Early changes in physiological variables after stroke

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Abstract

Several aspects of physiology, notably blood pressure, body temperature, blood glucose, and blood oxygen saturation, may be altered after an ischemic stroke and intracerebral hemorrhage. Generally, blood pressure and temperature rise acutely after a stroke, before returning to normal. Blood glucose and oxygen levels may be abnormal in individuals, but they do not follow a set pattern. Several aspects of these physiological alterations remain unclear, including their principal determinants - whether they genuinely affect prognosis (as opposed to merely representing underlying processes such as inflammation or a stress response), whether these effects are adaptive or maladaptive, whether the effects are specific to certain subgroups (e.g. lacunar stroke) and whether modifying physiology also modifies its prognostic effect. Hypertension and hyperglycemia may be helpful or harmful, depending on the perfusion status after an ischemic stroke; the therapeutic response to their lowering may be correspondingly variable. Hypothermia may provide benefits, in addition to preventing harm through protection from hyperthermia. Hypoxia is harmful, but normobaric hyperoxia is unhelpful or even harmful in normoxic patients. Hyperbaric hyperoxia, however, may be beneficial, though this remains unproven. The above-mentioned uncertainties necessitate generally conservative measures for physiology management, although there are notably specific recommendations for thrombolysis-eligible patients. Stroke unit care is associated with better outcome, possibly through better management of poststroke physiology. Stroke units can also facilitate research to clarify the relationship between physiology and prognosis, and to subsequently clarify management guidelines.

Keywords

Blood glucose, blood pressure, body temperature, cerebrovascular disorders, oxygen

Introduction

It is well established that stroke unit care improves outcome.[1] How this is achieved remains unclear, but close monitoring and maintenance of physiological homeostasis may contribute significantly to this benefit.[2-4] However, our understanding of the changes in the main modifiable physiological parameters, namely blood pressure, body temperature, blood glucose and blood oxygen saturation, and the impact that these changes have on stroke outcome remains incomplete. Threshold levels for instituting treatment to modify these parameters, targets to be achieved with treatment and the effectiveness of such treatment remain uncertain. In this paper, we will review what is known about acute poststroke changes in these physiological variables, the causes of these changes, their prognostic significance, and the effects of treatment to modify these parameters.

Blood Pressure

Ischemic stroke

Changes in blood pressure (BP) after an ischemic stroke are important because there is impairment of cerebral autoregulation,[5] which, in normal circumstances, acts to maintain constant cerebral blood flow despite changes in systemic BP. With impairment of autoregulation, changes in systemic BP may affect cerebral perfusion, especially in the penumbral tissues, and may therefore affect the survival of ischemic tissue and the neurological outcome.

Both the systolic and diastolic BP are higher after stroke. It appears to rise acutely at the time of stroke.[6] Blood pressure then falls over the next 7-10 days,[7,8] with most of this fall occurring within the first 1-2 days.[9,10]

The mechanisms driving these BP changes are uncertain, though there are several plausible explanations.
relationship between severe stroke and high poststroke BP has been documented,\(^{[13]}\) although others have found that severe stroke is associated with a lower BP than stroke of mild to moderate severity.\(^{[10,12]}\) How stroke severity might modulate BP is unknown. Acute psychological stress related to the process of hospital admission has been suggested to be a cause;\(^{[13]}\) although a study in which high BP was documented after admission with stroke but not after medical admissions with other acute problems suggests that the BP elevation is stroke-specific.\(^{[14]}\) However, since psychological stress cannot be quantified, it is possible that the stroke group experienced more psychological stress than the control group. A neuroendocrine stress response may contribute and BP has been correlated with salivary\(^{[15]}\) and serum\(^{[16]}\) cortisol levels.\(^{[18]}\) Inflammation and a neuroendocrine stress response may be linked, given the reported relationship between interleukin 6 (IL-6) and cortisol levels.\(^{[19]}\) Other associations with high poststroke BP include a history of hypertension\(^{[10]}\) and the requirement for antihypertensive medications,\(^{[10]}\) although the latter is likely to be an effect rather than a cause of higher BP. It is hypothesized that BP elevations after ischemic stroke represent an adaptive response that helps to maintain the cerebral blood flow and perfusion of the ischemic penumbra, despite loss of cerebral autoregulation.\(^{[20]}\) Conversely, it is of clinical concern that excessive rise in BP could lead to neurological deterioration from hemorrhagic transformation, especially in the presence of a damaged blood brain barrier. The association between BP and the outcome of stroke is unclear, with poor outcome being associated with either absolute high\(^{[11]}\) or low\(^{[21]}\) BP, or having no association with BP.\(^{[22]}\) Recent studies have identified a U-shaped relationship between BP and outcome, with poor outcome at either end of the BP spectrum.\(^{[12,23]}\) Methodological issues, including cohort selection, the timing of BP measurements, and the timing and selection of endpoints, might contribute to the differing conclusions drawn by investigators. The prognostic impact of BP levels appears to vary between ischemic stroke subtypes. One study found a U-shaped relationship between admission BP and mortality only in cardioembolic but not lacunar strokes\(^{[24]}\) and another found that the relationship between admission BP and mortality in lacunar stroke was linear, with no harm resulting from low BP.\(^{[23]}\) These findings might be explained by the lack of an ischemic penumbra in a lacunar stroke,\(^{[25]}\) where low BP might not significantly worsen hypoperfusion and therefore, tissue survival in the ischemic territory. Lower admission BP has also been associated with poor outcome in thrombolysis-eligible patients.\(^{[26]}\) Patients eligible for thrombolysis must present within three hours of stroke onset, when there is likely to be a large penumbra and, therefore, a proportionately greater vulnerability to hypoperfusion. However, thrombolysis protocols also exclude patients with high BP (>185/110 mm Hg); so any deleterious effect of high BP might not be evident in these cohorts. One study also showed that cardioembolic stroke patients had lower BP in the first 24 h and poorer outcome,\(^{[21]}\) as compared to those with non-cardioembolic strokes, although this may merely reflect the impact that more severe stroke in cardioembolic patients has on both BP levels and outcome. Although absolute systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) values are the most commonly studied indices of BP, other aspects of BP have been linked with stroke outcome. Elevated pulse pressure,\(^{[27]}\) wide fluctuations in both SBP and DBP within the first three hours of stroke,\(^{[28]}\) greater variability of the DBP within the first 72 hours\(^{[26]}\) and increased beat-to-beat SBP and DBP variability within 24-72 hours of stroke\(^{[29]}\) have all been associated with poor prognosis. The normal circadian variation in BP, where nocturnal BP falls relative to daytime BP (dipping), may be disrupted after stroke.\(^{[30,31]}\) This is possibly more common after right-sided\(^{[32]}\) or insular or thromboembolic\(^{[33]}\) infarction, and may recover in the subacute and chronic phases.\(^{[16]}\) There is some evidence that loss of dipping may be associated with poor outcome\(^{[34]}\) and that its preservation is associated with better outcome.\(^{[35]}\) There are no trials investigating the effects of maintaining a nocturnal BP dip, although there is some interest in the chronotherapeutic maintenance of circadian rhythms in other situations.\(^{[36]}\) The prognostic significance of dynamic fluctuations in postadmission blood pressure varies. Poor outcome may be seen with spontaneous falls in systolic\(^{[37]}\) and diastolic\(^{[38]}\) BP; it can also be seen with spontaneous BP elevations.\(^{[11]}\) Conversely, good outcome has been seen with spontaneous BP falls.\(^{[39]}\) This has resulted in the investigation of both pharmacological BP elevation and reduction as potential strategies for the treatment of acute stroke. Therapeutic BP elevation has been studied particularly in cases where relative hypoperfusion was suspected.
such cases include patients with lower BP (SBP <140 mm Hg), [40] clinical deficits that fluctuate in parallel with BP changes [41] or perfusion-diffusion mismatch (a marker for the presence of penumbral tissue) on MRI. [42] In these small studies, BP elevation was shown to be safe and to partially reverse neurological deficits. [40-42] Pharmacological BP elevation may be beneficial in carefully selected stroke subgroups, but this requires further study. [43]

Pharmacological BP lowering after ischemic stroke remains a controversial topic. Long-term BP lowering is clearly beneficial, significantly reducing the incidence of recurrent stroke events. [44] However, what remains uncertain is the optimum timing of the initiation of therapy; specifically, whether it is safe to initiate BP therapy within the time window for the persistence of penumbral tissue, with the attendant theoretical risk of affecting penumbral salvage and overall neurological outcome. Whether to continue pre-existing antihypertensive therapy is also unclear and the subject of an ongoing study. [45]

Caution is suggested by the results of research on the calcium channel blocker nimodipine, which, when studied as a neuroprotective agent, produced a worse outcome, possibly as a result of BP lowering in the treated group, [46] although this effect may have varied, depending on the stroke subtype. [47] Conversely, the ACCESS study was terminated prematurely when it was found that early treatment with candesartan was associated with a reduction in 12 month mortality and recurrent vascular events, despite there being no significant difference in the BP between treatment arms; however, no effect on early functional outcome was seen. [48] Some antihypertensive agents may lower systemic BP without affecting cerebral blood flow, as seen in the studies of perindopril [49] and glyceryl trinitrate. [50] Such agents may be safe to use early, or even beneficial; however, this remains unproven.

