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CONTROVERSIES IN THE INTENSIVE CARE MANAGEMENT OF ACUTE ISCHEMIC STROKE

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Abstract

Purpose of the review

To discuss recent advances in the critical care management of acute ischaemic stroke patients, and highlight controversies and consensus.

Recent findings

Intravenous thrombolysis and endovascular thrombectomy are standard of care reperfusion therapies which have revolutionized the management of acute ischaemic stroke and transformed outcomes for patients. They can now be delivered in extended time windows and to those previously ineligible for intervention based on advanced neuroimaging criteria. Secondary systemic insults, such as hypo- and hypertension, hyperthermia or hyperglycaemia, which can extend the area of ischaemia must also be prevented or corrected to minimize infarct progression. Meticulous blood pressure management is of central importance, particularly in patients that have undergone reperfusion therapies. Neurological deterioration can occur because of infarct extension, haemorrhagic transformation or worsening cerebral oedema. Transcranial Doppler ultrasonography allows bedside, non-invasive evaluation of cerebral haemodynamics and is increasingly used in acute stroke triage, management and recovery prediction. The management of acute ischemic stroke raises several ethical issues, and shared decision making is essential to ensure outcomes that are compatible with an individual's expectations.

Summary

A bundle of medical, endovascular and surgical strategies implemented by a multidisciplinary team working to locally agreed protocols can improve long-term stroke outcomes.

Keywords

acute ischaemic stroke, decompressive craniectomy, endovascular thrombectomy, intensive care, thrombolysis, transcranial Doppler

Introduction

Acute ischemic stroke (AIS) is characterized by sudden loss of blood flow to an area of brain because of thrombosis or embolism. Despite improvements in treatment over the last decade, AIS remains the third leading cause of death worldwide and the leading cause of permanent disability in developed countries, with enormous social and economic consequences [1]. The primary goal of acute management is urgent restoration of blood flow to limit the degree of irreversible brain tissue damage. Intravenous thrombolysis and endovascular thrombectomy (EVT) are standard of care revascularization interventions in appropriate patients. Intravenous (IV) thrombolysis with alteplase, a tissue plasminogen activator (tPA), was initially recommended in AIS patients within 3.0 - 4.5 h, but recent studies using imaging criteria rather than known time of stroke onset suggest that IV-tPA is efficacious and safe up to 9 h after stroke onset [2]. This substantially increases the eligibility for IV thrombolysis after AIS; almost 50% of wake-up strokes and daytime strokes of unknown onset are IV-tPA candidates when MRI eligibility criteria are used [3].

If intravenous thrombolysis fails to achieve recanalization in patients with large vessel occlusion, the addition of EVT within 6 h of stroke onset doubles the rate of angiographic revascularisation at 24 h and functional independence at 90 days [4]. This effect is consistent among all age groups and in the almost 69% of patients who are ineligible for IV-tPA due to delayed presentation. Recent studies provide strong evidence for EVT beyond 6 h from stroke onset based on mismatch between clinical symptoms and infarct size, or perfusion mismatch on neuroimaging [5]. The 2019 update of the American Heart Association/American Stroke Society (AHA/ASA) guidelines recommends EVT up to 16 hours from stroke onset in carefully selected patients [6]. As advanced imaging increasingly becomes the norm to identify patients eligible for EVT, it is likely that those with less favourable imaging characteristics might also derive benefit [7]. For example, it is possible that more patients with larger established infarctions could be offered intervention than currently, or that EVT could be advantageous in those with low stroke severity.

General principles of critical care management

A more interventional approach to AIS management has resulted in increasing numbers of stroke patients being admitted to the intensive care unit (ICU). Depending on local arrangements, 5%-20% of AIS patients will require admission to an ICU for advanced neurological and systemic physiological monitoring, systemic organ system support (including mechanical ventilation), and management of intracranial complications that cannot be delivered on a stroke unit [8]. Input from a multidisciplinary team of medical, nursing, and allied health professionals working to evidence-based clinical protocols is essential for optimal outcomes irrespective of the care location [9].

