage and three with malignant phase hypertension with focal arteriolar necroses).

In another (separate) investigation we looked at 335 consecutive Middlesex Hospital necropsy records of people who had died with strokes. In 10% of cases, infarcts and haemorrhages were both present. The heart weights of all subjects had been independently recorded by the post-mortem room technicians. For each sex, the mean heart weights were the same for those with infarcts and for those with haemorrhages: 0.7 < p < 0.8 for men, and 0.2 < p < 0.3 for women. Many reports in the last 50 years confirm that preceding ischaemic damage usually underlies intracerebral bleeding. A recent review of the contribution of hypertensive small vessel disease to stroke emphasized the contribution of fibrinoid necrosis to ICH as well as to lacunar infarcts, but admitted that lacunar infarcts often appeared distal to ‘small vessel atherosclerosis’ with occlusive lesions of small penetrating arteries. The appearance of microbleeds preceding frank ICH does not rule out their essentially ischaemic causation.

The ischaemic origin of intracerebral haemorrhage has been confirmed in an entirely different way by a genetic study of the common forms of stroke, in which ICH, CI and transient ischaemic attacks were lumped together. This study identified a stroke susceptibility gene at 5q21, which the authors named ‘STRK1’. It was associated with the common forms of stroke, with a highly significant lod score of 4.4. A commentator regarded this as extraordinary for ‘what intuitively should be two distinct pathological processes—but it is precisely what would be expected if all ‘common forms of stroke’ have the same cause: that is, a restricted cerebral blood supply. It is noteworthy that in the stroke-prone hypertensive rat(SHRSP) the incidence of brain haemorrhages and infarcts is of a similar order.

**The probable sequence of events after acute cerebral artery occlusion**

There must obviously be a time gap between an acute cerebral artery occlusion and the appearance of symptoms, and before blood vessel walls as well as neurones are irretrievably dead. When human intracranial arteries were temporarily occluded during saccular aneurysm surgery under neurosurgical anaesthesia, there were only 5% of infarcts after 19 min, but all patients with complete arterial occlusions of 31 min or more suffered infarcts.
Middle cerebral artery occlusion in awake monkeys caused microscopic focal infarcts after 15–30 min, and infarcts large enough to cause paralysis were seen after 2 h. Temporarily common carotid artery occlusion in rats seldom infarcted the brain after 30 min, but invariably did so after 90 min. Some of these time intervals could be longer if arterial obstruction is incomplete; and ischaemic preconditioning may also limit ischaemic damage.

The only beneficial treatment of ischaemic strokes is to dissolve the clot with intravenous (IV) tissue plasminogen activator (tPA), but only between 1% and 5% of acute ischaemic stroke patients get this treatment. Clinical diagnosis of stroke type is difficult. Scanning all stroke patients by computer tomography (CT) before beginning treatment is cost-effective because it enables immediate sorting of strokes/non-strokes and ischaemic/haemorrhagic strokes into appropriate treatment bins, but necessarily introduces delay. A commonly accepted clinical guideline suggests that once bleeding has been excluded by imaging, intravenous thrombolysis is worth giving within 3 h after a completed stroke. This guideline seems to me unduly optimistic—even if we allow for an ischaemic penumbra in which ischaemic neurones stop working but are not yet dead.

How soon does bleeding start after a cerebral infarct? How much does thrombolysis affect it?

In dogs with experimental thalamic infarction, red cells began to leak from capillaries and infarcts large enough to cause paralysis were seen after 2 h. Temporary common carotid artery occlusion in rabbits subjected to small venules after 2 h, but there was no early red cells began to leak from capillaries and infarcts in dogs with experimental thalamic infarction. How soon does bleeding start after a cerebral infarct? How much does thrombolysis affect it?

In rabbits subjected to 2 h of halothane-induced hypotension combined with middle cerebral artery occlusion, followed an hour later by IV streptokinase, there was no significant intracerebral bleeding. In another investigation, rabbits were injected with autologous thrombi, to block major cerebral arteries, then given IV tPA within 30 min to 4 h. This caused no significant intracerebral bleeding. In another rabbit study, IV thrombolysis of brain infarcts with recombinant tPA alone, or with tPA plus heparin, appeared ‘relatively safe’, although aspirin pretreatment increased the risk of haemorrhage. In awake baboons, a 3 h occlusion of the middle cerebral artery, followed by 30 min reperfusion, regularly produced petechial infarcts, but IV rTPA (at doses between 0.3 and 10 mg/kg) did not increase either the incidence or severity (volume) of haemorrhage ‘when given early (≤ 3.5 h) after the onset of focal cerebral ischemia’. There is no animal evidence that immediate thrombolysis of acute cerebral artery occlusions risks producing intracerebral haemorrhage within the first hour of an arterial obstruction. Serious bleeding evidently takes longer than this. But early thrombolysis could obviously be dangerous when blood vessels—veins as well as arteries in an infarcted area—are already diseased and weakened. How often is this the case in man? We simply do not know. In 1992, a pilot study was published of 74 selected patients with acute stroke, diagnosed as ischaemic by CT, then treated with IV rtPA 0.35 to 1.08 mg/kg, infused over 60–90 min, starting within 90 min of the event. This remarkable study deserves to be called ‘classic’. No patient given less than 0.85 mg/kg tPA bled significantly, but three given higher doses developed a ‘hematoma’ with neurological deterioration. ‘When administered very early after symptom onset, IV rtPA was relatively safe with regard to hemorrhagic complications’. Treatment delays between 1.5 and 3 h increased the risk of haemorrhage.