Some unrelated interventions and even routine activities can influence systemic BP after stroke. Insulin therapy, [51] therapeutic hypothermia [52] and experimental neuroprotective agents [46] may alter BP, potentially affecting the results of clinical trials; therefore, knowledge of the relationship between BP and prognosis is critical for the accurate interpretation of trial results. Even elevating the head of the bed to 15° or 30° can cause the MAP and cerebral perfusion pressure to fall significantly. [53] In another study, after a meal, SBP fell >10 mm Hg in a quarter of the stroke patients. [54] Clarifying whether these alterations in systemic and cerebral pressure are clinically significant is important, given that these activities are potentially modifiable in almost all stroke patients.

Intracerebral hemorrhage
Blood pressure also rises after intracerebral hemorrhage (ICH), perhaps even more than after an ischemic stroke, and falls over the next seven days. [55] It is also possible that the rise may sometimes precede and trigger the ICH. [56]

The mechanisms behind BP changes after ICH remain uncertain. Because there is no ischemic penumbra around hematomas, [57] the BP rise is unlikely to be adaptive, especially as autoregulation seems to be preserved after ICH, and changes in systemic BP are not completely transmitted to the cerebral circulation. [58]

A rise in BP may also be harmful, higher BP having been associated with hematoma enlargement [59] and poor prognoses. [60]

Systemic BP, however, has not been universally shown to affect hematoma enlargement [61] or ICH prognosis [62] and lowering of BP has not yet been shown to improve prognosis, [63] although prospective trials are ongoing. [44]

Temperature
Ischemic stroke
Body temperature rises by about 0.2°C over the first 24-36 h [65,66] after an ischemic stroke. The temperature rise is greater after moderate to severe stroke (0.35°C in a cohort with National Institutes of Health Stroke Scale (NIHSS) scores ≥ 6). [66] Boysen and Christensen, for example, observed a temperature rise only in those with severe stroke (Scandinavian Stroke Score, SSS ≤ 25), with no temperature change after mild to moderate stroke. [67] They also found that the admission temperature was more often low (<36°C) after severe stroke, possibly due to immobility and low environmental temperatures. [67] Higher temperatures have also been seen in cohorts where severe stroke was defined by large infarct volumes. [68]

Following this rise, temperatures appear to fall over the first five days after stroke, [69] although the rate of normalization has not been specifically studied.

The normal circadian rhythm of temperature is also disrupted after severe stroke, possibly due to impaired consciousness or physical inactivity [70] and this may be associated with a poor prognosis. [71] Although it is not clear that the relationship is independent of stroke severity.

Although the association between temperature elevation and stroke severity seems firm, the mechanism through which this effect is generated remains unclear.
Infection is common after stroke, affecting 25-35% of the patients.\textsuperscript{[73]} In some cases, the infection may precede the stroke and has been implicated in the causation.\textsuperscript{[74]} Vila et al. found that IL-6 levels were associated with higher temperatures and larger infarctions in a cohort of patients without infection.\textsuperscript{[75]} Audebert et al. found that the CRP, white cell count and temperature were high in the acute phase of stroke, but normalized within days of successful thrombolysis.\textsuperscript{[76]} These results suggest that ischemic or infarcted brain tissue promotes inflammation and hyperthermia. There may also be a role for a neuroendocrine stress response, with a correlation between cortisol levels and serial temperatures being documented.\textsuperscript{[17,77]} Higher temperatures are more common in those requiring antipyretics, but this is more likely to have been a consequence of higher temperatures rather than a cause.\textsuperscript{[86-87]}

Low admission temperatures have been correlated with poor prognosis,\textsuperscript{[67]} although this relationship was not shown to be independent of stroke severity. Most investigators, however, have found the opposite effect.

In one meta-analysis, high poststroke temperatures increased mortality with an odds ratio (OR) of 1.19\textsuperscript{[78]} and this relationship has been replicated subsequently.\textsuperscript{[79]} High temperatures appear particularly harmful in those treated with thrombolysis,\textsuperscript{[80]} although the mechanism for this remains unclear.

Although temperature appears to influence stroke prognosis,\textsuperscript{[78]} stroke severity,\textsuperscript{[67]} and inflammation\textsuperscript{[81]} may be responsible for some or all of its apparent effect. Stroke severity influences both stroke prognosis\textsuperscript{[86,67]} and temperature\textsuperscript{[66]} and the effect of temperature on outcome has been variably lost\textsuperscript{[82]} or retained\textsuperscript{[83]} after adjustment for stroke severity. Inflammation similarly influences both temperature\textsuperscript{[76]} and stroke prognosis.\textsuperscript{[81]} Again, the relationship between temperature and outcome has been variably lost\textsuperscript{[68]} or retained\textsuperscript{[75]} after adjustment for inflammation. It is also possible that inflammation itself is an epiphenomenon of stroke severity,\textsuperscript{[84]} although this theory is not universally supported.\textsuperscript{[85]} Alternatively, each of these factors could independently affect prognosis, and one study found independent associations between all three factors and early neurological worsening.\textsuperscript{[79]} These relationships require clarification to enable determining which of these factors might be suitable targets for treatment. It is, of course, hoped that simply lowering body temperature poststroke might improve outcome.

To this end, antipyretic agents administered orally,\textsuperscript{[86]} rectally\textsuperscript{[87]} or intravenously\textsuperscript{[87]} have been used to modify temperature. The effect of antipyretics varies from zero\textsuperscript{[67]} to around 0.2°C.\textsuperscript{[65,88]} The effect of antipyretics, however, is more marked when larger temperature rises are expected; a 0.4°C treatment effect was seen in a cohort treated within 24 h of stroke onset.\textsuperscript{[69]} There is no effect from these agents at 5 days poststroke.\textsuperscript{[69]} These findings suggest that antipyretic agents prevent fever rather than actively lower temperature poststroke. Clarification of the effects of these agents would facilitate the assessment of protocols that combine treatments.\textsuperscript{[89]}

Active cooling techniques are highly effective at lowering body temperature and are generally employed with the aim of inducing hypothermia. The two main methods used are surface\textsuperscript{[90,92]} and endovascular\textsuperscript{[93-95]} cooling. Methods to selectively cool the brain,\textsuperscript{[96]} for example with a cooling helmet,\textsuperscript{[87]} have also been tried. Very low temperatures can be achieved with these techniques, but most protocols aim for a target temperature of 32-33°C.\textsuperscript{[94,98]} This generally requires the patient to be intubated, with neuromuscular blockade used to manage shivering. Protocols avoiding the need for intubation would be more widely applicable, but the depth of hypothermia possible in awake patients is generally limited to around 35.5-36.4°C,\textsuperscript{[90,92]} although a recent study achieved median core body temperatures of 33.4°C with endovascular cooling, in awake patients.\textsuperscript{[93]}

Several technical issues regarding induced hypothermia require clarification before this treatment can be evaluated in large randomized trials. These issues are related to the following – the most appropriate patients to be treated, the time window for commencing temperature lowering treatments, how low the temperature should be reduced to, how long the hypothermia should be maintained and how quickly to re-warm the patient.\textsuperscript{[99]}

Given the intensive resources required for monitoring patients undergoing therapeutic hypothermia and the need for large potential treatment effects to find benefit with small numbers, most studies, to date, have focused on patients with more severe stroke,\textsuperscript{[90]} for example large middle cerebral artery (MCA) territory infarcts.\textsuperscript{[91,94]}

There are no studies that have specifically addressed the issue of the time window for initiation of hypothermia. For practical reasons, subjects have had hypothermia initiated between 4 h\textsuperscript{[91]} and 60 h\textsuperscript{[90]} poststroke. It would seem likely that the maximum benefit will result from earlier initiation of treatment.

Most investigators have maintained hypothermia for one to three days,\textsuperscript{[52,90,94,95]} although durations from six hours\textsuperscript{[92]} to three weeks\textsuperscript{[98]} have been studied. The optimal duration of hypothermia is unclear, these reports suggesting no clear benefits from either shorter or longer durations of hypothermia.
Slower rewarming seems to be safer than more rapid rewarming, there being a lower incidence of rebound elevations in Intracranial Pressure (ICP) and a lower risk of transtentorial herniation.\(^\text{[100]}\)

Other side effects of these techniques include hypotension (patients often require BP support), for example, with inotropes\(^{[90,95]}\) and pneumonia.\(^{[95]}\)

To date, studies involving these techniques have primarily been aimed at evaluating the feasibility and safety of treatment rather than at demonstrating its effectiveness. Overall, these techniques do appear to be feasible and relatively safe.\(^{[92,95,98]}\) Clinical endpoints have not clearly been improved with treatment, but there are studies demonstrating improvement in surrogate outcome; for example, microdialysis studies have shown lower concentrations of glycerol (a neuronal membrane component released from infarcted neurons) and lactate (indicating anerobic metabolism) with body temperatures under 34°C, and less ICP elevation\(^{[91]}\) and cerebral edema\(^{[101]}\) with lower body temperatures. Definitive studies are awaited.

