Brain attack: needing resuscitation

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ABSTRACT

The brain is extremely susceptible to focal ischaemia. Following vascular occlusion, a core of severely damaged brain tissue develops, surrounded by an ischaemic penumbra. This potentially-salvageable penumbra may be estimated by advanced neuroimaging techniques, particularly by diffusion-perfusion mismatch. Clinical trials have demonstrated the efficacy of intravenous thrombolysis within three hours of onset of ischaemic stroke in reducing short-term disability. Recanalisation is enhanced by intra-arterial thrombolysis, sonothrombolysis and clot-retrieval devices. Occasionally, reperfusion injury may lead to clinical deterioration. The search continues for effective neuroprotectants. Brain perfusion needs to be maintained through blood and intracranial pressure management. Hemicraniectomy for 'malignant' cerebral oedema reduces death and disability. Elevated glucose should be controlled and hypoxia alleviated. Public education of symptoms and the need for immediate presentation to a medical facility is needed. Stroke unit care reduces death and disability with little increase in cost. Current evidence supports urgent efforts to resuscitate the brain after stroke.

Keywords: brain attack, cerebrovascular disease, penumbra, resuscitation, stroke

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INTRODUCTION

Stroke or 'brain attack' is a major cause of death and disability in many countries in the world.[1] In Singapore, it is the fourth leading cause of death, accounting for 9% of all deaths, an age-gender standardised mortality rate of 44/100,000, a prevalence of 4% among adults aged ≥ 50 years and an annual incidence of 1.8/1,000 among adults aged 18–70 years. It is among the top ten causes of hospital admissions.[2] With an ageing population, the number of new stroke patients and stroke survivors with varying grades of disability will likely increase. There is growing evidence supporting early interventions that improve outcome after stroke onset, both in the short and longer term.[3]

NATURAL HISTORY OF STROKE

The term 'brain attack' and the much-quoted slogan 'time is brain' have been used to emphasise that stroke is a medical emergency requiring appropriate, evidence-based and aggressive management as opposed to the nihilistic attitudes of the past. It has been estimated that the typical stroke patient loses nearly two million neurons, 14 billion synapses and 12 km of myelinated nerve fibres for every minute that stroke remains untreated.[4] Generally, approximately one-third of stroke patients recover fully, one-third partially and one-third not at all, with a 10% mortality. The prognosis is dependent on stroke subtypes; the likelihood of dying or becoming dependent at one year post stroke ranges from 86%–96% in the case of total anterior circulation infarcts to 39% in lacunar infarcts, with intermediate results in partial anterior infarcts and posterior circulation infarcts.[5] Haemorrhage carries a particularly poor immediate prognosis, with high early mortality.[6]

PRINCIPLES OF BRAIN RESUSCITATION AFTER STROKE

The brain is a complex but delicate organ that is highly sensitive to ischaemia and hypoxia. The goal of brain resuscitation in stroke is to restore neurological function. The principal thrusts revolve around restoring blood flow, neuroprotection of ischaemic brain, managing factors that compound brain injury and sustaining early efforts to gain long-term benefits. They include:

- Early recognition of stroke symptoms—education of the public and medical personnel
- Early commencement of the chain of recovery—activation/utilisation of medical services
- Early diagnosis and ascertaining of brains at risk for further injury—clinical and neuroimaging studies
- Reperfusing ischaemic brain—clot disruption
- Neuroprotection—maintaining metabolic and physiologic milieu
- Care environment—stroke unit

CEREBRAL VASCULAR ANATOMY

The extracranial anterior circulation comprises the two common carotid arteries (CCAs) and their principle branch, the internal carotid arteries (ICAs), with a subsidiary role played by the external carotid arteries (ECAs). The

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intracranial ICA gives off the ophthalmic artery (OA) and the posterior communication artery (PCommA) before finally bifurcating into the middle cerebral artery (MCA) and anterior cerebral artery (ACA). The MCA supplies the bulk of the lateral cerebral hemisphere. It also gives off the lenticulostriate branches that supply the deep white matter. The ACA supplies the medial anterior cerebral hemisphere and is linked to the contralateral ACA by the anterior communicating artery (ACommA).

The extracranial posterior circulation comprises the vertebral arteries (VAs). The intracranial VAs join to form the basilar artery (BA) at the pontomedullary junction. The BA gives off small penetrators that supply the pons, and ends as the posterior cerebral arteries (PCAs). The PCAs connect to the ICA via the PCommAs. The cerebellum is supplied by the posterior inferior cerebellar arteries, the anterior inferior cerebellar arteries and superior cerebellar arteries, arising from the VAs and BA.

Collateral flow

When blood flow is obstructed in any vessel, there exist vascular pathways that allow blood to flow though alternate routes. These pathways allow the connection of the external circulation to the internal, and the anterior to the posterior. They include:

- Ophthalmic collaterals: In instances of critical pre-OA stenosis, flow is reversed in the OA. Blood from branches of the ECAs (such as the nasal arteries) goes to the ICA siphon through reversed OA flow.
- Occipital-vertebral anastomoses: These anastomoses between the occipital artery (branch of the ECA) and the muscular branches of third portion of the VA open when the proximal VA becomes critically stenosed.
- Circle of Willis: This consists of the MCAs, ACAs and PCAs, which are connected by the ACommA and PCommAs.
- Leptomeningeal anastomoses: These are pial arteries that connect between two major cerebral arteries, supplying two different cortical territories. These include the MCAs, ACAs and PCAs.