In addition to targeted monitoring and management of intracranial complications, the ICU management of AIS focuses on optimization of systemic physiological homeostasis to prevent or rapidly correct secondary systemic insults, such as hypertension, hypotension, hyperthermia or hyperglycemia, which can extend the area of brain infarction and worsen clinical outcomes [10;11]. Interventions to reduce common complications, such as aspiration pneumonia, venous thromboembolism and pressure ulcers should also be routine. A summary of the ICU management of AIS patients is shown Table 1, and a more detailed discussion of specific aspects follows in subsequent sections.

Blood pressure management

Management of systemic blood pressure (BP) is a major therapeutic target to prevent or reduce poor functional outcomes after AIS. Almost 80% of stroke patients present with hypertension from a variety of causes, including as a protective autoregulatory response to maximize perfusion to ischemic brain regions. Acute BP management must balance potential improvements in tissue perfusion with higher BP against the increased risk of haemorrhagic transformation and/or cytotoxic enema and cardiorespiratory complications associated with severe hypertension. Blood pressure management should be individualized,

taking account of whether the patient has received reperfusion therapies as well as the degree of revascularization and perfusion status [7]. The AHA/ASA guidelines recommend permissive hypertension (BP ≤ 220/120 mm Hg) for the first 24–48 h in those not undergoing IV-tPA or EVT. However, blood pressure reduction below 185/110 mmHg is recommended prior to IV-tPA to reduce the risk of thrombolysis-associated haemorrhagic conversion of infarcted tissue [6].

Both high BP and low BP are associated with worse outcomes after AIS. In a retrospective study of 228 patients with anterior circulation stroke, higher maximum systolic BP in the first 24 h after EVT was independently associated with worse 90-day functional outcomes and higher rates of haemorrhagic complications [12]. Moreover, a retrospective cohort study including adults with anterior-circulation stroke enrolled in randomized clinical trials investigating anaesthetic techniques for EVT found that critical mean BP thresholds and durations for poor outcomes were < 70mmHg for more than 10 minutes and > 90mmHg for more than 45 minutes [13]. In a recent randomized controlled trial, intensive systolic BP management (100–129 mm Hg) after successful EVT did not reduce radiographic intraparenchymal haemorrhage rates at 24–36 h as compared with standard care (130–185 mm Hg) [14]. Of note, these findings are applicable only to patients with successful reperfusion and systolic BP > 130 mmHg at the end of the procedure. In the absence of clear evidence, systolic BP is often maintained < 160 mmHg for 24 h post-EVT [8], but with individualization of targets depending on degree of revascularization, collateral blood flow, extent of infarction and cardiac and renal comorbidities [11].

Symptomatic hypotension after AIS should be treated as a matter of urgency, but there are no data to support the use of induced hypertension or choice of vasopressors or inotropes [6;15]. Hypovolaemia should initially be treated with haemodynamic-guided fluid therapy, with avoidance of hypotonic solutions. Unnecessary use of vasopressors should also be avoided.

Neurological deterioration post-thrombectomy

Neurologic deterioration (ND) after IV thrombolysis or EVT, defined variably as an increase in National Institutes of Health Stroke Scale (NIHSS) by ≥2 or ≥4 points in a 24-h period, is associated with prolonged hospitalization, worse functional outcome, and increased mortality [16;17]. The incidence of early ND defined as ≥4-point increase in NIHSS score within the first 24 h ranges from 10% to 40% [18;19]. About 20% cases of ND are attributable to intracranial haemorrhage and malignant cerebral enema each [19], while other causes include ischaemia progression because of inadequate reperfusion, re-occlusion, thrombus propagation or extension of ischemic penumbra, and procedural complications [19;20]. Early recurrent ischaemic stroke (clinical and imaging evidence of ischaemic stroke in an independent arterial territory) accounts for approximately 2.6% of cases of ND and is believed to result from new embolic events due to thrombolysis induced fragmentation of pre-existing intracardiac or arterial thrombus [21]. Deterioration in neurological status may also be due to delirium, which can affect between 10% and 30% of patients in the acute phase after stroke [22]. Seizures, which have been reported in up to 3.14% of patients within 7-days of acute reperfusion therapies, may also contribute to ND [23], as can systemic abnormalities such as hyperglycaemia, metabolic disturbances or infection [24].