**Intracerebral hemorrhage**

Temperature rises after ICH,\(^{[67]}\) probably more so than after an ischemic stroke.\(^{[102]}\) The magnitude of the rise seen by Boysen and Christensen,\(^{[67]}\) after severe (SSS < 25) ICH was about 1°C, beginning at about 4-6 h and being complete by about 12 h after the stroke. As with ischemic stroke, the temperature rise is more pronounced after severe ICH as assessed either clinically\(^{[67]}\) or by hematoma volume.\(^{[103]}\)

As opposed to the uncertainty surrounding temperature changes after ischemic stroke, temperature elevations after ICH seem to be mostly an epiphenomenon of the severity of the hemorrhage. Unadjusted analyses have suggested a poor prognosis, with higher temperatures.\(^{[103,104]}\) However, analyses incorporating adjustment for stroke severity have found no association with prognosis.\(^{[67,103]}\) One study did show that 24-48 h or >48 h with a temperature above 37.5°C was associated with a poor Glasgow Outcome Scale (GOS) score at discharge, independent of Glasgow Coma Score (GCS) and hematoma volume,\(^{[106]}\) suggesting that there may be a dose effect.

There are a few studies examining the effects of temperature lowering after ICH. Better 3-month outcome have been seen with nasopharyngeal cooling and indomethacin, as compared with no treatment.\(^{[107]}\) Other groups have studied surface cooling in cohorts including both ischemic stroke and ICH. These results were discussed previously.\(^{[90]}\) Overall, however, little is known about the benefits of temperature lowering after ICH.

### Glucose

#### Ischemic stroke

Glucose levels appear to rise after stroke. One study involving nondiabetic patients demonstrated a rise in median blood glucose level from 5.9 mmol/L at 2.5 h to 6.2 mmol/L at 6 h poststroke.\(^{[22]}\) Indeed, poststroke hyperglycemia is a frequent phenomenon, with up to 50% of the patients having an initial blood glucose of above 6.0–7.0 mmol/L.\(^{[108,109]}\) Glucose levels that, in the fasting state, would be consistent with a pre-diabetic state.\(^{[110]}\) In comparison, the prevalence of diabetes or impaired fasting glycaemia is 34% in people aged over 60 years.\(^{[111]}\) As one might expect, glucose levels poststroke are higher in patients with diabetes than in those without diabetes.\(^{[112-114]}\)

Some have suggested that the initial poststroke hyperglycemia resolves spontaneously in the acute phase.\(^{[112,115]}\) Others have found no such change.\(^{[108]}\) Dysregulated glucose metabolism has also been shown to extend for months poststroke. In patients without known diabetes, half of one cohort\(^{[116]}\) and two-thirds of another\(^{[117]}\) had diabetes or impaired glucose tolerance at three months poststroke. At three years after stroke, two thirds of another cohort had either diabetes or a pre-diabetic state, with half of these patients unaware of their status.\(^{[118]}\)

Hyperglycemia appears to be associated with more severe stroke, as assessed either with a clinical stroke scale\(^{[119]}\) or by lesion volume.\(^{[120]}\) A neuroendocrine stress response\(^{[121]}\) and an inflammatory response\(^{[122]}\) may also play a role in generating hyperglycemia.

Stroke location may be important, with infarction of the insular cortex, a structure involved in the autonomic control of the neuroendocrine stress response associated with hyperglycemia;\(^{[123]}\) however this association has been refuted.\(^{[124]}\)

Support for a neuroendocrine stress response comes from groups that have reported a correlation between glucose and cortisol levels after stroke,\(^{[117,125]}\) although others have not found glucose to be associated with either cortisol\(^{[27]}\) or catecholamine levels.\(^{[126]}\)

Although not a universal finding,\(^{[127]}\) poststroke hyperglycemia has been associated with poor outcome\(^{[128]}\) and seems to particularly affect outcome in patients without diabetes. In the meta-analysis by Capes et al., the relative risk of in-hospital/30-day mortality in patients with admission hyperglycemia (>6.1–7.0 mmol/L) was 3.28 (95% CI 2.32 to 4.64) in ischemic stroke patients without diabetes, but not significantly increased in patients with diabetes.\(^{[129]}\) Similar findings have been...
published since this meta-analysis.[114,130] Outcome other than mortality have also been shown to be worse in hyperglycemic patients without diabetes than in other stroke patients.[113,131]

Why hyperglycemia particularly affects stroke prognosis in patients without diabetes is unclear. Despite being apparently protective against ischemic damage in vitro, in vivo studies have consistently associated high glucose levels with harm.[135] Diabetes is associated with microcirculatory abnormalities in the brain, including arteriovenous shunting and a reduction in glucose transport across the blood-brain barrier.[133] These processes would reduce the delivery of glucose from the blood to the brain of a patient with diabetes, thus possibly protecting them from high glucose levels after stroke.

Other factors could potentially explain the relationship between glucose and stroke prognosis. Hyperglycemia only increases growth of the infarct core in patients with surrounding hypoperfusion, suggesting that hyperglycemic blood is only toxic to ischemic brain. Similarly, several studies have shown that non-ischemic brain surrounding lacunar infarcts[135] and, in turn, stroke prognosis, is unaffected[136] or perhaps even improved[137] by hyperglycemia. Conversely, Toni et al. found that a collateral blood supply could improve the prognosis if hyperglycemia coexists,[138] suggesting that glucose can protect ischemic brain. Several biochemical mechanisms, including excessive glutamate or lactate, vascular reactivity, or oedema formation[132] could possibly link glucose and stroke prognosis. However, these relationships remain too unclear to reconcile these apparently contradictory findings.

Hyperglycemia has a particularly potent adverse effect after thrombolysis. Hyperglycemic patients more commonly develop intracerebral hemorrhage after thrombolysis[139] and have overall poorer clinical[140] and radiological[141] outcome. Hyperglycemic patients are also less likely to recanalise with thrombolysis.[142] Even if recanalization occurs, hyperglycemic patients are more likely to deteriorate,[143] particularly if hyperglycemia occurs early after recanalization.[144]

Hyperglycemia may be merely an epiphenomenon of other underlying processes. Given the association between stroke severity and hyperglycemia,[129,139] the repeated finding that hyperglycemia has no association with prognosis after adjustment for stroke severity[142,145] suggests that in some cases hyperglycemia is an epiphenomenon of stroke severity. In other cases, however, hyperglycemia has affected prognosis independent of stroke severity.[146,147] Glucose has variably lost[148] or retained[75] an independent effect on stroke prognosis, after adjustment for IL-6 levels. Similarly, glucose has variably lost[129] or retained[149] its independent association with stroke prognosis after adjustment for cortisol levels. As glucose is associated with both inflammation[75,122] and cortisol levels,[17,125] and as stroke prognosis is also associated with both inflammation[81] and cortisol[77] it is possible that these factors drive stroke prognosis and that hyperglycemia is merely an epiphenomenon of one or both of these factors.

Given the frequency of hyperglycemia and its effect on outcome, glucose-lowering therapy has potential as a widely applicable treatment after stroke. Insulin, specifically glucose-potassium-insulin (GKI) infusions, have been shown to be feasible and safe in acute stroke patients.[116,151] Insulin appears to have beneficial effects, including anti-inflammatory, antioxidant and nitric oxide effects, which are independent of its ability to lower glucose levels, and which may be beneficial in stroke.[152]

Unfortunately, the large Glucose Insulin in Stroke Trial (GIST-UK)[51] was terminated prematurely due to slow recruitment, after 933 patients were randomized to either GKI or intravenous saline. Being correspondingly underpowered, the study failed to identify a treatment effect on mortality or other outcome. Further studies are clearly warranted.

There have been few studies with other agents used in the treatment of diabetes, although sulfonylureas were not shown to affect stroke prognosis in one trial.[153]

**Intracerebral hemorrhage**

Hyperglycemia after ICH is less well-characterized than after ischemic stroke. Apart from diabetes,[154] the most significant determinant of hyperglycemia is the severity of the ICH, as assessed by the hematoma size[155] or other markers of severity.[154]

In the meta-analysis by Capes et al., admission hyperglycemia was not associated with higher mortality in unadjusted analyses of either diabetic or nondiabetic ICH patients.[129] Since this meta-analysis, one group found that hyperglycemia had no association with outcome after adjustment for ICH volume and growth, two strong predictors of outcome after ICH.[62] Other studies, however, have shown an independent effect from glucose, even after adjusting for the volume[106,156] or other markers of mass effect[154] of the ICH. These subsequent results suggest that glucose does have an independent effect on ICH prognosis.

There are no treatment trials specifically addressing the effects of glucose lowering in ICH patients.
Oxygenation

Hypoxia is frequently reported after stroke, although the frequency depends on the definition used. Pulse oximetry identified arterial oxygen saturations (SaO2) <90% for >10% of the recording time in 20% of one stroke cohort,[157] while 63% of another cohort had SaO2 < 96% for at least 5 min.[158]

Hypoxia in stroke patients is commonly associated with co-morbidities such as respiratory tract infections and cardiac failure.[157] It also occurs overnight, with SaO2 falling below 90% for >30 min in 25% of patients in one study.[159] Hypoxia does not seem to be related to stroke severity.[157]

Transient hypoxia has been observed during routine maneuvers such as MRI scanning (18% patients had SaO2 <90% for at least 1 min),[160] bed transfers (SaO2 fell ≥3% in 18% patients),[157] and nasogastric tube insertion, when difficult or prolonged (SaO2 fell below 90% in 21% patients).[161] Hypoxia is not related to overnight nasogastric tube feeding.[162] Hypoxia may[163] or may not[160] occur with oral feeding; this inconsistency may be due to the use of differing criteria for classifying patients as safe to feed orally.