CEREBRAL PHYSIOLOGY IN HEALTH AND STROKE

Approximately 40% of the total brain blood flow comes from each of the two carotid systems and 20% from the vertebrobasilar system. The brain relies on oxygen and glucose to drive cellular processes, and is able to tolerate only brief periods of blood flow reduction. The healthy brain has a relatively constant blood flow (CBF) of approximately 50 ml/100 g/min, higher in grey matter and within perfusion pressures of 50–150 mmHg. If vascular occlusion occurs, the initial responses include focal cerebral arteriolar dilatation with an increase in cerebral blood volume and opening up of the collateral channels, maintaining CBF and thus no resultant symptoms. If these are inadequate, oxygen extraction fraction begins to increase. If these fail, cerebral metabolism ($CMRO_2$) begins to fall and symptoms begin to set in, usually at CBF of 15–18 ml/100 g/min. Lower levels of CBF would begin to injure the brain, with irreversible injury at CBF constantly below 10–12 ml/100 g/min.[7] Thus, the brain has a fair amount of reserve; symptoms develop only when these are overcome.

With the interruption of flow, a 'core' of severely damaged brain tissue will most likely die within minutes. This core is surrounded by an 'ischaemic penumbra' that will succumb if the flow is not restored. The penumbra is surrounded by a ring of 'benign oligaemia' that, while ischaemic, is able to function normally. While little can be done to save the core, it is the penumbra that is the target of salvage therapies.[8] Advanced imaging is needed to identify it so that targeted therapies can be administered.[9]

ACUTE STROKE IMAGING

The aims of imaging include confirming the diagnosis, differentiating ischaemic from haemorrhagic stroke, ruling out other structural stroke mimics and clarifying vascular anatomy. More importantly, for resuscitation, it identifies brain tissue at risk for further infarct that may be amendable to acute intervention, the 'ischaemic penumbra'.

Computed tomography

Computed tomography (CT) is widely available, fast, relatively inexpensive and reliably detects intracranial haemorrhage.[10] It is often the first-line investigation in patients suspected to have had a stroke. CT signs may not be obvious in small or lower brainstem infarcts. While early infarcts may not be easily visible, subtle parenchymal findings, including poor grey-white matter differentiation, loss of the insular ribbon and local mass effect with effacement of the overlying cerebral sulci and/or ventricular compression, may be seen. The acute thrombus within the middle cerebral artery may be visualised as the classic 'hyperdense MCA sign' or the 'MCA dot sign' in the Sylvian fissure.

Magnetic resonance imaging

Magnetic resonance (MR) imaging is more sensitive than CT in detecting infarcts, more so in the lower brainstem.[11] The addition of T2* and FLAIR sequences reliably detects haemorrhage. Diffusion-weighted imaging (DWI), based

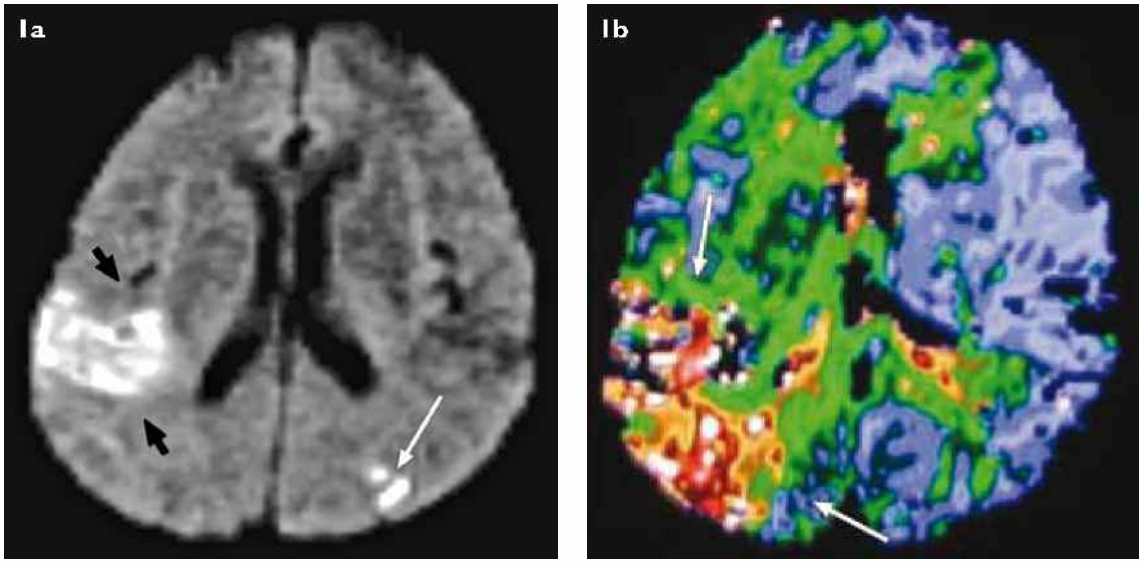

Fig. 1 (a) Diffusion-weighted image (DWI) shows an area of acute infarct in the right hemisphere (arrowheads) and a smaller area in the left posterior cerebral hemisphere (arrow). (b) Perfusion-weighted image (PWI) presented as a mean transit time (MTT) map shows hypoperfusion over the right hemisphere. Severe hypoperfusion is shown in orange/red (white arrows), while mild hypoperfusion is shown in green. Normal perfusion is shown in blue. There is thus a PWI-DWI mismatch between the area of infarct and the area of hypoperfusion. The region of the small infarct in the left posterior cerebral hemisphere is not imaged, as it is not in the same plane on the perfusion MTT map.

on reduced water mobility in cytotoxic oedema, is much more sensitive and specific, and shows changes within 30 minutes of onset before other MR evidence of injury. MR has the problem of cost, availability and contraindications. However, imaging durations are falling with newer machines and sequences.

