

CONTEMPORARY NEUROLOGICAL DILEMMAS

Management pressure in



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Management of blood pressure in acute stroke

ACUTE STROKE AND HIGH BLOOD PRESSURE

'High' blood pressure (BP) is defined by the World Health Organization as systolic BP > 140 mmHg and diastolic BP > 90 mmHg. High BP is common in both acute ischaemic and haemorrhagic stroke, affecting about 80% of the patients, and this reflects several mechanisms (International Society of Hypertension Writing Group 2003):

- pre-existing hypertension;
- the stress of hospitalization;
- raised intracranial pressure (Cushing reflex);
- activation of neuro-endocrine pathways (sympathetic nervous system, mineralocorticoid and glucocorticoid).

The BP normally falls over the first week after stroke but it can fluctuate considerably making it difficult to discern trends in individuals. The relationship between BP and outcome is 'U-shaped' with both high and low BP being associated independently with death or dependency (Fig. 1) (Leonardi-Bee *et al.* 2002). This link between high BP and a poor outcome appears to be related to an increased risk of early recurrence and fatal cerebral oedema, but not haemorrhagic transformation of the infarct (Leonardi-Bee *et al.* 2002).

Extrapolating primary and secondary prevention data showing that long-term BP lowering reduces the risk of recurrent stroke (Collins *et al.* 1990; Rashid *et al.* 2003a), it seems logical to lower BP during the *acute* phase of ischaemic stroke with the aim of reducing the risk of *early*

recurrence, and also perhaps of improving outcome by reducing cerebral oedema. Also, in acute primary intracerebral haemorrhage, lowering the BP might reduce the risk of haematoma expansion and re-bleeding. However, cerebral auto-regulation is dysfunctional following acute stroke leading to fears that reducing BP would reduce cerebral blood flow (CBF) and so tissue perfusion, especially in patients

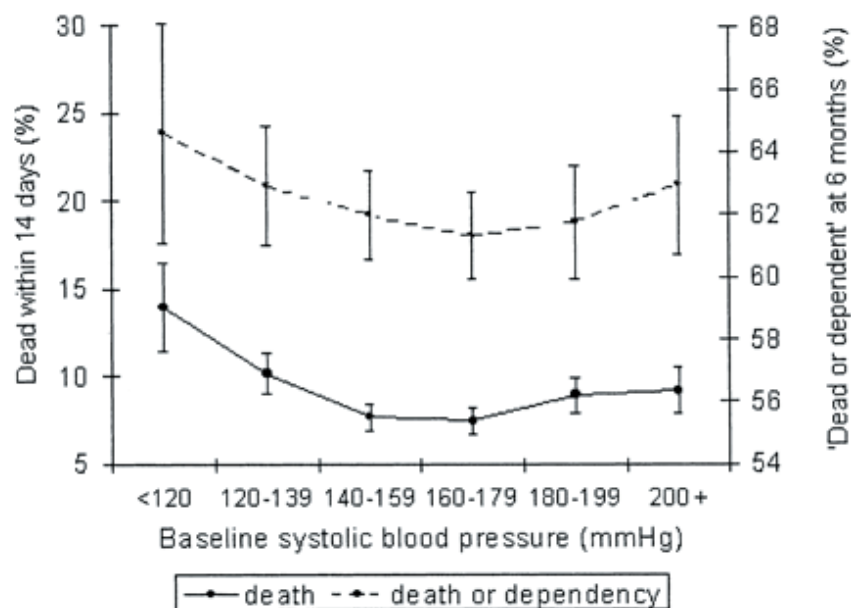


Figure 1 Relationship between blood pressure and outcome in acute stroke. Proportion of patients who died within 14 days (solid lines) or were dead or dependent at 6 months (dashed lines) by baseline systolic blood pressure within each blood pressure subgroup; 95% confidence intervals represented by error bars (Leonardi-Bee *et al.* 2002).

with chronic hypertension whose limits of auto-regulation are shifted to the right. Further, if the BP were lowered in patients with very stenotic or occluded carotid arteries, or an inadequate collateral blood supply, this might further compromise cerebral perfusion (Rothwell *et al.* 2003).

This balance between potential benefit and harm of lowering the BP in acute stroke has yet to be answered in large trials (Bath & Bath 1997; International Society of Hypertension Writing Group 2003; Robinson & Potter 2004). Unsurprisingly therefore clinical practice varies considerably (Bath *et al.* 2000). Furthermore, about 60% of patients with acute stroke *already* have pre-existing hypertension and most are taking anti-hypertensive drugs (International Society of Hypertension Writing Group 2003); whether these patients should continue or temporarily discontinue their prior anti-hypertensive medication remains unclear. Again, in view of the lack of evidence, clinical practice varies (Lindley *et al.* 1997; Bath *et al.* 2000).