Posture may affect oxygenation, with higher SaO2 levels when sitting upright or semi-recumbent, as compared with fully recumbent posture.[165] Positioning may be more likely to affect oxygenation in stroke patients who have coexisting respiratory problems.[166]

It is generally assumed that hypoxia carries a poor prognosis and is rarely untreated in clinical practice or research settings. In a mixed cohort of ischemic and hemorrhagic stroke, there was a univariate association between hypoxia (SaO2 < 90% for > 10% of the recording time) and death at three months poststroke, but this was nonsignificant after adjusting for stroke severity.[157] There is a corresponding lack of evidence that correction of hypoxia improves stroke prognosis.

Oxygen supplementation has been studied as a way to improve stroke outcome in normoxic patients. Understandably, most research has focused on ischemic stroke, where oxygen supplementation is seen as having a potential for neuroprotection. Potential benefits suggested by the results of animal studies include suppression of excitotoxicity, oxidative and nitrosative stress, inflammation, and apoptosis.[167] Despite theoretical concerns about the production of harmful superoxide free radicals and hyperoxia-induced vasoconstriction, some human studies suggest an overall beneficial effect. Indeed, oxygen-induced vasoconstriction in nonischemic areas has been shown to shunt blood towards ischemic areas, thus paradoxically improving perfusion.[168]

Oxygen supplementation using both hyperbaric (HBO) and normobaric oxygen (NBO) to improve outcome in normoxic patients has been studied. Hyperbaric oxygen (HBO) has been more widely studied and the early studies showed occasional dramatic improvements temporally related to HBO therapy, with some of these improvements occurring even several weeks and months after stroke.[169,170] More recent studies have focused on acute stroke, but the results have either been neutral[171] or have suggested better outcome in the non-HBO group.[172]

Various methodological explanations for these conflicting results have been offered. The optimum treatment pressure remains unclear, with pressures from 1.5 atmospheres absolute (ATA) to 2.5 ATA promoted as being the most appropriate.[167,173] The use of oxygen therapies by control groups, usually in an attempt to maintain blinding, may have offered some treatment effect and, therefore, may also have affected the results in some studies.[171,172] The initiation of HBO therapy beyond the first few hours after stroke has also been criticized, because extrapolation from other stroke therapies[173] and animal studies[174] suggests that poor outcome from treatment this late after stroke are to be expected.

Normobaric oxygen (NBO) is capable of increasing the SaO2 in normoxic stroke patients,[175] but unselected patients appear to do poorly with NBO therapy.[176] Patients presenting with large MCA territory infarcts appeared to benefit from oxygen supplementation (FiO2 40% by Venturi mask), when treated within 48 h of stroke, perhaps because these patients are more likely to have a penumbra.[177] Similarly, diffusion weighted imaging (DWI) volumes were smaller during treatment with high-flow (45 L/min) mask oxygen given within 12 h of stroke in patients with MRI evidence of perfusion-diffusion mismatch.[168] As with HBO, the dose and timing issues are unclear for NBO therapy also.

Oxygen therapy might protect the ischemic penumbra by suppressing harmful processes such as edema,[178] inflammation and apoptosis.[167] While NBO does not appear to provide permanent protection from recruitment of the ischemic penumbra into the infarct core,[179] it might be used to maintain the penumbra whilst awaiting reperfusion and thus prolonging the therapeutic time window for reperfusion therapies.[168] Applying HBO in the same way poses significant logistical challenges. Treatment would be restricted to a small subgroup of the already small percentage of thrombolysis-eligible patients.[180]
Monitoring of physiology in the stroke unit

While stroke-unit care reduces mortality and improves functional independence,\textsuperscript{[1]} the mechanisms for this benefit remain unclear. One mode that stroke-unit care may help patients is through careful monitoring and optimization of physiological variables.\textsuperscript{[181]}

Table 1: Summary of recommendations from published guidelines regarding management of physiological variables after acute stroke

| Physiological Variable | USA\textsuperscript{[183, 184]} | Europe\textsuperscript{[185, 186]} | Australian\textsuperscript{[187]} |
|------------------------|-----------------|-----------------|------------------|
| **Blood Pressure**     | IS: Patients with markedly elevated BP (SBP > 220 mm Hg or DBP > 120 mm Hg) may have their BP lowered. A reasonable goal would be to lower BP by ~15%. Patients for tPA should be stabilized with SBP < 185 mm Hg and DBP < 110 mm Hg before starting treatment. Hypotension should be corrected (eg, hypovolemia with fluid replacement). ICH: (i) If SBP > 200 mm Hg or MAP > 150 mm Hg, consider aggressive BP reduction. (ii) If SBP > 180 mm Hg or MAP > 130 mm Hg and evidence/suspicion of elevated ICP, consider monitoring ICP and reducing BP to keep CPP >60–80 mm Hg. (iii) If SBP > 180 mm Hg or MAP > 130 mm Hg and no evidence/suspicion of elevated ICP, consider modest BP reduction (target BP 160/90 mm Hg or MAP 110 mm Hg). | IS: Routine BP lowering is not recommended, except for extremely elevated values (SBP > 200–220 mm Hg or DBP > 120 mm Hg). Recommended target BPs: Prior hypertension: 180/100–105 mm Hg No prior hypertension: 160–180/90–100 mm Hg Thrombolysis: SBP <180 mm Hg ICH: Treatment is recommended if BP is above the following levels: (i) Patients with hypertension: SBP > 180 mm Hg and/or DBP > 105 mm Hg. (Target BP 170/100 mm Hg or MAP 125 mm Hg); (ii) Patients without hypertension: SBP > 160 mm Hg and/or DBP > 95 mm Hg. (Target BP 150/90 mm Hg or a MAP 110 mm Hg). (iii) Avoid reducing MAP by > 20%. (iv) In patients undergoing monitoring for increased ICP ensuring CPP > 70 mm Hg. | IS: If extremely high BP (> 220/120 mm Hg), institute or increase antihypertensive therapy, but BP should be cautiously reduced (by no more than 10–20%) ICH: In patients with a history of hypertension, MAP should be maintained < 130 mm Hg |
| **Temperature**        | IS and ICH: Sources of fever should be treated and antipyretic medications should be administered to lower temperature in febrile patients | IS and ICH: Treatment of body temperature ≥ 37.5°C is recommended. Search for a possible infection and consider appropriate antibiotic therapy. | IS and ICH: Antipyretic therapy, comprising regular paracetamol and/or physical cooling measures, should be used routinely where fever occurs |
| **Glucose**            | IS and ICH: Persistent hyperglycemia with glucose > 185 mg/dl (10.2 mmol/l), and possibly > 140 mg/dl(7.8 mmol/l), should probably trigger administration of insulin. Hypoglycemia should be treated to achieve normoglycemia. | IS and ICH: Treatment of blood glucose > 200 mg/dl (11 mmol/l) with insulin titration is recommended. Immediate correction of hypoglycemia is recommended. | IS and ICH: Patients with hyperglycemia should have their blood glucose level monitored and appropriate glycemic therapy instituted to ensure euglycemia, especially if the patient is diabetic. Intensive early maintenance of euglycemia is currently not recommended. Hypoglycemia should be avoided. |
| **Oxygenation**        | IS: Hypoxic patients should receive supplemental oxygen (maintain SaO₂ ≥ 92%). Nonhypoxic patients do not need supplemental oxygen therapy ICH: No specific advice other than to ensure adequate oxygenation | IS and ICH: Oxygen supplementation is recommended if SaO₂ < 92% | IS and ICH: Patients who are hypoxic should be given oxygen supplementation (no SaO₂ threshold specified). |

IS: Ischemic Stroke, ICH: intracerebral hemorrhage, BP: blood Pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, CPP: cerebral perfusion pressure, ICP: intracranial pressure, SaO₂: arterial oxygen saturation.

(Please refer to full text of guidelines for details of specific recommendations)
Stroke units might facilitate the maintenance of physiological homeostasis by bringing together medical, nursing and other staff experienced in stroke care; the necessary equipment for monitoring physiological parameters; and protocols to manage aberrant physiology. Monitoring in stroke units also facilitates data collection for subsequent refinement of management protocols.

There is some evidence that intensive physiological monitoring in a stroke unit improves outcome.[2,3] In a randomized study of 54 ischemic stroke patients,[2] continuous monitoring of BP, electrocardiogram (ECG), body temperature, and pulse oximetry for at least 48 h improved 3-month mortality, as compared with 6th-hourly manual measurements of BP, temperature, and heart rate and intermittent pulse oximetry (3.7% vs 25.9%; \( P=0.05 \)). The same protocol for managing abnormal physiology was used in both groups, suggesting that early detection and management of abnormalities through continuous monitoring improved outcome. Improved outcome was also observed in a nonrandomized comparison between continuous monitoring of BP, ECG, temperature, oxygen saturation, respiratory frequency and electroencephalogram (EEG), and intermittent monitoring of BP, heart rate, and temperature. Aberrant physiology was more frequently detected in the continuously monitored group (64% vs 19%; \( P<0.0001 \)), perhaps leading to more timely intervention and resulting in improved outcome.[3] One randomized study of 206 ischemic stroke patients showed that less DBP variability was associated with more frequent discharge to home at six weeks, although it is unclear whether this was due to more frequent monitoring or earlier mobilization in the stroke unit.[182]

As can be seen from the above discussion, the optimum strategies for managing these physiological variables remain uncertain. Many stroke units have developed local management protocols guided by the available evidence, informed by experience, and modified according to the resources available locally. Internationally, published evidence-based stroke-management guidelines provide some guidance.