Perfusion imaging

Perfusion imaging is an advanced imaging technique that evaluates blood flow in a given region of the brain. In acute ischaemic stroke, the hypoperfused area includes an infarcted tissue core and the surrounding ischaemic tissue at risk of progression to full infarction. Perfusion imaging indicates areas of hypoperfusion, while DWI indicates regions of irreversible parenchymal injury. Perfusion-diffusion mismatch indicates potentially salvageable tissue (Fig. 1). Perfusion imaging techniques can be performed on CT or MR imaging machines.[12,13] Both utilise the principle of 'first pass' technique of a bolus of intravenously injected contrast material.

Single photon emission CT

Single photon emission CT measures regional cerebral blood flow using radioactive isotopes.[14] It is noninvasive and is able to provide good resolution within a short scanning time with the use of modern cameras with multiple receivers. Xenon-133 is able to provide a quantitative measurement of regional cerebral blood flow. Hexamethylpropyleneamine oxime and ethyl cysteinate dimer are the two Technetium 99-based tracers that are able to provide semi-quantitative measurement of brain perfusion relative to the cerebellum. Brain vascular reserve is measured after intravenous injection of acetazolamide (Diamox®; Wyeth, New York, NY, USA).

Ultrasonography (US) has the advantage of being a portable, inexpensive and fast screening tool.[15] Extracranial duplex US is widely used to screen for extracranial carotid or vertebral occlusive diseases. Transcranial Doppler (TCD) studies the intracranial vessels through the natural 'thin bone windows' in the skull, temporal, orbital and foramen magnum. Up to 40%–50% of Asian stroke patients have poor or absent temporal windows, especially in women and those with increasing age. Traditionally used to detect vasospasm in patients with subarachnoid haemorrhage, TCD is used in acute stroke to identify intracranial stenosis, collateral flow, emboli, and cerebrovascular reactivity. Vascular anatomy is shown by both CT angiography on a newer generation multi-slice CT scanner or by MR angiography, often done during MR imaging.[16,17] Catheter angiography remains the gold standard.

INITIAL MANAGEMENT

Optimal and timely medical management by way of early airway control, management of respiration and circulation, together with close neurological monitoring aimed at the early detection of deleterious adverse events, remain the mainstay of treatment.[18,19]

With impaired consciousness or brainstem dysfunction, airway compromise, can lead to further

neurological damage. Continuous pulse oximetry and blood gas determination would indicate hypoxia, necessitating the use of supplemental oxygen. If respiration is further compromised, or if signs of malignant cerebral oedema and raised intracranial pressure ensue, endotracheal intubation and mechanical ventilation would be necessary.

While electrocardiogram monitoring during the first 24 hours of stroke is recommended to monitor for cardiac arrhythmias and myocardial ischaemia, the control of blood pressure to prevent extremes in blood pressure swings is more pertinent with regard to brain resuscitation. Both elevated and low blood pressures are associated with a poor outcome in stroke.[20] The rationales for controlling elevated blood pressure include the reduction of cerebral oedema, the prevention of haemorrhagic conversion and limitation of haematoma expansion in spontaneous intracerebral haemorrhage (ICH). Conversely, overzealous blood pressure reduction may lead to reduction of cerebral perfusion, especially in ischaemic areas, thus worsening the neurological injury. The ideal blood pressure in the setting of acute ischaemic and haemorrhagic stroke remains controversial. Persistent systolic blood pressure > 180 mmHg and a diastolic pressure > 110 mmHg (mean > 130 mmHg) would be appropriate levels to start anti-hypertensives for haemorrhagic stroke or if the patient is for thrombolysis; for ischaemic stroke in general, the threshold for treatment is higher, at 220 mmHg systolic. However, it is important to note that blood pressure often spontaneously falls several hours after the onset of stroke or when raised intracranial pressure is treated. Especially in acute ischaemic stroke, too rapid a reversal of blood pressure is potentially harmful, as some strokes are due to haemodynamic factors. Tissue in the ischaemic penumbra also remains vulnerable to large swings in blood pressure. A reasonable goal would be to lower blood pressure by not more than 15%–25% within the first 24 hours and with close neurological monitoring.

RECANALISATION OF OCCLUDED ARTERIES

Intravenous (IV) thrombolysis is effective when used within three hours of symptom onset in acute ischaemic stroke. Recombinant tissue plasminogen activator (rTPA) (Boehringer Ingelheim, Ingelheim am Rhein, Germany) is the only FDA-approved agent for this indication.[21] The standard recommended dose is calculated as 0.9 mg/kg body weight, with 10% given as bolus and the remaining infused over one hour. There is a 30% increased chance of good outcome at three months among treated patients compared to controls, without excess haemorrhage. A pooled analysis of six large multicentre trials of rTPA in acute stroke revealed that the clinical outcomes are significantly better if the treatment is started within 90 minutes of symptom onset.[22] The analysis further revealed that the potential benefit of rTPA may exist even beyond three hours.[22]

The strict time-window and limited benefits have led to the evaluation of various alternative therapeutic strategies in ongoing clinical trials in acute stroke (www.strokecenter.org/trials/). Various trials (EPITHET, IST-III, ECASS-III) are currently looking into the safety and efficacy of IV rTPA thrombolysis within 3–6 hours of stroke onset. In addition, some other thrombolytic agents are also being evaluated in acute stroke (DIAS-desmoteplase, Paion GmbH, Aachen, Germany), ASPIII-Ancrod (Nordmark, Uetersen, Germany) and ROSIE-Reopro with Retevase (Eli Lilly, Indianapolis, IN, USA).