Close monitoring with frequent NIHSS score assessment is essential to detect ND. In addition, the 4-Assessment Test (4AT) and the Confusion Assessment Method-Intensive Care Unit (CAM-ICU) should be used to detect delirium. Incorporating appropriate diagnostic imaging and electroencephalography is often necessary to identify the aetiology of ND. With routine non-contrast computed tomography scanning, early signs of cerebral infarction can be visualized 3-6 hours after stroke onset. Dual energy computed tomography allows improved detection of early infarction, differentiation of acute intracerebral haemorrhage from contrast staining and small calcifications after EVT, and detection of clot persistence or early re-thrombosis without the need for additional contrast administration [25]. The

presence of a large diffusion weighted lesion on magnetic resonance imaging may be predictive of malignant cerebral oedema [26].

Prevention of hypovolaemia, hypo- and hypertension, hyperglycaemia and hyperthermia are primary targets for preserving collaterals to prevent ND [7;10;11]. Supportive care with attention to oxygenation, hydration, infection prevention, temperature management, thromboprophylaxis and biochemical parameters is essential (Table 1). Antiplatelet agents are used to reduce the risk and severity of recurrent stroke [7;11]. Prophylactic anticonvulsant therapy is not recommended although patients experiencing seizures require prompt treatment. Post-stroke haemorrhagic conversion may range in severity from petechiae within an area of infarcted tissue to a parenchymal hematoma causing mass effect (Figure 1). Larger, symptomatic bleeds require aggressive treatment of coagulopathy and hypertension while petechial haemorrhages can typically be observed. Surgical evacuation is not routinely recommended [11].

Cytotoxic cerebral oedema after AIS is unresponsive to steroids, hyperventilation or osmotic agents [11]. Hemispheric infarction due to occlusion of the internal carotid artery or proximal MCA can lead to significant cerebral oedema resulting in intracranial hypertension, cerebral herniation and death despite maximal medical therapy. This is often referred to as ‘malignant’ MCA infarction because of its life-threatening nature (Figure 2). Early randomized controlled trials demonstrated a mortality benefit of decompressive hemicraniectomy compared to best medical management in patients with malignant MCA infarction aged <60 years, although they did not demonstrate improved functional outcomes in survivors [27]. Considering the current evidence based on pooled analyses of randomized studies and meta-analyses, early DC within 48 hours of malignant MCA infarction is recommended in patients ≤60 years to reduce the risk of death and major disability (modified Rankin score [mRS] > 4-5) [27;28]. In patients >60 years of age, decompressive craniectomy improves survival but with major disability (mRS 4–5) [28;29]; if performed later than 48 hours after

symptom onset, decompressive hemicraniectomy is not superior to medical management in this age group.

The role of transcranial Doppler ultrasonography in stroke

Transcranial Doppler (TCD) ultrasonography allows bedside, non-invasive evaluation of cerebral haemodynamics [30]. Applications of TCD in AIS patients include:

- *Assessment and monitoring of recanalization* - According to a recent Cochrane analysis, TCD and transcranial colour Doppler accurately rule in or rule out occlusion or stenosis of intracranial arteries with 95% sensitivity and specificity [31]. Recanalization can be inferred by the appearance of flow in the vessel or an improvement in flow velocity.
- *Prognostication* - A normal TCD waveform pattern at 6 h after AIS is an independent predictor of early improvement, while flow velocity <30 cm/s within 12 h after middle cerebral artery (MCA) stroke correlates with poor recovery [32;33]. Moreover, MCA occlusions within 6 h of stroke onset predict haemorrhagic transformation with a positive predictive value of 72% [32;33]. The presence of microemboli independently predicts early ischemic recurrence.
- *Assessment of collateral flow* - Collateral enhancing strategies are important to restore blood flow within ischemic brain regions. In patients with haemodynamically significant extracranial internal carotid disease, a decrease in mean flow velocity with diminished flow acceleration and reduced pulsatility is seen in the ipsilateral MCA [32;33]. Collateralization is indicated by increased flow velocities in contralateral and posterior circulation arteries, with velocity gradient and reversal of flow in the ipsilateral anterior cerebral and/or ophthalmic artery (Figure 3) [32;33].
- *Detection of intracranial stenosis* - Identifying intracranial arterial stenosis has therapeutic implications in AIS patients for the prevention of further ischaemic insults. Though TCD reliably identifies high grade stenosis, its role in diagnosing lower

grades of stenosis is unclear. The TCD characteristics of intracranial stenosis are a focal increase in flow velocity with decreased velocity and increased pulsatility upstream from the lesion and abnormal flow immediately downstream from the lesion [31].