What do published guidelines say about management of physiological variables?

Table 1 summarizes the recommendations from published American, European, and Australian stroke treatment guidelines, regarding management of physiological parameters after acute stroke. There is general consistency across the guidelines, with some minor differences, generally in areas in which there is a lack of strong evidence to guide practice.

The guidelines generally recommend tolerating higher than usual BP after both ischemic stroke and intracerebral hemorrhage. Excessive elevations should be treated, but thresholds for initiating treatment and targets for treatment vary. All caution should be taken against aggressive and abrupt BP reductions. Treatment of fever with antipyretic agents is recommended, with a search for infection and antibiotics when appropriate. Treatment of hyperglycemia for both forms of stroke is recommended, although thresholds for initiating therapy vary. Treatment of hypoglycemia is advised. Hypoxic stroke patients should receive oxygen therapy, but evidence is insufficient for the guidelines to recommend oxygen therapy for normoxic patients.

Conclusions

Our understanding of the changes in BP, temperature, glucose, and oxygen levels after stroke remains incomplete. Further study should clarify the natural history of acute physiological changes, the mechanisms behind these changes, and the effect these changes have on outcome. If physiological abnormalities contribute significantly to poststroke outcome, they offer an obvious target for treatment. Intensive early monitoring and control of physiological parameters might then become the standard of care in the stroke units of the 21st century.

References

1. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev 2002;CD000197.
2. Sulter G, Elting JW, Langedijk M, Maurits NM, De Keyser J. Admitting acute ischemic stroke patients to a stroke care monitoring unit versus a conventional stroke unit: A randomized pilot study. Stroke 2003;34:101-4.
3. Cavallini A, Micieli G, Marcheselli S, Quagliani S. Role of monitoring in management of acute ischemic stroke patients. Stroke 2003;34:2599-603.
4. Leira R, Blanco M, Rodriguez-Yanez M, Flores J, Garcia-Garcia J. Non-pharmacological neuroprotection: Role of emergency stroke management. Cerebrovasc Dis 2006;21:89-98.
5. Dawson SL, Blake MJ, Panerai RB, Potter JF. Dynamic but not static cerebral autoregulation is impaired in acute ischemic stroke. Cerebrovasc Dis 2000;10:126-32.
6. Sugimori H, Ibayashi S, Fujiy K, Yao H, Sadoshima S, Fujishima M. Brain infarction developed in hypertensive and normotensive patients during hospitalization--hemodynamic factors. Angiology 1995;46:473-80.
7. Morish L, Schwartz RS, Poulo H, Howes LG. Blood pressure changes in acute cerebral infarction and hemorrhage. Stroke 1997;28:1401-5.
8. Wallace JD, Levy H. Blood pressure after stroke. JAMA 1981;246:2177-80.
9. Britton M, Carlson A, de Faire U. Blood pressure course in patients with acute stroke and matched controls. Stroke 1986;17:861-4.
10. Wong AA, Davis JP, Schluter PJ, Henderson RD, O'Sullivan DJ, Read SJ. The time course and determinants of blood pressure within the first 48 h after ischemic stroke. Cerebrovasc Dis 2007;24:426-33.
11. Aslanian S, Fazezak F, Weir CJ, Horner S, Lees KR. Effect of blood pressure during the acute period of ischemic stroke on stroke outcome: A tertiary analysis of the GAIN International Trial. Stroke 2003;34:2420-5.

12. Leonard-Bee J, Bath PM, Phillips S, Sandercock P. Blood pressure and clinical outcome in the International Stroke Trial. Stroke 2002;33:1315-20.

13. Carlborg B, Asplund K, Hagg E. Factors influencing admission blood pressure levels in patients with acute stroke. Stroke 1991;22:527-30.

14. Morff L, Schwartz R, Lykos D, Zagami A, Pryor D, Howes LG. 24 hour ambulatory blood pressure profiles in the acute phase of stroke. Clin Exp Pharmacol Physiol 1995;22:775-7.

15. Ahmed N, de la Torre B, Wahlgren NG. Salivary cortisol, a biological marker of stress, is positively associated with 24-hour systolic blood pressure in patients with acute ischemic stroke. Cerebrovasc Dis 2004;18:206-13.

16. Fujishima S, Abe I, Okada Y, Saku Y, Sadoshima S, Fujiyama S. Serial changes in blood pressure and neurohormone levels after the onset of lacunar stroke. Angiology 1996;47:579-87.

17. Christensen H, Boysen G, Johannesen HH. Serum-cortisol reflects severity and mortality in acute stroke. J Neurol Sci 2004;217:175-80.

18. Di Napoli M, Papa F. Association between blood pressure and C-reactive protein levels in acute ischemic stroke. Hypertension 2003;42:1117-23.

19. Johansson A, Olsson T, Carlborg B, Karlsson K, Fagerlund M. Hypercortisolism after stroke--partly cytokine-mediated? J Neurol Sci 1997;147:43-7.

20. Wityk RJ. The management of blood pressure after stroke. J Neurol 2004;255:125-7.

21. Marcheselli S, Cavallini A, Tosi P, Quaglini S, Miceli G. Impaired blood pressure increase in acute cardioembolic stroke. J Hypertens 2006;24:1849-56.

22. Christensen H, Boysen G. Blood glucose increases early after stroke onset: A study on serial measurements of blood glucose in acute stroke. Eur J Neurol 2002;9:297-301.

23. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos V, et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med 2004;255:257-65.

24. Vemmos KN, Spengos K, Tsivgoulis G, Zakopoulos N, Manios E, Kotis V, et al. Factors influencing acute blood pressure values in stroke subtypes. J Hum Hypertens 2004;18:253-9.

25. Gerraty RP, Parsons MW, Barber PA, Darby DG, Desmond TM, Bress BM, et al. Examining the lacunar hypothesis with diffusion and perfusion magnetic resonance imaging. Stroke 2002;33:2019-24.

26. Yong M, Diener HC, Kaste M, Mau J. Characteristics of blood pressure profiles as predictors of long-term outcome after acute ischemic stroke. Stroke 2005;36:2619-25.

27. Aslanayan S, Weir CJ, Lees KR. Elevated pulse pressure during the acute period of ischemic stroke is associated with poor stroke outcome. Stroke 2004;35:e153-5.

28. Stead LG, Gilmore RM, Vedula KC, Weaver AL, Decker WW, Brown RD Jr. Impact of acute blood pressure variability on ischemic stroke outcome. Neurology 2006;66:1878-81.

29. Dawson SL, Manktelow BN, Robinson TG, Panerai RB, Potter JF. Which parameters of beat-to-beat blood pressure and variability best predict early outcome after acute ischemic stroke? Stroke 2000;31:463-8.

30. Pandian JD, Wong AA, Lincoln DJ, Davis JP, Henderson RD, O'Sullivan JD, et al. Circadian blood pressure variation after acute stroke. J Clin Neurosci 2006;13:558-62.

31. Jain S, Nambodiri KK, Kumar S, Prabhakar S. Loss of circadian rhythm of blood pressure following acute stroke. BMC Neurol 2004;4:1.

32. Sander D, Klingelhofer J. Changes of circadian blood pressure patterns and cardiovascular parameters indicate lateralization of sympathetic activation following hemispheric brain infarction. J Neurol 1995;242:313-8.

33. Sander D, Klingelhofer J. Changes of circadian blood pressure patterns after hemodynamic and thromboembolic brain infarction. Stroke 1994;25:1730-7.

34. Sander D, Winbeck K, Klingelhofer J, Elgten T, Conrad B. Prognostic relevance of pathological sympathetic activation after acute thromboembolic stroke. Neurology 2001;57:833-8.

35. Bhalia A, Wolfe CD, Ruddy AG. The effect of 24 h blood pressure levels on early neurological recovery after stroke. J Intern Med 2001;250:121-30.

36. Hermlis RC, Ayala DE, Calvo C, Portaluppi F, Smolensky MH. Chronotherapy of hypertension: Administration-time-dependent effects of treatment on the circadian pattern of blood pressure. Adv Drug Deliv Rev 2007;59:923-39.

37. Castillo J, Leira R, Garcia MM, Serena J, Blanco M, Dalavos A. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke 2004;35:520-6.

38. Vicem M, Schilling M, Lang W, Laloussche W, Bur A, Hirsch M. Association between course of blood pressure within the first 24 hours and functional recovery after acute ischemic stroke. Ann Emerg Med 2003;42:619-26.

39. Sartori M, Benetton V, Carraro AM, Calo LA, Macchini L, Giont V, et al. Blood pressure in acute ischemic stroke and mortality: A study with noninvasive blood pressure monitoring. Blood Press Monit 2006;11:199-205.

40. Marzan AS, Hungerbuhler HJ, Studer A, Baumgartner RW, Georgiadis D. Feasibility and safety of norepinephrine-induced arterial hypertension in acute ischemic stroke. Neurology 2004;62:1193-5.