INTRA-ARTERIAL THROMBOLYSIS

Intra-arterial (IA) thrombolysis carries a considerable appeal due to potentially higher rates of recanalisation. While there are currently no FDA-approved IA thrombolytic agents, several studies have evaluated IA thrombolysis in acute ischaemic stroke. The Prolyse in Acute Cerebral Thromboembolism (PROACT) I and II trials evaluated the recanalisation, safety and efficacy of IA recombinant pro-urokinase (Abbott Laboratories, Abbott Park, IL, USA) in patients with symptomatic occlusions of M1 or M2 segments of the MCA. Although significantly higher rates of arterial recanalisation (66%) were observed with this modality of treatment, it resulted in higher rates of treatment-related ICH.[23,24]

COMBINED IV-IA THROMBOLYSIS

IV thrombolysis is the fastest way to initiate treatment, as the initiation of IA thrombolysis may be delayed by about 40–60 minutes due to the preparation time. A combination of these two modalities in acute stroke appears to be an attractive therapeutic approach that was evaluated in the Emergency Management of Stroke (EMS) trial.[25] This trial showed a significantly higher mortality rate despite higher rates of angiographic recanalisation in the treatment group. The feasibility of the combined approach within three hours of symptom onset was further evaluated in the IMS-I trial,[26] the encouraging results of which led to the currently ongoing IMS-III trial.

DEVICES FOR TREATMENT OF ACUTE ISCHAEMIC STROKE

The Merci® Retrieval System (Concentric Medical Inc,

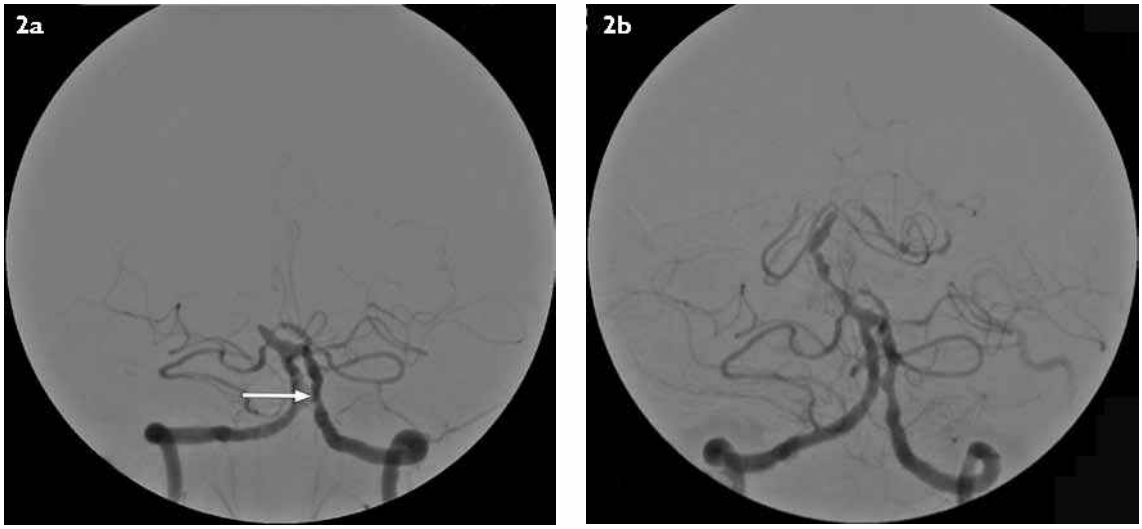

Fig. 2 (a) Left vertebral injection angiogram shows acute cut-off of flow in the mid-basilar artery due to occlusion by a thrombus (arrow). (b) Final check angiogram post thrombectomy device retrieval of thrombus with adjuvant 5 mg intra-arterial rTPA shows good recanalisation of flow in the basilar artery. There is also re-establishment of flow distally into both the posterior cerebral and bilateral superior cerebellar arteries. Note that the basilar artery has an irregular outline due to underlying atherosclerotic disease.

Mountain View, CA, USA) is an FDA-approved device comprising a tapered cockscrew nitinol wire with helical loops of decreasing diameter at the distal end. It is advanced through a microcatheter, positioned beyond the clot and deployed. The coil is then withdrawn, pulling the clot along with it. The clot is retrieved under negative suction into the main guiding catheter that is positioned proximally in the parent artery. The Mechanical Embolus Removal in Cerebral Ischaemia (MERCI) trial included acute ischaemic stroke patients presenting within 3–8 hours of symptom onset who were deemed to be ineligible for IV rTPA.[27] The trial demonstrated better clinical outcomes in patients achieving arterial recanalisation. The device restored vascular patency in 48% of patients (Fig. 2).

The ongoing Magnetic Resonance and Recanalisation of Stroke Clots Using Embolectomy (MR-Rescue) trial uses MR imaging to compare embolectomy with the Merci® device with standard treatment in ischaemic stroke patients presenting within eight hours of symptom onset. In addition, the Multi-MERCI trial is designed to determine the safety and efficacy of a second generation Merci® clot retrieval device used within 3–4 hours after failed IV thrombolysis.