Intravenous tPA or streptokinase has been given to many thousands of patients with acute myocardial infarcts. In England, 58% of patients currently receive thrombolytic treatment by paramedics within 60 min of calling for professional help, and 83% of eligible patients are given this treatment within 30 min of arriving at hospital. In this context neither tPA nor streptokinase provoke more than 1% of intracerebral bleeds. But there may be a higher incidence of bleeding than this when tPA is given to people with ischaemic strokes. If bleeding has already begun, thrombolysis will make it worse. Thrombolytic drugs are not intentionally infused intravenously into anyone known to be bleeding into the brain, although they have been locally infused into established clots to reduce their size. In acute stroke in man, immediate thrombolysis is everywhere regarded as too dangerous to consider; bleeding must first have been excluded by brain imaging. Bleeding may also appear after IV rtPA, even when it has not been previously seen, although the study cited above suggests that it may not do so within the first 90 min. But in a recent German study of 300 consecutive ischaemic stroke patients (diagnosed by imaging) and treated with intravenous rtPA within 3 h, the drug had to be stopped because of suspicion of bleeding into the brain in three cases. Two days later, 11.3% of patients had ‘haemorrhagic infarcts’.

In 1995, the reporters of the European Cooperative Stroke Study (of 620 patients) concluded that there were so many haemorrhagic complications...
that IV thrombolysis with recombinant tissue plasminogen activator ‘cannot be recommended for use in an unselected population of acute ischemic stroke’.17 This gloomy verdict has been only slightly modified since. In a Cochrane review of 18 trials involving 5727 patients, half of whom were treated with rtPA, there was an ‘overall small benefit’ in functional recovery, although there was also an increase in both early and late deaths.34 Getting stroke patients quickly to imaging centres is difficult. On an event-to-treatment time scale extending to 6 h, the chance of a favourable clinical outcome at 3 months after a stroke decreases as the event-to-treatment time lengths.35

The available evidence suggests that significant bleeding is unlikely to begin within the first hour after a cerebral infarct. Is it ever possible to start IV thrombolysis within this time? Would this prevent later bleeding? The available animal and clinical evidence suggests that giving IV tPA to an acute stroke patient within 60 min after the event gives a good chance of saving neural function if the stroke is thromboembolic, and might not risk precipitating intracerebral haemorrhage even in patients already taking aspirin. However, managing acute stroke in this way has never been done—or if it has, it has not been reported.

A stroke may be due to a brain tumour or to subarachnoid or subdural bleeding. How serious would early thrombolysis be in such conditions? We do not know. The clinical presentation of subarachnoid haemorrhage (SAH) is usually different from other forms of stroke. It is curious that anti-thrombolytic or anti-fibrinolytic drugs do not help patients with SAH. A 2003 update of a Cochrane review of nine trials involving 1399 patients suggested that anti-fibrinolytic therapy for SAH had no beneficial effect on the risk of death, vegetative state or severe disability. Rebleeding was reduced, but ischaemic damage increased.36 The comprehensive failure of anti-fibrinolysis even raises the possibility that thrombolysis itself might have little overall effect on SAH if the drug were to be given by mistake.

Has acute thrombolysis a realistic place in the therapy of stroke?

It will not have escaped the notice of my readers that I have been presenting arguments against our current therapeutic guidelines for the use of intravenous thrombolysis in acute stroke. These guidelines seem to me unduly optimistic. There is no realistic possibility, in any country of the world, that significant numbers of patients with acute strokes can have their brains imaged and be given intravenous rtPA within 60 min of the event—which is what is needed to make a real difference to outcome. Three hours is the currently approved upper time limit for IV thrombolysis. But immediate, or at least, very rapid thrombolytic treatment for acute stroke without imaging might be possible in several situations: in the home by a general practitioner, in the workplace or in the ambulance by paramedic personnel, or in the accident and emergency department of any hospital, however small. In the developed world, many people suffering strokes during daylight hours could receive immediate IV thrombolysis. Designing a controlled clinical trial to test this approach would clearly present formidable ethical difficulties,37 but it is not impossible. It might at least be worth discussing. Obtaining prior agreement for acute thrombolysis in a series of at-stroke-risk patients might succeed in some situations, at some times and in some places in which early CT imaging was not available. But a bad acute stroke is an emotional and physical catastrophe for a previously fit individual. It is widely recognized as such by many intelligent people, who might be persuaded by carefully-presented and honest arguments to allow themselves to participate in a trial.

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References