41. Rordorf G, Cramer SC, Elft JD, Schwamm LH, Buonanno F, Korshetz WJ. Pharmacological elevation of blood pressure in acute stroke. Stroke 1997;28:2133-8.

42. Koenig MA, Geocadin RG, de Grouchy M, Glasgow J, Vimal S, Restrepo L, et al. Safety of induced hypertension therapy in patients with acute ischemic stroke. Neurocrit Care 2006;4:3-7.

43. Misti AK, Robinson TG, Potter JF. Pressor therapy in acute ischemic stroke: Systematic review. Stroke 2006;37:1565-71.

44. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischemic attack. Lancet 2001;358:1033-41.

45. The COSSACS trial group. COSSACS (Continue or Stop poststroke Antihypertensive Collaborative Study): Rationale and design. J Hypertens 2005;23:455-8.

46. Wahlgren NG, Macmahon DG, De Keyser J, Indredavik B, Ryman T; for the INWEST study group. The Intravenous Nimodipine West European Trial (INWEST) of nimodipine in the treatment of acute thromboembolic stroke. Neurology 2001;57:833-8.

47. Koenig MA, Geocadin RG, de Grouchy M, Glasgow J, Vimal S, Restrepo L, et al. Safety of induced hypertension therapy in patients with acute ischemic stroke. Neurocrit Care 2006;4:3-7.

48. Misti AK, Robinson TG, Potter JF. Pressor therapy in acute ischemic stroke: Systematic review. Stroke 2006;37:1565-71.

49. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischemic attack. Lancet 2001;358:1033-41.

50. The COSSACS trial group. COSSACS (Continue or Stop poststroke Antihypertensive Collaborative Study): Rationale and design. J Hypertens 2005;23:455-8.

51. Wahlgren NG, Macmahon DG, De Keyser J, Indredavik B, Ryman T; for the INWEST study group. The Intravenous Nimodipine West European Trial (INWEST) of nimodipine in the treatment of acute ischemic stroke. Cerebrovasc Dis 1994;4:204-10.

52. Ahmed N, Wahlgren NG. Effects of blood pressure lowering in the acute phase of total anterior circulation infarcts and other stroke subtypes. Cerebrovasc Dis 2003;15:235-43.

53. Schrader J, Ludens S, Kulscheewski A, Berger J, Zidek W, Treib J, et al. The ACCESS Study: Evaluation of acute Candesartan Cilexetil therapy in stroke survivors. Stroke 2003;34:1699-703.

54. Nazir FS, Overtall JR, Boltar A, Hilditch TE, Lees KR. Effect of perindopril on cerebral and renal perfusion on normotensives in mild early ischemic stroke: A randomized controlled trial. Cerebrovasc Dis 2005;19:77-83.

55. Willmot M, Ghadami A, Whysall B, Clarke W, Wardlaw J, Bath PM. Transdermal glyceryl trinitrate lowers blood pressure and maintains cerebral blood flow in recent stroke. Hypertension 2006;47:1209-15.

56. Gray CS, Hildreth AJ, Sandercock PA, O'Connell EJ, Johnston PM. Transdermal glyceryl trinitrate lowers blood pressure and maintains cerebral blood flow in recent stroke. Hypertension 2006;47:1209-15.