SONOTHROMBOLYSIS

A significant proportion of patients with acute ischaemic stroke do not achieve arterial recanalisation with systemic thrombolysis alone. US exposure has effects such as reversible disaggregation of uncross-linked fibrin fibres, microcavity formation in the shallow layers of thrombus, increase in the enzymatic transport of rTPA improving its uptake and penetration of TPA into clots, residual flow enhancement with microstreaming and vessel dilation. These multiple effects have been shown to result in higher blood clot dissolution quantity and rate.[28] The Combined Lysis of Thrombus in Brain Ischaemia Using Transcranial Ultrasound and Systemic TPA (CLOTBUST) trial demonstrated that the lytic activity of IV rTPA can be safely augmented with continuous two-hour monitoring with 2 MHz diagnostic TCD in human beings.[29] Significantly higher rates of arterial recanalisation occurred; 49% in the target group vs. 30% in the controls. This was associated with a trend toward better clinical outcomes in patients treated with IV rTPA and continuous US exposure by TCD, with no increase in the rates of ICH. The feasibility of US-assisted thrombolysis in Singapore has been evaluated in a recent study.[30] Partial or complete recanalisation with reduction in the stroke severity was noted in four out of the five patients during IV rTPA infusion. None of the patients developed symptomatic ICH, and four patients demonstrated good functional outcome at one month.[30]

REPERFUSION INJURY

Restoration of blood supply to ischaemic brain tissue is the primary goal of thrombolysis and embolectomy. Although this can prevent extension of brain tissue injury by salvaging the reversibly damaged penumbra, it does, however, carry certain risks,[31] principally 'cerebral reperfusion injury'. This may exacerbate tissue damage and lead to fatal cerebral oedema or intracranial haemorrhage.[32]

The cause of reperfusion injury is multi-factorial, but appears to be strongly associated with an inflammatory response. Several inflammatory processes may potentiate ischaemic injury with the return of blood flow.[33] These include leucocyte adhesion and infiltration, free radical release and neuronal membrane breakdown, which in itself may produce more free radicals.

Much of this inflammatory response appears to be mediated by interleukins. Leucocytes also appear to play a critical role in reperfusion injury. In addition to injuring the endothelium and neurons, leucocytes, along with red blood cells and platelets, can obstruct the microcirculation directly; resulting in secondary cerebral ischaemia.[34] This leucocyte capillary plugging may be the major mechanism of the 'no reflow phenomenon', which is defined as incomplete restoration of blood flow following a period of ischaemia. These mechanisms may contribute to the increased risk of intracranial haemorrhage after rTPA treatment occurring in major infarcts with large DWI changes.[35]

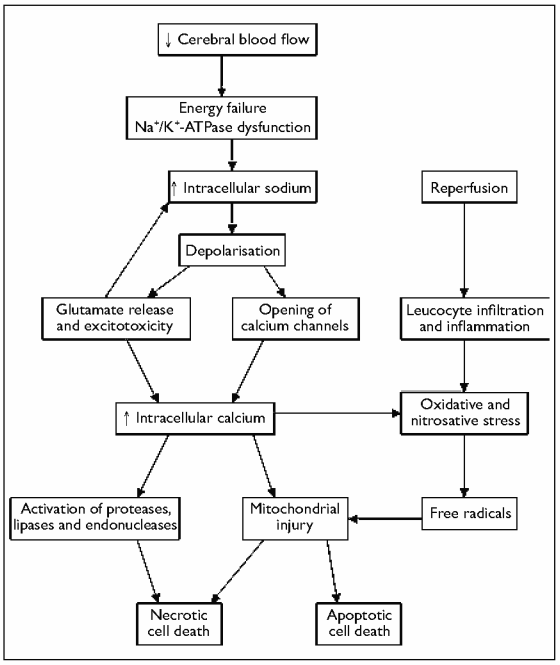

Fig. 3 Ischaemic cascade in acute stroke.

NEUROPROTECTION

With cessation of cerebral blood supply, an ischaemic cascade of biochemical reactions is initiated, which results in neuronal, glial and endothelial cell injuries (Fig. 3). Neuroprotective therapy aims to interrupt these reactions, with possible preservation of the ischaemic penumbra and/or prolong the time-window of reperfusion therapy. After the failure of a large number of neuroprotective drugs in human studies, guidelines on pre-clinical evaluation of these agents before translation to human trials were established.[36] Subsequently, an agent that appeared to satisfy most of these criteria in pre-clinical and early clinical development was tested in clinical trials, but failed to demonstrate efficacy.[37]

This has led scientists and clinicians to reconsider future approaches in stroke neuroprotective therapy.[38] Possible strategies include targeting processes that occur over a prolonged time-window after stroke onset, e.g. reperfusion injuries (by free radicals, oxidative stress and nitric oxide), cell repair and regeneration. Therapies for excitotoxicity and calcium cytotoxicity that have been emphasised in the past are, in contrast, only likely to be effective during the first few hours of stroke onset, and therapeutic levels of these agents are difficult to achieve in the ischaemic penumbra without arterial recanalisation. Combination treatment of neuroprotective agents and reperfusion therapy is therefore another promising strategy. Increased use of human brain cells, tissues and human subjects, with careful case selection using advanced neuroimaging techniques during the early phase of drug development is recommended so as to ensure clinical relevance of these agents.

HYPOTHERMIA

Mild-to-moderate hypothermia (core temperature 32°C–34°C) improves outcome in patients with out-of-hospital cardiac arrest.[39] Induced hypothermia, especially if initiated at or shortly after onset of cerebral ischaemia, may be neuroprotective in animal models by interfering with the ischaemic cascade.[40] However, early hypothermia is rarely possible in stroke patients. Delayed induction of hypothermia is sometimes applied to patients with large hemispheric infarcts, with the aim of decreasing cerebral metabolism to control oedema.[41] Its use is associated with decreased mortality compared to usual intensive care treatment, but its efficacy appears to be inferior to hemicraniectomy. Induced hypothermia requires admission to the intensive care unit, neuromuscular blockade to prevent shivering, and frequently, intubation and general anaesthesia.

Adverse effects are common (e.g. hypotension, arrhythmias, pneumonia and thrombocytopaenia) and usually limit the maximal duration of treatment to three days. Rebound in cerebral oedema is a potentially fatal complication during the rewarming period. Therefore, the use of hypothermia is currently limited to a highly selected subgroup of patients with large hemispheric infarct and contraindications to hemicraniectomy, and in those with life-threatening increase in intracranial pressure (ICP) despite hemicraniectomy.