TRIALS OF ALTERING BLOOD PRESSURE

Calcium channel blockers

Most data on altering BP in acute stroke come from randomised trials which tested calcium channel blockers, usually given as potential neuroprotective agents rather than for their effects on BP. A Cochrane meta analysis of 29 trials including 7665 patients showed no benefit with calcium channel blockers, in fact there was a non-significant increase in death and disability (Horn *et al.* 2001). The Blood Pressure in Acute Stroke Collaboration (2001) also found a trend towards a poor outcome in a review of 11 trials of patients taking oral calcium channel blockers. Neither can parenteral administration be recommended (International Society of Hypertension Writing Group 2003); the INWEST trial of intravenous nimodipine found more neurological deterioration in parallel with effects on diastolic BP (Ahmed *et al.* 2000). In fact, calcium channel blockers have multiple actions in addition to their vasodepressing effects and some may be harmful: in particular, they may reduce regional CBF and induce 'steal' away from the area of infarction.

β -receptor antagonists

β -receptor antagonists should theoretically

reduce the metabolic demand of ischaemic brain tissue, as well as reduce the BP. However, in a randomised trial RCT of atenolol and propranolol in 302 acute stroke patients, there was a trend towards increased early death and poor functional outcome (Barer *et al.* 1988). β -receptor antagonists have negative inotropic activity so they may have reduced global CBF.

Labetalol

Labetalol is a combined alpha and β -receptor antagonist with some inhibitory effect on alpha-receptors. It was used as part of the protocol for managing hypertension in the National Institutes of Neurological Disorders and Stroke (NINDS) trial of intravenous thrombolysis in acute ischaemic stroke. Although associated with a reduction in death, this BP lowering was a non-randomised comparison and therefore the data are difficult to interpret (Brott *et al.* 1998).

Nitric oxide donors

Nitric oxide donors are neuroprotective, and lower BP, whilst maintaining CBF in experimental stroke (Willmot *et al.* 2003). In two small trials, transdermal glyceryl trinitrate (GTN) reduced BP without altering platelet activity or middle cerebral artery blood flow velocity (Bath *et al.* 2001; Rashid *et al.* 2003b). A recent trial found that GTN reduced systolic BP by 14% and diastolic BP by 4% without reducing global, hemispheric or regional CBF; furthermore, GTN did not cause 'cerebral steal'. (Willmot & Bath, unpublished data).

Angiotensin modifying drugs

Angiotensin modifying drugs reduce the activity of the renin-angiotensin system and increase CBF at low perfusion pressures by shifting the lower limit of cerebral auto regulation to the left. In a small trial of perindopril, an angiotensin converting enzyme (ACE) inhibitor, there were significant reductions in systemic BP without adverse effects on global CBF or middle cerebral artery blood flow velocity (Dyker *et al.* 1997). Similar results were seen with losartan, an angiotensin receptor antagonist (ARA) (Nazir *et al.* 2003). In the ACCESS trial of candesartan, another ARA, there was a significant reduction in the composite outcome of death, cerebral and cardiovascular events (Schrader *et al.* 2003). However, this trial is difficult to interpret because the reduction in morbidity or mortality did not occur

Table 1 Possible indications for lowering blood pressure acutely in acute stroke

BP > 220/120
BP > 200/100 with end-organ involvement
– Aortic dissection
– Hypertensive encephalopathy
– Cardiac ischaemia
– Pulmonary oedema
– Acute renal failure
BP > 200/120 and intracerebral haemorrhage

until well after the 7-day period of treatment, there was no difference in BP between active and control groups, and the trial was stopped early.

Other blood pressure lowering agents

Not all blood pressure lowering agents lower BP in the time frame of acute or subacute stroke; for example, the thiazide diuretic, bendrofluzide, failed to reduce BP over one week in a small trial ($n = 36$) (Eames *et al.* 2004). Centrally acting drugs such as alpha-methyl-dopa and moxonidine have not been assessed in acute stroke.

CURRENT PRACTICE

In the absence of any proven benefit for lowering BP, current guidelines recommend that BP should not be actively lowered in acute stroke. Exceptions to this rule (Table 1) include hypertensive patients with severe concomitant vascular complications, e.g. those with aortic dissection, encephalopathy, cardiac ischaemia

or failure, and acute renal failure. Patients with primary intracerebral haemorrhage and high BP are theoretically at higher risk of haematoma expansion and rebleeding than those with lower BP – some guidelines recommend that they too should have their BP lowered (Adams *et al.* 2003; International Society of Hypertension Writing Group 2003; Robinson & Potter 2004).

When treatment for hypertension is indicated the choice of agent is important, and the rate of BP lowering should be cautious. Reduction should probably be in a proportional manner, relative to the baseline blood pressure, rather than target driven (International Society of Hypertension Writing Group 2003). Possible treatment regimes, not yet supported by randomized trials, are given in Table 2. Some general tips are:

- Parenteral agents have the advantage that they can be titrated carefully to ensure gradual BP reduction, although this does require close haemodynamic monitoring in a high dependency environment.
- Although there are no definitive data to support their use, both labetalol and nitrates (sodium nitroprusside or glyceryl trinitrate) have been recommended. But, importantly, sodium nitroprusside has antiplatelet properties (Butterworth *et al.* 1998) and should probably be avoided in intracranial haemorrhage.
- Sublingual agents such as calcium antagonists and ACE inhibitors should be avoided because they have rapid absorption and onset of action which may lead to fast and precipitous falls in BP.