57. Gray CS, Hildreth AJ, Sandercock PA, O'Connell EJ, Johnston PM. Transdermal glyceryl trinitrate lowers blood pressure and maintains cerebral blood flow in recent stroke. Hypertension 2006;47:1209-15.
cerebral artery infarction. Acta Neurochir Suppl 1998;71:131-4.
53. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of body position on intracranial pressure and cerebral perfusion in patients with large hemispheric stroke. Stroke 2002;33:497-501.
54. Rowat AM, Wardlaw JM, Dennis MS, Warlow CP. The influence of food ingestion on blood pressure in stroke patients. Cerebrovasc Dis 2001;12:152-8.
55. Harper G, Castleden CM, Potter JF. Factors affecting changes in blood pressure after acute stroke. Stroke 1994;25:1726-9.
56. Leira EC, Acharya AB, Cruz-Flores S, Albaker OJ, Rao VK, Abdulauf SL. Blood pressure surge precedes intracerebral hemorrhage. Neurol Care 2002;5:43-5.
57. Zazula AR, Diringer MN, Viden TO, Adams RE, Yundt K, Aiyagari V, et al. Hyperperfusion without ischemia surrounding acute intracerebral hemorrhage. J Cereb Blood Flow Metab 2001;21:804-10.
58. Powers WJ, Zazula AR, Viden TO, Adams RE, Yundt KD, Aiyagari V, et al. Autoregulation of cerebral blood flow surrounding acute (6 to 22 hours) intracerebral hemorrhage. Neurology 2001;57:18-24.
59. Ohwaki K, Yuge E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: Relationship between elevated blood pressure and hematoma enlargement. Stroke 2004;35:1364-7.
60. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: A systematic review. Hypertension 2004;43:18-24.
61. Jauch EC, Lindsell CJ, Adeoye O, Khoury J, Barsan W, Broderick J, et al. Lack of evidence for an association between hemodynamic variables and hematoma growth in spontaneous intracerebral hemorrhage. Stroke 2006;37:2061-5.
62. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology 2006;66:1175-81.
63. Qureshi AI, Harris-Lane P, Kirmani JF, Ahmed S, Jacob M, Zada Y, et al. Treatment of acute hypertension in patients with intracerebral hemorrhage using American Heart Association guidelines. Crit Care Med 2006;34:1975-80.
64. Qureshi AI. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH); Rationale and design. Neurorcc 2007;6:56-66.
65. Dippe DW, van Breda EJ, van der Worp HB, van Gemert HM, Kappelle LJ, Algra A, et al. Timing of the effect of acetaminophen on body temperature in patients with acute ischemic stroke. Neurology 2003;61:677-9.
66. Wong AA, Davis JP, Schluter PJ, Henderson RD, O'Sullivan DJ, Read SJ. The time course and determinants of temperature within the first 48h after ischemic stroke. Cerebrovasc Dis 2007;24:104-10.
67. Boyden G, Christensen H. Stroke severity determines body temperature in acute stroke. Stroke 2001;32:413-7.
68. Leira R, Rodriguez-Yanez M, Castellanos M, Blanco M, Nombela F, Sobrino T, et al. Hyperthermia is a surrogate marker of inflammation-mediated cause of brain damage in acute ischemic stroke. J Intern Med 2006;260:343-9.
69. Dippe DW, van Breda EJ, van Gemert HM, van der Worp HB, Meijer RJ, Kappelle LJ, et al. Effect of paracetamol (acetaminophen) on body temperature in acute ischemic stroke. Stroke 2001;32:1607-12.
70. Takekawa H, Miyamoto M, Miyamoto T, Yokota N, Hirata K. Alteration of circadian periodicity in core body temperatures of patients with acute stroke. Psychiatr Clin Neurops 2002;56:221-2.
71. Takekawa H, Miyamoto M, Miyamoto T, Hirata K. Circadian rhythm abnormalities in the acute phase of cerebral infarction correlate with poor prognosis in the chronic phase. Auton Neurosci 2007;131:131-6.
72. Grau AD, Buggle F, Schnitzler P, Spiel M, Lichy C, Hacke W. Fever and infection early after ischemic stroke. J Neurol Sci 1999;171:115-20.
73. Castillo J, Davalos A, Marrugat J, Noya M. Timing for fever-related brain damage in acute ischemic stroke. Stroke 1998;29:2455-60.
74. Bova IY, Bornstein NM, Korczyn AD. Acute infection as a risk factor for ischemic stroke. Stroke 1996;27:2204-6.
75. Vila N, Castillo J, Davalos A, Chamorro A. Proinflammatory cytokines and early neurological worsening in ischemic stroke. Stroke 2000;31:2325-9.
76. Audebert HJ, Rott MM, Eck T, Haberl RL. Systemic inflammatory response depends on initial stroke severity but is attenuated by successful thrombolysis. Stroke 2004;35:2128-33.
77. Slowik A, Turaj W, Pankiewicz J, Dzdziec T, Szermer P, Szczudlik A. Hypercortisolosmia in acute stroke is related to the inflammatory response. J Neurol Sci 2002;196:27-32.
78. Hajat C, Hajat S, Sharma P. Effects of poststroke pyrexia on stroke outcome: A meta-analysis of studies in patients. Stroke 2000;31:410-4.
79. Jorgensen HS, Reith J, Nakayama H, Kammersgaard LP, Houth JG, Raaschou HO, et al. Potentially reversible factors during the very acute phase of stroke and their impact on the prognosis: Is there a large therapeutic potential to be exploited? Cerebrovasc Dis 2001;11:207-11.
80. Ermon L, Schrooten M, Thijis V. Body temperature and outcome after stroke thrombolysis. Acta Neurol Scand 2006;114:23-8.
81. Smith CJ, Emsley HC, Gavin CM, Georgiou RF, Vaii A, Barberan EM, et al. Peak plasma interleukin-6 and other peripheral markers of inflammation in the first week of ischemic stroke correlate with brain infarct volume, stroke severity and long-term outcome. BMC Neurol 2004;4:2.
82. Szczudlik A, Slowik A, Turaj W, Zvolinska G, Wynicz-Petkow U, Kasprzyk K, et al. Early predictors of 30-day mortality in supratentorial ischemic stroke patients--first episode. Med Sci Monit 2000;6:75-80.
83. Szczudlik A, Turaj W, Slowik A, Strojny J. Microalbuminuria and hyperthermia independently predict long-term mortality in acute ischemic stroke patients. Acta Neurol Scand 2003;107:96-101.
84. Christensen H, Boysen G, Johannesen HH, Christensen E, Bendtzen K. Deteriorating ischemic stroke: Cytokines, soluble cytokine receptors, ferritin, systemic blood pressure, body temperature, blood glucose, diabetes, stroke severity, and CT infarction-volume as predictors of deteriorating ischemic stroke. J Neurol Sci 2002;201:1-7.
85. Rodriguez-Yanez M, Castellanos M, Bianco M, Garcia MM, Nombela F, Serena J, et al. New-onset hypertension and inflammatory response/poor outcome in acute ischemic stroke. Neurology 2006;67:1973-8.
86. Dippe DW, van Breda EJ, van der Worp HB, van Gemert HM, Meijer RJ, Kappelle LJ, et al. Effect of paracetamol (acetaminophen) and ibuprofen on body temperature in acute ischemic stroke patients--PISA, a phase II double-blind, randomized, placebo-controlled trial [ISRCTN98608890]. BMC Cardiovasc Disord 2003;3:2.
87. Sultar G, Elting JW, Maurits N, Luyckx GJ, De Keyser J. Acetylsalicylic acid and acetaminophen to combat elevated body temperature in acute ischemic stroke. Cerebrovasc Dis 2004;17:118-22.
88. Kasper SE, Wein T, Piriyawat P, Villar-Cordova CE, Chalela JA, Krieger DW, et al. Acetaminophen for altering body temperature, blood glucose, diabetes, stroke severity, and CT infarction-volume as predictors of deteriorating ischemic stroke. J Cereb Blood Flow Metab 2005;31:439-49.
89. Slowik A, Turaj W, Haberl RL. The low normal thermorhyme concept--maintaining a core body temperature between 36 and 37 degrees C in acute stroke unit patients. J Neurosurg Anesthesiol 2002;14:304-8.
middle cerebral artery infarction. Stroke 1998;29:2461-6.
92. Kammersgaard LP, Rasmussen BH, Jørgensen HS, Reith J, Weber U, Olsen TS. Feasibility and safety of induced modest hypothermia in awake patients with acute stroke through surface cooling: A case-control study. Stroke 2000;31:2251-6.
93. Guluma, KZ, Hemmen TM, Olsen SE, Rapp KS, Lyden PD. A trial of therapeutic hypothermia via endovascular approach in awake patients with acute ischemic stroke: Methodology. Acad Emerg Med 2006;13:820-7.
94. De Georgia MA, Krieger DW, Abou-Chebl A, Devlin TG, Jauss M, Davis SM, et al. Cooling for Acute Ischemic Brain Damage (CCOL AID): A feasibility trial of endovascular cooling. Neurology 2004;63:312-7.
95. Georgiadis D, Schwarz S, Aschoff A, Schwab S. Hemicraniectomy and moderate hypothermia in patients with severe ischemic stroke. Stroke 2002;33:1584-8.
96. Wagner KR, Zuccarello M. Local brain hypothermia for neuroprotection in stroke treatment and aneurysm repair. Neurou Res 2005;27:238-45.
97. Wang H, Olivero W, Lanzino G, Elkins W, Rose J, Honings D, et al. Rapid and selective cerebral hypothermia achieved using a cooling helmet. J Neurosurg 2004;100:272-7.
98. Milhaud D, Thouvenot E, Heroum C, Escuret E. Prolonged moderate hypothermia in massive hemispheric infarction: Clinical experience. J Neurosurg Anesthesiol 2005;17:49-53.
99. Schaller B, Graf R. Hypothermia and stroke: The pathophysiological background. Pathophysiology 2003;10:7-35.
100. Steiner T, Friede T, Aschoff A, Schellingier PD, Schwab S, Hacke W. Effect and Feasibility of controlled rewarming after moderate hypothermia in stroke patients with malignant infarction of the middle cerebral artery. Stroke 2001;32:2833-5.
101. Kurokawa Y, Kano H, Yonemasu Y, Sasaki T, Inaba K, Uede K. Hypothermia in stroke patients with malignant infarction of the middle cerebral artery. Neurol Med Chir (Tokyo) 2001;41:53-62.
102. Lin SH, Chuang KL, Lin CC. Temporal patterns of body temperatures in the acute stage of stroke. Acta Neurol Taiwan 2006;15:177-83.
103. Suzuki S, Kelley RE, Dandapani BK, Reyes-Iglesias Y, Dietrich WD, Duncan RC. Acute leukocyte and temperature response in temperatures in the acute stage of stroke. Acta Neurol Taiwan 2001;41:53-62.
104. Roy MK, Ray A. Effect of body temperature on mortality of acute hypertensive intracerebral hemorrhage. Stroke 1995;26:1020-3.
105. Dohi K, Jimbo H, Ikeda Y, Fujita S, Ohtaki H, Shioda S, et al. Pharmacological brain cooling with indomethacin in acute hemorrhagic stroke. Neurology 2000;54:354-61.
106. Doshi K, Jimbo H, Ikeda Y, Fujita S, Ohtaki H, Shioda S, et al. Pharmacological brain cooling with indomethacin in acute hemorrhagic stroke: Antiinflammatory cytokines and antioxidative effects. Acta Neurochir Suppl 2006;96:57-60.
107. Wong AA, Davis JP, Schluter PJ, Henderson RD, O’Sullivan DJ, Read SJ. The natural history of blood glucose within the acute stage of stroke. A case-control study. Stroke 2000;31:2251-6.
108. Goldberg AP, et al. Frequency and temporal pro-
109. Poststroke hyperglycemia: Natural history and immediate management. Stroke 2004;35:122-6.
110. Kernan WN, Viscoli CM, Inzucchi SE, Brass LM, Bravata DM, Shulman GI, et al. Prevalence of abnormal glucose tolerance following a transient ischemic attack or ischemic stroke. Arch Intern Med 2005;165:227-33.
111. Vancheri C, Curcio M, Burgio A, Salvadori S, Gualandi A, Lunetta MC, et al. Impaired glucose metabolism in patients with acute stroke and no previous diagnosis of diabetes mellitus. Q J Med 2005;98:871-8.
112. Ivey FM, Ryan AS, Hafer-Macko CE, Garrity BM, Sorkin JD, Goldberg AP, et al. High prevalence of abnormal glucose metabolism and poor sensitivity of fasting plasma glucose in the chronic phase of stroke. Cerebrovasc Dis 2006;22:368-71.
113. Kiers L, Davis SM, Larkins R, Hopper J, Tress B, Rossiter SC, et al. Stroke topography and outcome in relation to hyperglycaemia and diabetes. J Neurol Neurosurg Psychiatry 1992;55:263-70.
114. de Falco FA, Sepe Visconti O, Fucci G, Caruso G. Correlation between hyperglycaemia and cerebral infarct size in patients with stroke: A clinical and X-ray computed tomography study in 104 patients. Schweiz Arch Neurol Psychiatr, 1993;144:233-9.
115. Mitchell A, Kirkpatrick P. Hyperglycaemia after acute stroke: May occur as result of neuroendocrine response. BMJ 1997;315:810-1.
116. Dziedzic T, Pera J, Slowlk A, Gryz-Kurek EA, Szczudlik A. Hypoaalbuminemia in acute ischemic stroke patients: Frequency and correlates. Eur J Clin Nutr 2007;61:1318-22.
117. Allport LE, Butcher KS, Baird TA, MacGregor L, Desmond PM, Tress BM, et al. Insular cortical ischaemia is independently associated with acute stress hyperglycaemia. Stroke 2004;35:1886-91.
118. Moreton FC, McCormick M, Muir KW. Insular cortex hypoperfusion and acute phase blood glucose after stroke: A CT perfusion study. Stroke 2007;38:407-10.
119. O’Neill PA, Davies I, Fullerton KJ, Bennett D. Stress hormone and blood glucose response following acute stroke in the elderly. Stroke 1991;22:842-7.
120. van Kooten F, Hoogerbrugge N, Naarding P, Koudstaal PJ. Hyperglycaemia in the acute phase of stroke is not caused by stress. Stroke 1993;24:1129-32.
121. Jørgensen HS, Reith J, Nakayama H, Kammersgaard LP, Raaschou HO, Olsen TS. What determines good recovery in patients with the most severe strokes? The Copenhagen Stroke Study. Stroke 1999;30:2008-12.
122. Williams LS, Rotich J, Qi R, Fineberg N, Espay A, Bruno A, et al. Effects of admission hyperglycaemia on mortality and costs in acute ischemic stroke. Neurology 2002;59:67-71.
123. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycaemia and prognosis of stroke in non-diabetic and diabetic patients: A systematic review. Stroke 2001;32:2426-32.
124. Sarkar RN, Banerjee S, Basu A. Comparative evaluation of diabetic and non-diabetic stroke—effect of glycaemia on outcome. J Indian Med Assoc 2004;102:551-3.
125. Jørgensen H, Nakayama H, Raaschou HO, Olsen TS. What determines good recovery in patients with the most severe strokes? The Copenhagen Stroke Study. Stroke 1999;30:2008-12.
126. Mehta S. The glucose paradox of cerebral ischaemia. J Postgrad Med 2003;49:299-301.
127. Mooradian AD. Central nervous system complications of diabetes mellitus: A perspective from the blood-brain barrier. Brain Res Brain Res Rev 1997;23:210-8.
128. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, et al. Acute hyperglycaemia adversely affects stroke outcome: A magnetic resonance imaging and spectroscopy study. Ann Neurol 2002;52:20-8.
135. Sultor G, Elting JW, De Keyser J. Increased serum neuron specific enolase concentrations in patients with hyperglycemic cortical ischemic stroke. Neurosci Lett 1998;253:71-3.