MANAGEMENT OF ICP AND CEREBRAL OEDEMA

Treatment of raised ICP has largely evolved from experience with traumatic brain injury, and its specifics may not necessarily apply directly to that in ICH. Many patients with small ICHs will likely not have raised ICP, as would be the case for many patients with ischaemic stroke. However, when clinical evidence of raised ICP appears, an appropriate response would be to start simple and less aggressive measures, such as head elevation by 30°, adequate analgesia and sedation. Second tier efforts include osmotic therapy with mannitol (target serum osmolality 300–320 mosm/kg), cerebrospinal fluid drainage if there is evidence of hydrocephalus and modest hyperventilation (keeping PCO_2 at 30–35 mmHg).[42]

While there is a paucity of data with regard to the efficacy of monitoring ICP and cerebral perfusion pressure in the setting of ICH, it would be reasonable to proceed to invasive ICP monitoring if more aggressive ICP-lowering techniques, such as the institution of barbiturate coma, neuromuscular blockade and hypothermia, are initiated. ICP is also often routinely monitored postoperatively (both after surgery for haematoma evacuation and decompressive craniectomy for malignant brain oedema).

Hemicraniectomy for malignant middle cerebral artery infarct has been shown to reduce mortality and improve functional outcome in survivors.[43] The benefits of decompressive craniectomy is seen in conjunction with medical therapy when compared to medical therapy alone. Moreover, this benefit is seen only when certain criteria are fulfilled (e.g. age between 18–60 years, surgery within 48 hours and deficits suggesting MCA territory involvement). Surgery for spontaneous ICH has not been shown to improve outcome, and this has again been confirmed with the results of the STICH trial.[44] However, surgery may be beneficial in superficial cortical bleeds and in cerebellar bleeds of > 3 cm in diameter. Stereotactic clot aspiration can also be considered in deep nuclei haemorrhages.

METABOLIC MILIEU

Hyperglycaemia

Hyperglycaemia is detected on admission in approximately one-third of patients with stroke. It may be a manifestation of underlying diabetes mellitus or a secondary stress response. As hyperglycaemia is associated with poor outcomes after stroke in both diabetic and non-diabetic patients, it must be appropriately managed.[45] A reasonable blood glucose range is 4.4–7.7 mmol/L (80–140 mg/dL). To achieve this goal, subcutaneous soluble insulin according to a sliding scale six-hourly has been traditionally used.

In 2001, Van den Berghe and colleagues published a landmark clinical trial demonstrating that intensive insulin therapy focused on maintaining tight normoglycaemic control significantly reduced the mortality of surgical intensive care patients.[46] As a result, continuous insulin infusion had become a standard of care for critically ill patients of all types around the world. Such intensive measures involve substantial cost, effort, medical and nursing hours and a risk of hypoglycaemia. When applied to stroke patients, however, the clinical outcome was not improved.[47,48] Additional trials are needed to determine the effect of this intervention in acute stroke.

Electrolyte and acid-base abnormalities

Early recognition and appropriate management of electrolyte and acid-base abnormalities favourably reduce secondary brain injury and are important for haemodynamic stability. Fluid restriction, a previous norm for brain infarcts, is now recognised to be harmful, leading to dehydration and impaired cerebral perfusion. Patients should be kept euvolaemic. Hyperosmolar therapy, used to reduce brain oedema, may cause hypokalaemia, hypocalcaemia and nephrotoxicity. Dextrose 5% or hypotonic solutions should be avoided; isotonic saline infusions should be used.

Hypoxia

Maintaining tissue oxygenation is important in order to prevent ischaemia and potential worsening of brain injury. The most common causes of hypoxia are airway obstruction, pneumonia, cardiac failure and pulmonary embolism. Patients with stroke are at risk of airway obstruction due to impaired consciousness, bulbar dysfunction and loss of protective reflexes. Pulse oximetry should be kept at > 92% saturation. Supplementary oxygen is not needed unless there is hypoxia. The use of hyperbaric oxygen is promising but unproven.[49]

STROKE UNIT AND STROKE TEAM

All the abovementioned interventions are best provided in a suitable environment. The evidence shows that patients suspected of having a stroke are better managed in a stroke unit, whenever available. Admission of stroke patients into a stroke unit improves their chances of good clinical outcome by reducing the odds of death and dependency by more than 20%.[50] The durability of this benefit lasts up to five years after the stroke. Different models of geographical stroke units include acute stroke unit, combined acute and rehabilitation stroke unit, and stroke rehabilitation ward. All are equally efficacious. The stroke team is multi-disciplinary, usually comprising