- *Microemboli detection* - Microemboli after successful EVT can originate from atheromatous lesions of carotid arteries or cardiac sources [32-34]. They are independent markers of recurrent embolic events within 90 days and can guide medical treatment in higher risk patients [35], though their association with adverse outcomes has recently been questioned [34].
- *Detection of right to left shunts* - In patients with cryptogenic stroke, right-to-left shunt may be a risk factor for ischaemic stroke. Compared to transoesophageal echocardiography, a “bubble study” involving injection of agitated saline followed by TCD-detection of microemboli in the cerebral circulation has a sensitivity of 95% and a specificity of 75% in detection of a patent foramen ovale [32;33].
- *Cerebral autoregulation assessment* – cerebral autoregulation is impaired in AIS patients who do not respond to thrombolytic therapy [36]. Transcranial Doppler can allow autoregulation-guided haemodynamic management and prognostication after AIS. Near infrared spectroscopy may be easier to use than TCD, and the feasibility of continuous estimation of optimal blood pressure and limits of cerebral autoregulation using near infrared spectroscopy has been demonstrated [37]. Not surprisingly, exceeding individual thresholds of autoregulation is associated with haemorrhagic conversion and worse functional outcome, while blood pressure below the lower limit of cerebral autoregulation is associated with greater infarct progression [37].

While TCD has clinically relevant applications in AIS triage, management and recovery prediction, it relies primarily on expert interpretation of TCD waveforms. There is a need for automated analysis techniques that can be employed when experts are not available [32].

Ethical issues

The management of AIS raises several ethical issues. Stroke-related deficits in cognition can limit a patient's ability to make informed and rational decisions about their care and communication problems can impact their ability to express those decisions [38]. In the absence of a clear advanced directive, interpretation of a patient's wishes by family members and clinicians are often imperfect in gaining a valid understanding of what an individual would have chosen in a particular circumstance [39].

Two invasive interventions warrant particular discussion – mechanical ventilation and decompressive hemicraniectomy. The requirement for mechanical ventilation is associated with worse outcomes after AIS. In a recent multicentre study including AIS patients receiving mechanical ventilation between 1997 and 2016, ICU-, hospital- and 1-year survival rates were 46.6%, 37.2% and 30.2%, respectively [40]. While such data can lead to reluctance to offer mechanical ventilation to certain groups, such as the elderly or those with severe strokes, systematic withholding of mechanical ventilation in any sub-group of stroke patients cannot be justified. Most prognostic studies of mechanical ventilation after AIS are out-dated and of poor quality, and it is unclear exactly what drives poor outcomes in some ventilated AIS patients while others go on to make a good recovery. The Stroke Prognosis in Intensive Care (SPICE) is a prospective multicentre cohort study which will investigate 1-year outcomes, ethical issues and care pathways of AIS patients requiring mechanical ventilation in an attempt to identify those who may benefit from prolonged mechanical ventilation [41].

Decompressive craniectomy is an effective intervention to reduce critically raised intracranial pressure and mortality in patients with malignant MCA infarction, but with attendant risk of survival with moderate or severe disability [42]. Though clinical trials report high rates of favourable outcomes after craniectomy in AIS patients younger than 60 years of age, the definition of 'favourable' outcome in clinical studies (mRS $\geq$4) may not reflect real-world

outcome expectations of patients [29;42]. Individuals categorized as mRS 4 are unable to walk or attend to their own bodily needs without assistance; though attitudes to levels of disability vary considerably, many would not find this degree of disability a good outcome (for them). However, it is overall quality of life (rather the functional outcome in isolation) that is most important to many individuals, and patients' perceptions of well-being and satisfaction with life are often discordant with their objective health status. Many individuals appear to adapt to life-changing events and subsequently accept a degree of disability that they would previously have judged to be unacceptable [43].