Table 2 Possible agents for managing hypertension in acute stroke

AGENTS	GUIDELINES
Intravenous agents	Need continuous haemodynamic monitoring Aim for gradual reduction in BP by 5–15%
Labetalol	10–20 mg bolus over 1–2 mins. Dose can be repeated up to maximum dose of 300 mg. Alternatively, labetalol infusion 2 mg/min can be used.
Glyceryl trinitrate	10–200 µg/min titrated according to BP
Sodium nitroprusside	0.5–1.5 µg/kg/min titrated according to BP (avoid in intracerebral haemorrhage due to antiplatelet properties)
Nicardipine	5 mg/h infusion titrated according to BP up to maximum of 15 mg/h
Sublingual agents	Should be avoided as may cause precipitous falls in BP
Oral agents	Not always possible as up to 50% patients dysphagic
Transdermal agents	Glyceryl trinitrate patch 5–10 mg/24 h titrated according to BP

Transdermal preparations have the advantage of a relatively slow onset of action and they are titratable.

- Oral treatments are not always possible as up to 50% of patients have dysphagia in acute stroke.
- Transdermal preparations have the advantage of a relatively slow onset of action and they are titratable; patches can be removed or additional patches added, in response to BP change.

ACUTE STROKE AND LOW BLOOD PRESSURE

Low blood pressure is not common in acute stroke but it is, like high BP, associated with a poor outcome (Leonardi-Bee *et al.* 2002). Reasons for low BP include potentially reversible conditions such as hypovolaemia, sepsis, impaired cardiac output secondary to cardiac failure, arrhythmias or cardiac ischaemia, and aortic dissection. Where present, these conditions need early detection and rapid management with fluid replacement, anti-arrhythmic drugs and inotropic support, as appropriate. Theoretically, raising the BP in hypotensive patients with acute ischaemic stroke might increase perfusion to the ischaemic penumbra. But, aside from vasospasm following subarachnoid haemorrhage, where drug-induced hypertension is standard clinical practice (in

combination with hypervolaemia), there are no trial data for treating hypotension in ischaemic stroke. Sympathomimetic vasopressors (e.g. phenylephrine) are used to raise BP in other fields of acute medicine, but have potential safety drawbacks in acute stroke, including cardiac ischaemia and activating platelet function. Trial data are therefore required before vasopressor therapy can be recommended routinely in hypotensive patients with acute stroke.

ONGOING TRIALS

To date all studies on BP in acute stroke have been either too small or observational rather than randomised. Data from large randomised trials are urgently needed, as they have been for decades, to provide evidence-based guidelines for the management of hypertension, hypotension and for those on prior anti-hypertensive therapy in acute stroke. A number of ongoing trials are set to address these important questions:

- The Efficacy of Nitric Oxide in Stroke (ENOS) trial is a prospective multicentre randomised trial to assess the safety and efficacy of lowering BP with 1 week of daily transdermal glyceryl trinitrate. Patients re-

CONCLUSIONS

- High blood pressure is a common problem in acute stroke and is associated with an adverse outcome.
- Pre-existing hypertension is also common in stroke patients, many of whom are taking anti-hypertensive therapy.
- In general, high blood pressure should not be lowered acutely unless there is evidence of acute end-organ damage.
- When blood pressure does need to be lowered acutely, a cautious proportional approach is recommended with parenteral or transdermal treatment.
- ACE inhibitors, angiotension receptor antagonists and nitric oxide donors are each effective at lowering blood pressure in acute stroke although their effect on outcome is unknown.
- There are safety concerns surrounding the use of β -receptor antagonists and calcium channel blockers in acute stroke
- Low blood pressure in acute stroke is also associated with poor outcome; detection and correction of any reversible cause should be a priority.

ceiving prior anti-hypertensive agents will also be randomised to temporarily continue or stop. The trial will assess the effect of these interventions in 5000 patients with acute (< 48 h) ischaemic or haemorrhagic stroke at 3 months (<http://www.enos.ac.uk>). (Bath 2001)

- The Continue Or Stop post Stroke Antihypertensives Collaborative Study (COSSACS) is a multicentre randomised open trial assessing whether prior anti-hypertensive agents should be stopped or continued in both ischaemic and haemorrhagic stroke patients within 24 h of onset. The primary outcome is death or dependency assessed at 14 days; 2900 patients will be enrolled (cossacs@le.ac.uk).
- The Scandinavian Candesartan Acute Stroke Trial (SCAST) is following up the interesting findings of ACCESS by randomizing 2500 patients with acute ischaemic or haemorrhagic stroke (< 30 h) to candesartan or placebo.
- The Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) study will assess pressor therapy (phenylephrine) in hypotensive ischaemic stroke, and depressor therapy (labetalol or lisinopril) in hypertensive ischaemic and haemorrhagic stroke (chips@le.ac.uk).

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