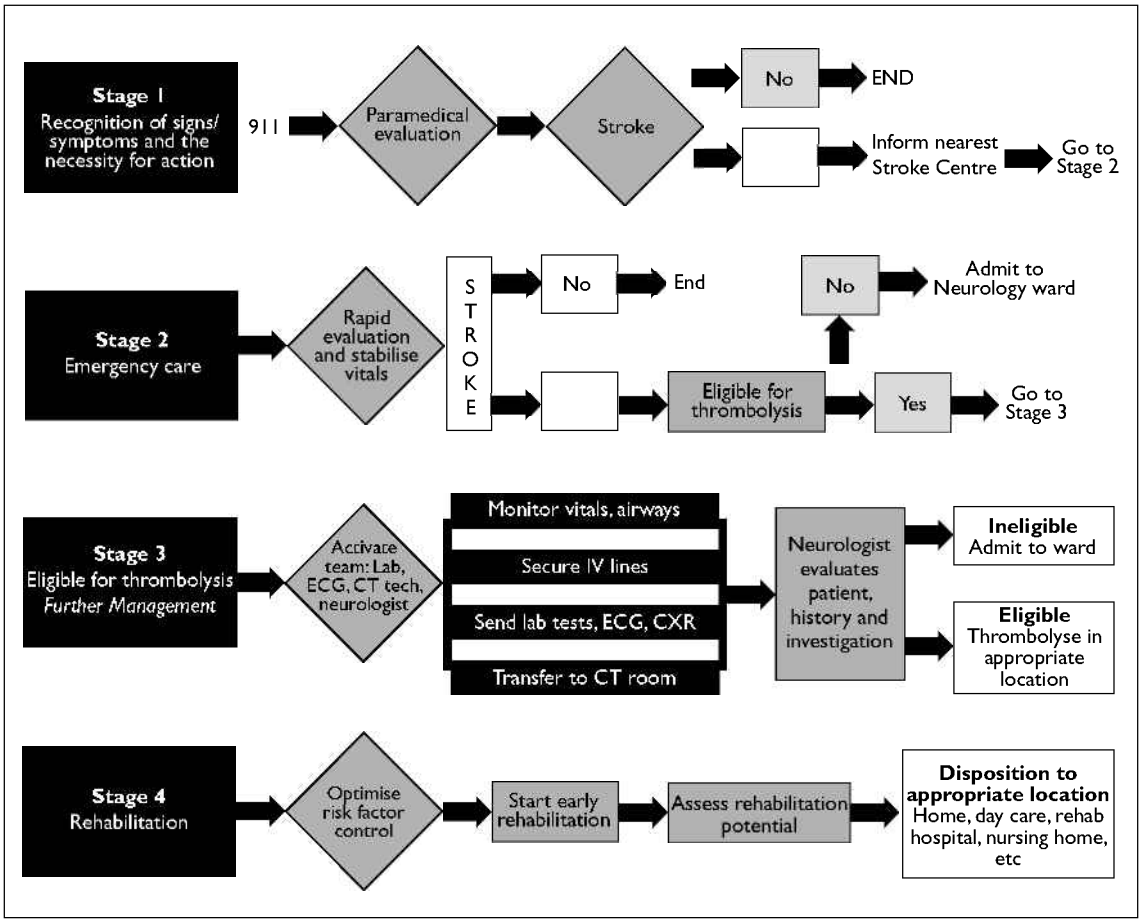

Fig. 4 Stroke chain of recovery.

members from the medical, surgical, rehabilitation, nursing, dietary and social services. A mobile stroke team, although occasionally implemented in lieu of a physical stroke unit, may not be as effective as a geographical stroke unit.

The improved outcome from stroke unit admission is mainly due to prevention and early recognition and management of medical complications.[51] These may be neurological (e.g. recurrent stroke, seizures), cardiovascular (e.g. arrhythmia, myocardial infarction), infective (e.g. urinary tract infection, pneumonia), thromboembolic (e.g. deep venous thrombosis, pulmonary embolism), gastrointestinal (e.g. gastrointestinal bleeding, constipation), urinary (e.g. retention, haematuria), psychological (e.g. depression) or musculoskeletal (e.g. pressure sores, falls, joint pain). Rapid assessment, early intervention, close monitoring, early mobilisation and anticipatory discharge planning are hallmarks of effective stroke units. These features also translate to shorter hospital stay.

The main advantage of the stroke unit as a treatment is its applicability to almost all patients who suffer a stroke, both ischaemic and haemorrhagic, unlike other stroke treatments that may be limited to certain subsets of stroke patients due to contraindications.[52]

EMERGENCY SERVICES, CHAIN OF RECOVERY AND PUBLIC EDUCATION

From the above discussions, it is clear that acute stroke is an emergency, and an ultra-rapid response holds the key to better outcome. This endeavour requires a seamless coordination between the prehospital responders and expertise of multiple disciplines in a comprehensive stroke centre.[53] A Chain of Recovery (Fig. 4) or 'code-stroke'—beginning with the identification (either by the patient or an onlooker) of a possible acute stroke and ending with a rehabilitation plan—must be established by every community stroke programme.[54]

The general public, including the immediate family members, play the most significant role in initiating the ultra-rapid 'code-stroke' response. However, severe deficits exist in their knowledge about identifying stroke symptoms as well as the advantages of activating EMS. Significant improvements can be achieved by their education.[55] The public must learn that stroke is a medical emergency, that a treatment is now available for some stroke patients and that this treatment is only effective when given within a few hours of the onset of symptoms.[21] EMS personnel must be trained to treat

stroke as a time-dependent and urgent medical emergency. They carry the utmost responsibility of resuscitation and correctly identifying potential candidates for definitive treatment, and they work closely with hospital emergency departments to transport these patients rapidly to appropriate stroke centres. Constant communication between the EMS and emergency department may help in formulating a better management plan.

Emergency departments must have specialised protocols in place for identifying potential candidates for definitive therapy within a narrow therapeutic time-window. Rapid and close coordination with stroke neurologists as well as radiologists is an essential ingredient of an acute stroke protocol. Although the identification of patients eligible for thrombolytic therapy is often done by physicians, it may also be accomplished by others, e.g. pre-hospital care providers, triage nurses, or other individuals competent to apply categorisation criteria. Patients deemed ineligible for thrombolytic therapy undergo a different rapid categorisation to establish the appropriate treatment.

Response systems, including optimal time frames, must be established, maintained and monitored in all emergency departments. The goal should be to perform an initial patient evaluation within ten minutes of arrival in the emergency department, notify the stroke team early, initiate an early CT and transfer the patient's care to appropriate hands within the shortest possible time from arrival.