If patient and caregiver preferences are not taken into account prior to embarking on time-sensitive interventions such as decompressive craniectomy, there are significant risks on the one hand of producing outcomes that may be judged unacceptable to survivors and, on the other, of not offering life-saving interventions that could be beneficial to patients according to their own values [44]. The importance of shared decision making based on likely outcomes of therapeutic options, prolonged recovery times and potential post-procedure quality of life and need for life-long therapy cannot be over-estimated.

Conclusion

Effective reperfusion strategies, including tPA and EVT, have revolutionized the management of AIS over the last decade and can now be delivered in extended time windows and to those previously ineligible for intervention based on advanced neuroimaging criteria. Secondary systemic insults, such as hypo- and hypertension, hyperglycaemia and hyperthermia, can extend the region of brain ischaemia and must be prevented or corrected to minimize infarct progression. Together, a bundle of medical, endovascular and surgical strategies, when applied in a timely and consistent manner, can improve long-term stroke outcomes.

Key points

- Effective reperfusion strategies, including intravenous thrombolysis and endovascular thrombectomy, can now be delivered in extended time windows and to those previously ineligible for intervention based on advanced neuroimaging criteria.
- Systemic physiological insults, such as hypo- and hypertension, hyperglycaemia or hyperthermia, must be prevented or corrected to minimize infarct progression.
- Causes of neurological deterioration after reperfusion therapies include infarct extension, haemorrhagic conversion or worsening cerebral oedema, amongst others.
- Transcranial Doppler ultrasonography is increasingly used in acute stroke triage, management and recovery prediction.
- Acute ischemic stroke management raises several ethical issues, and shared decision making is essential to ensure outcomes that are compatible with an individual patient's expectations.

Conflicts of interest

DS receives research funding from the Agency for Healthcare Research and Quality (AHRQ) for improving patient safety in subarachnoid haemorrhage using transcranial Doppler simulation for bedside diagnosis of cerebral vasospasm. MS is Editor-in-Chief of the *Journal of Neurosurgical Anesthesiology*. The authors have no other conflicts to declare.

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Commentary and case scenarios discussing approaches to ensure that patients'

values are elicited and incorporated, and the possible range and nature of outcomes are discussed, prior to embarking on life-saving interventions associated with a risk of survival with severe disability.

LEGENDS TO FIGURES

Figure 1

Terminal carotid occlusion with haemorrhagic conversion of infarcted tissue after endovascular thrombectomy

A. CT angiogram showing left carotid terminus occlusion (arrow)
B. Pre-procedure non-contrast CT scan
C. Post-thrombectomy non-contrast CT showing subarachnoid blood and developing area of infarction in the MCA territory
D. Non-contrast CT scan 24 h post-thrombectomy showing haemorrhagic conversion of infarcted tissue

CT, computerised tomography; MCA, middle cerebral artery

Figure 2

Malignant middle cerebral artery infarction

Non-contrast axial CT scan showing:

A. Extensive left MCA territory infarction with midline shift and effacement of the left lateral ventricle.
B. Post left-sided decompressive craniectomy with expansion of infarct oedema beyond the craniectomy margins and resolution of midline shift.

CT, computerised tomography; MCA, middle cerebral artery

Figure 3

Transcranial Doppler ultrasonography to assess collateral flow after acute ischaemic stroke

A. The right MCA Doppler signal is dampened with lower velocity and pulsatility index than left.
B. The left ACA is normally directed but velocity is increased so that it can crossover to the right. The right ACA flow is reversed, hence, crossing over from the left to feed the right MCA.