136. Audebert HJ, Pellkofer TS, Wimmer ML, Haberl RL. Progression in lacunar stroke is related to elevated acute phase parameters. Eur Neurol 2004;51:125-31.

137. Uyttenboogaart M, Koch MW, Stewart RE, Vroomen PC, Luijckx GJ, De Keyser J. Moderate hyperglycaemia is associated with favourable outcome in acute lacunar stroke. Brain 2007;130:1626-30.

138. Alonso D, De Michele M, Fiorelli M, Bastianello S, Camerlingo M, Sacchetti ML, et al. Influence of hyperglycemia on infarct size and clinical outcome of acute ischemic stroke patients with intracranial arterial occlusion. J Neurol Sci 1994;123:129-33.

139. Demchuk AM, Morgenstern LB, Krieger DW, Linda Chi T, Hu, Wein TH, et al. Serum glucose level and diabetes predict tissue plasminogen activator-related intracerebral hemorrhage in acute ischemic stroke. Stroke 1999;30:34-9.

140. Grotta JC, Welch KM, Fagan SC, Lu M, Frankel MR, Brott T, et al. Clinical deterioration following improvement in the NINDS rt-PA Stroke Trial. Stroke 2001;32:661-8.

141. Els T, Klisch J, Orszagh M, Hetzel A, Schulte-Monting J, Schumacher M, et al. Hyperglycemia in patients with focal cerebral ischemia after intravenous thrombolyis: Influence on clinical outcome and infarct size. Cerebrovasc Dis 2002;13:89-94.

142. Ribo M, Molina C, Montaner J, Rubiera M, Delgado-Mederos R, Arenillas JF, et al. Acute hyperglycemia state is associated with lower tPA-induced recanalization rates in stroke patients. Stroke 2005;36:1705-9.

143. Alvarez-Sabin J, Molina CA, Montaner J, Arenillas JF, Huertas R, Ribo M, et al. Effects of admission hyperglycemia on stroke outcome in reperfused tissue plasminogen activator-treated patients. Stroke 2003;34:1235-41.

144. Alvarez-Sabin J, Molina CA, Ribo M, Arenillas JF, Montaner J, Huertas R, et al. Impact of admission hyperglycemia on stroke outcome after thrombolysis: Risk stratification in relation to time to reperfusion. Stroke 2004;35:2493-8.

145. Wong AA, Davis JP, Schluter PJ, Henderson RD, O'Sullivan DJ, Read SJ. The effect of admission physiological variables on 30 day outcome after stroke. J Clin Neurosci 2005;12:905-10.

146. Kammersgaard LP, Jørgensen HS, Rungby JA, Reith J, Nakayama M, Baird TA, Parsons MW, Phanh T, Butcher KS, Desmond PM, Tress BM, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. Stroke 2003;34:2208-14.

147. Kimura K, Ichiguchi Y, Inoue T, Shibazaki T, Matsumoto N, Kobayashi K, et al. Hyperglycemia independently increases the risk of early death in acute spontaneous intracerebral hemorrhage. J Neurol Sci 2007;255:90-4.

148. Rowat AM, Dennis MS, Wardlaw JM. Hypoxiaemia in acute stroke is frequent and worsens outcome. Cerebrovasc Dis 2008;21:166-72.

149. Ali K, Sills S, Halim M, Wilde K, Allen MB, Jones PW, et al. Unexpected nocturnal hypoxia in patients with acute stroke. Stroke 2003;34:2641-5.

150. Miyazaki T, Miyata Y, Komatsu T, Tanaka T, Oekawa K, et al. Oxygenation in the brain and lungs in acute ischemic stroke patients with altered arterial oxygen saturation. Age Ageing 2003;32:116-9.

151. Lamping C, Ziers KJ, O'Sullivan DJ, Read SJ. Oxygen saturation in the treatment of acute ischemic stroke: A pilot study of normobaric oxygen therapy in acute ischemic stroke. Stroke 2005;36:797-802.

152. Heyman A, Saltzman HA, Whalen RE. The use of hyperbaric oxygenation in the treatment of cerebral ischemia and infarction. Circulation 1966;33:102-7.

153. Alfredsson C, Bengtsson A, Oberg K, Nilsson T, Neild J, et al. Oxygen therapy by normobaric rebreathing in ischemic stroke: A randomized, controlled study. Stroke 1991;22:972-8.

154. Nighoghossian N, Trouillas P, Adeleine P, Salor FD. Hyperbaric oxygen in acute ischemic stroke: A randomized, controlled trial. Stroke 1992;23:1193-8.

155. Hognasgnissan N, Trouillas P, Adeleine P, Salor FD. Hyperbaric oxygen in the treatment of acute ischemic stroke: A double-blind pilot study. Stroke 1995;26:1369-72.

156. Rusyniak DE, Kirk MA, May JD, Kao LW, Brightman EW, Welch JL, et al. Hyperbaric oxygen therapy in acute ischemic stroke: Results of the hyperbaric oxygen in acute ischemic stroke trial pilot study. Stroke 2003;34:571-4.

157. Helms AK, Whelan HT, Torby MT. Hyperbaric oxygen therapy of acute ischemic stroke. Stroke 2007;38:1137.

158. Zhang H, Thijs L, Staessen JA. Blood pressure lowering for primary and secondary prevention of stroke. Hypertension 2006;48:187-95.

159. Ali K, Sills S, Roffe C. The effect of different doses of oxygen on clinical deterioration in stroke patients due to thrombosis: A review of 122 patients. Stroke 1980;11:297-300.

160. Hognasgnissan N, Trouillas P, Adeleine P, Salor FD. Hyperbaric oxygen in acute ischemic stroke: A double-blind pilot study. Stroke 1995;26:1369-72.

161. Rusyniak DE, Kirk MA, May JD, Kao LW, Brightman EW, Welch JL, et al. Hyperbaric oxygen therapy in acute ischemic stroke: Results of the hyperbaric oxygen in acute ischemic stroke trial pilot study. Stroke 2003;34:571-4.

162. Helms AK, Whelan HT, Torby MT. Hyperbaric oxygen therapy of acute ischemic stroke. Stroke 2007;38:1137.

163. Zhang H, Thijs L, Staessen JA. Blood pressure lowering for primary and secondary prevention of stroke. Hypertension 2006;48:187-95.

164. Ali K, Sills S, Roffe C. The effect of different doses of oxygen administration on oxygen saturation in patients with stroke. Neurocrit Care 2005;3:24-6.

165. Ronning OM, Gulsvqv B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomised controlled trial. Stroke 1999;30:2033-7.
177. Chiu EH, Liu CS, Tan TY, Chang KC. Venturi mask adjuvant oxygen therapy in severe acute ischemic stroke. Arch Neurol 2006;63:741-4.

178. Imai K, Mori T, Izumo H, Takabatake N, Kunieda T, Watanabe M. Hyperbaric oxygen combined with intravenous edaravone for treatment of acute embolic stroke: A pilot clinical trial. Neurol Med Chir (Tokyo) 2006;46:373-8.

179. Singhal AB, Dijkhuizen RM, Rosen BR, Lo EH. Normobaric hyperoxia reduces MRI diffusion abnormalities and infarct size in experimental stroke. Neurology 2002;58:945-52.

180. Furlan AJ, Katzan IL, Caplan LR. Thrombolytic therapy in acute ischemic stroke. Curr Treat Options Cardiovasc Med 2003;5:171-80.

181. Diez-Tejedor E, Fuentes B. Homeostasis as basis of acute stroke treatment: Stroke units are the key. Cerebrovasc Dis 2005;20:129-34.

182. Indredavik B, Bakke F, Slordahl SA, Rokseth R, Haheim LL. Treatment in a combined acute and rehabilitation stroke unit: Which aspects are most important? Stroke 1999;30:917-23.

183. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: A guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcome in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007;38:1655-711.

184. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: A guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcome in Research Interdisciplinary Working Group. Stroke 2007;38:2001-23.

185. Toni D, Chamorro A, Kaste M, Lees K, Wahlgren NG, Hacke W. Acute treatment of ischemic stroke: European Stroke Initiative. Cerebrovasc Dis 2004;17:30-46.

186. Steiner T, Kaste M, Forsting M, Mendelow D, Kwiecinski H, Szikora I, et al. Recommendations for the management of intracranial haemorrhage - part I: Spontaneous intracerebral haemorrhage. The European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee. Cerebrovasc Dis 2006;22:294-316.

187. National Stroke Foundation. Clinical guidelines for acute stroke management. 2007. Available from: http://www.strokefoundation.com.au/images/stories/healthprofessionals/clinical%20guidelines%20for%20acute%20stroke%20management.pdf.