COSTS AND BENEFITS IN BRAIN RESUSCITATION

A question that is often asked of stroke physicians and advocates of aggressive salvage therapy is: "Is it all worthwhile?" Reported cost-benefit estimates are variable and dependent on the outcome measures used, study population characteristics and demographics, follow-up duration and completeness of accounting measures.

Of all the brain resuscitation measures, IV thrombolytic therapy has attracted the most attention. Initial analysis of the NINDS trial seemed to show that thrombolysis within the three-hour window of ischaemic stroke may have attractive pharmacoeconomics.[56] With its increasing acceptance and extensive use over a decade, multiple publications have suggested cost-benefit ratios that favour the use of IV rTPA. Meta-analysis and cost modelling also suggest that this is the case, although a key variable may be the cost of the imaging modality; if MR imaging is used instead of CT, the costs-benefit ratios may be lower. The synergistic effect of stroke unit care, with its widespread use of thrombolysis, may magnify the benefits.[57] Another area of interest is the potential to leverage on advances in telemedicine. Initial analysis of a regional network to increase thrombolysis suggests that this may be an additional measure to enhance the cost-effectiveness of existing centres.[58] However, the cost-benefit analysis of other salvage/neuroprotection strategies may be less favourable. As discussed earlier, most pharmacologic neuroprotectants have not lived up to their initial promise, and have failed the litmus test of clinical stroke trials.

There is relatively limited information with regard to cost-benefit ratio in hypothermia. Methods of hypothermia induction and maintenance vary. The benefits of hypothermia are currently undergoing evaluation and are not fully defined, but the costs are generally high, especially if a high-dependency or intensive care setting is involved. Surface-cooling equipment and catheters can also be expensive. The same cost concerns can apply to intracranial pressure monitoring and emergency neurosurgery. However, insulin and oxygen therapy are relatively cheap by comparison. Stroke units should not incur additional costs, as they merely represent a reorganisation of services and not the building of new physical infrastructure. Ultimately, once has to balance the cost of an intervention against the potential benefit and harm to a specific patient. The onerous task is in the hands of the treating physician and the team; it is difficult to place a price on the value of a human life.

CONCLUSION

There is evidence of efficacious interventions in the setting of an acute stroke. However, they must be delivered soon after symptom onset in order to be effective. Clinical trials will continue to provide new treatments that will help salvage the brain from succumbing to the effects of focal hypoxia and ischaemia due to stroke.

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SMA CME ACTIVITIES SEPTEMBER 2011

DATE & TIME	CME TOPIC	ORGANISER	VENUE	CME	SPECIALTY	CONTACT (TEL, EMAIL)
7 Sep 6.30 pm - 9.30 pm	Mastering Adverse Outcomes	SMA-MPS	Sheraton Towers Singapore	2	All Specialties	Margaret Chan 62231264 margaret@sma.org.sg
7 Sep 6.30 pm - 9.30 pm	Mastering Professional Interactions	SMA-MPS	Sheraton Towers Singapore	2	All Specialties	Margaret Chan 62231264 margaret@sma.org.sg
10 Sep 2.30 pm - 5.30 pm	Mastering Difficult Interactions with Patients	SMA-MPS	Sheraton Towers Singapore	2	All Specialties	Margaret Chan 62231264 margaret@sma.org.sg
10 Sep 2.30 pm - 5.30 pm	Mastering Your Risk	SMA-MPS	Sheraton Towers Singapore	2	All Specialties	Margaret Chan 62231264 margaret@sma.org.sg
11 Sep 2.30 pm - 5.30 pm	Mastering Professional Interactions	SMA-MPS	Sheraton Towers Singapore	2	All Specialties	Margaret Chan 62231264 margaret@sma.org.sg
14 Sep 6.30 pm - 9.30 pm	Mastering Adverse Outcomes	SMA-MPS	Sheraton Towers Singapore	2	All Specialties	Margaret Chan 62231264 margaret@sma.org.sg
14 Sep 6.30 pm - 9.30 pm	Mastering Difficult Interactions with Patients	SMA-MPS	Sheraton Towers Singapore	2	All Specialties	Margaret Chan 62231264 margaret@sma.org.sg
18 Sep 2.30 pm - 5.30 pm	Mastering Difficult Interactions with Patients	SMA-MPS	Sheraton Towers Singapore	2	All Specialties	Margaret Chan 62231264 margaret@sma.org.sg
21 Sep 6.30 pm - 9.30 pm	Mastering Professional Interactions	SMA-MPS	Sheraton Towers Singapore	2	All Specialties	Margaret Chan 62231264 margaret@sma.org.sg
21 Sep 6.30 pm - 9.30 pm	Mastering Your Risk	SMA-MPS	Sheraton Towers Singapore	2	All Specialties	Margaret Chan 62231264 margaret@sma.org.sg
24 Sep 2.30 pm - 5.30 pm	Mastering Adverse Outcomes	SMA-MPS	Sheraton Towers Singapore	2	All Specialties	Margaret Chan 62231264 margaret@sma.org.sg
25 Sep 2.30 pm - 5.30 pm	Mastering Professional Interactions	SMA-MPS	Sheraton Towers Singapore	2	All Specialties	Margaret Chan 62231264 margaret@sma.org.sg
28 Sep 6.30 pm - 9.30 pm	Mastering Difficult Interactions with Patients	SMA-MPS	Sheraton Towers Singapore	2	All Specialties	Margaret Chan 62231264 margaret@sma.org.sg

The above is a Continuing Medical Education (CME) Calendar, Category 1B.
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