ACA, anterior cerebral artery; MCA, middle cerebral artery

Figure 1

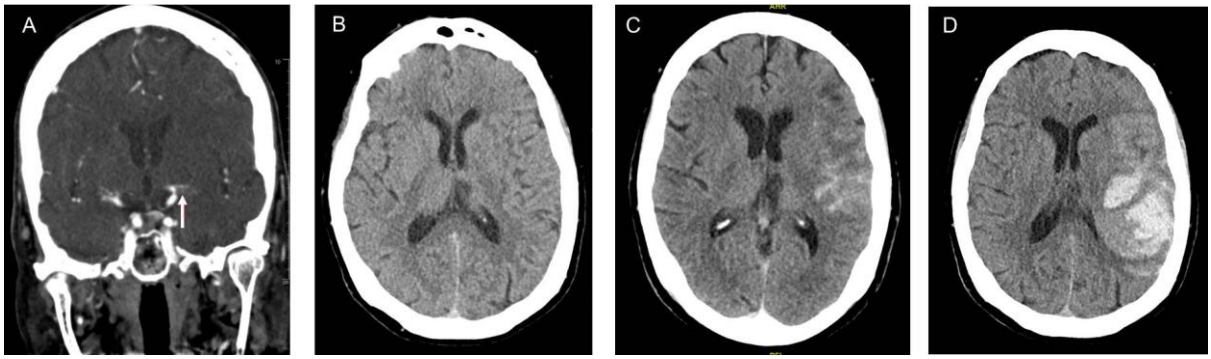

Figure 2

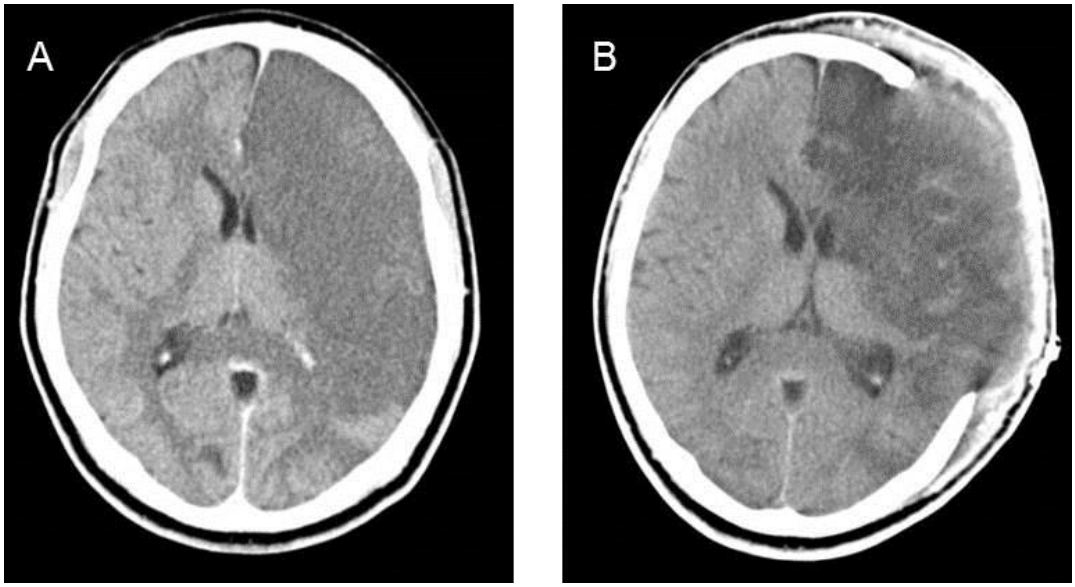

Figure 3

A

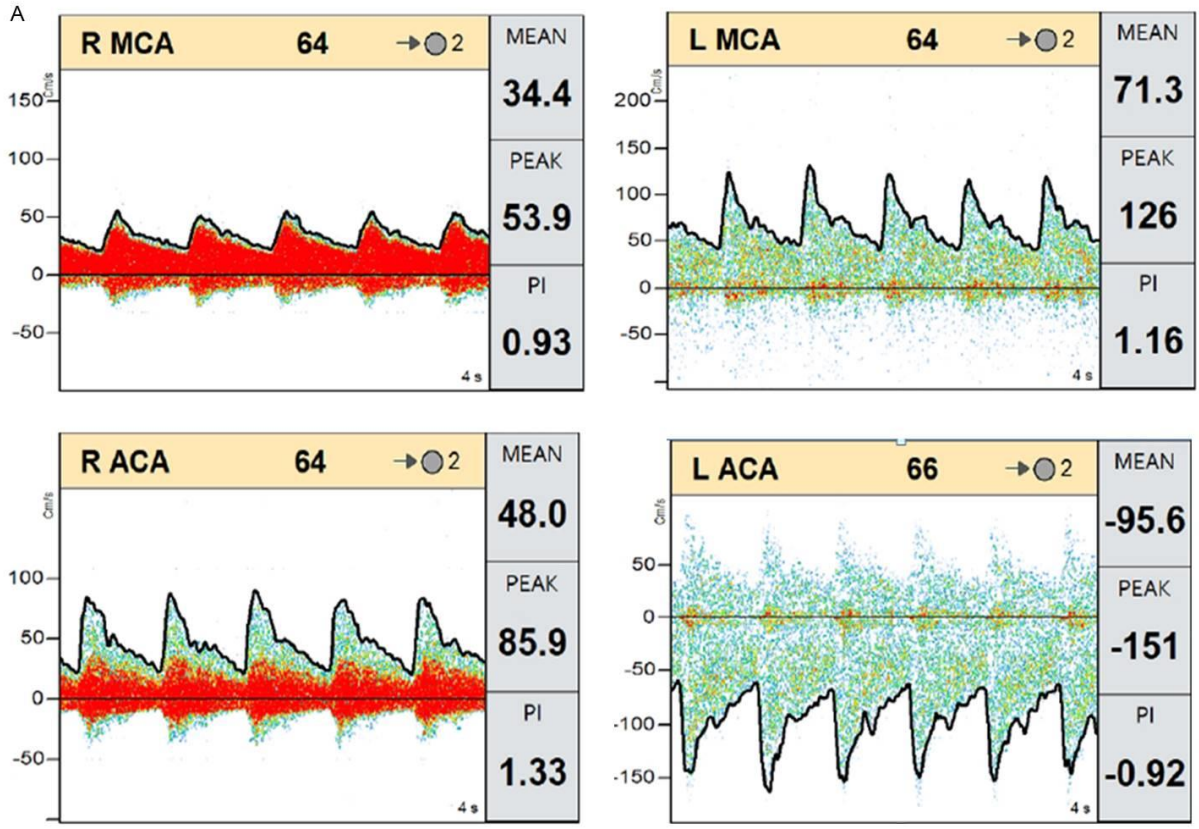
R MCA
64
2
MEAN
34.4
PEAK
53.9
PI
0.93
L MCA
64
2
MEAN
71.3
PEAK
126
PI
1.16
R ACA
64
2
MEAN
48.0
PEAK
85.9
PI
1.33
L ACA
66
2
MEAN
-95.6
PEAK
-151
PI
-0.92
4 s

Table 1

Systemic organ-specific critical care interventions in patients with acute ischaemic stroke

Airway and ventilation	• Continuous oxygenation monitoring • Avoid supplemental oxygen unless SpO_2 < 94% • Consider intubation and mechanical ventilation for: - reduced consciousness - impaired bulbar function - respiratory failure - ICP control
Haemodynamic and cardiac	• Continuous ECG and frequent BP monitoring • Advanced haemodynamic monitoring and echocardiogram for cardiovascular instability • Consider reducing BP < 220/120 mmHg by 15% if IV-tPA ineligible (avoid rapid BP lowering) • BP < 185/110 mmHg before IV-tPa and for 24 h after treatment • BP 160 mmHg for 24 h after EVT (individualised depending degree of revascularization, collaterals, extent of infarction • Fluid balance monitoring to target euvolaemia • Correct hypotension - initially with fluid (isotonic saline) - avoid unnecessary vasopressors/inotropes
Glucose and nutrition	• Close blood glucose monitoring • Treat hyperglycaemia to maintain glucose 140-180 mg/dL • Avoid hypoglycaemia (< 60 mg/dL) • Early swallow assessment (nil orally until then) • Enteral nutrition within 7 days (via NGT if impaired swallow)
Temperature	• Investigate/treat infective cause of pyrexia • Treat fever > 38°C - antipyretics - consider physical methods in sedated patients if antipyretics fail
Other	• Maintain haemoglobin > 7.0 g/dL • Aspirin (160 – 325 mg) within 24-48 h • VTE prophylaxis - intermittent calf compression in immobile patients - consider LMWH • early mobilisation • acute rehabilitation at level commensurate with tolerance

BP, blood pressure; GCS, Glasgow coma score scale; ICP, intracranial pressure; IV-tPA, intravenous tissue plasminogen activator; LMWH, low molecular weight heparin; SpO_2, arterial oxygen saturation; VTE, venous thromboembolism