

# “Triple H” Therapy for Aneurysmal Subarachnoid Haemorrhage: Real Therapy or Chasing Numbers?

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## ABSTRACT

*Despite technological and medical advances for the treatment of SAH that have had a positive impact on outcomes over the last 20 years, but the all-cause mortality for this often-catastrophic condition remains high at 12 - 15%. Survival will ultimately depend on the severity of the haemorrhage, the subsequent loss of functional neurones and the extracranial reserve of the patient. In this regard, advances in neuroradiology and operative techniques together with expert neurocritical care and rehabilitation provide the best chances of short- and long- term survival respectively.*

*In this context, the contribution of cerebral vasospasm to attributable morbidity and mortality remains conjectural albeit real, and whilst medical anti-vasospastic therapies should be considered in vulnerable patients, they should be used with circumspection and caution.*

*There is little or no evidence to justify the aggressive use of anti-vasospastic therapies as a preventative manner with exception of oral nimodipine in patients with low-grade aneurysmal subarachnoid haemorrhage. Concomitant use of induced hypertension/hypervolaemia/haemodilution cannot be recommended on current evidence, but if employed should be done on an individualised basis, considering the patients underlying neurological condition, cardiopulmonary reserve, adequacy of systemic and neurological monitoring and access to expert neuroradiological, neurosurgical and neurocritical care services. (Critical Care and Resuscitation 2005; 7: 206-212)*

**Key words:** Subarachnoid haemorrhage, Triple H therapy, resuscitation, review

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Aneurysmal subarachnoid haemorrhage (SAH) presents a substantial clinical challenge to neurosurgeons and intensive care physicians alike. Often presenting as a catastrophic intracranial haemorrhage with loss of consciousness, functional survival is dependent on the promptness of resuscitation, early identification of the site of the aneurysm, definitive ablative therapy (either surgical clipping or radiological implantation of endovascular coils), optimisation of the post-operative medical state and the prevention and treatment of delayed ischaemic neurological deficits.

Overall outcomes in patients with SAH have improved over the past 20 years, primarily due to advances in neurosurgery, interventional neuroradiology and neurocritical care. Within this therapeutic

paradigm, emphasis has focussed on the prevention and treatment of cerebral ischaemia related to vasospasm, which is regarded as an important cause of morbidity and mortality.

The development of delayed ischaemic neurological deficits following SAH constitutes a major complication, and has been associated with increased mortality rates in the first two weeks after SAH, as well as permanent disability in one third of cases.<sup>1</sup> Attention to the potential deleterious effects of vasospasm was highlighted following studies identifying the beneficial effects of calcium channel blockers such as nicardipine and nimodipine.<sup>2,3</sup> Whether the development of delayed ischaemic neurological deficit is indeed due to cerebral arterial vasospasm, microvascular thrombosis or

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neuronal apoptosis due to latent cerebral infarction is conjectural, and is almost certainly multifactorial.<sup>4</sup> However, in current clinical practice, the development of delayed ischaemic neurological deficit is invariably attributed to “vasospasm”. This perception has been highlighted by the demonstration of intracranial vasospasm by neuroimaging in up to 70% patients following SAH, of which a substantial proportion (up to 30%) may be asymptomatic.

Over the last 15 years, strategies to prevent and treat cerebral vasospasm following SAH have evolved from basic physical and haemodynamic principles, using a myriad of protocols titrated at a wide range of physiological and clinical endpoints. Despite widespread recognition of this important clinical problem, there is great variation in the application, design and usefulness of these clinical strategies, and a paucity of high-quality evidence upon which to base treatment algorithms.<sup>5</sup> Accordingly, most treatment algorithms have been designed according to individual clinician and institutional preferences, often justified by anecdotal reports of benefit. However, the use of aggressive haemodynamically-based anti-vasospastic strategies have been associated with significant morbidity and mortality, with some reports of excess mortality attributed to anti-vasospastic strategies above those attributable to primary and secondary subarachnoid haemorrhage.

The aim of this review is to summarise the physiological principles of haemodynamically-based anti-vasospastic strategies, assessment of efficacy of reversal of vasospasm, the evidence for the use of these strategies and some recommendations for future research.

### Historical Perspective

Prior to 1980, the medical management of SAH was directed at minimising fluctuations in systemic blood pressure and sympathetic tone to reduce the risk of aneurysmal rebleeding. Indeed, most patients with low grade SAH (i.e. deemed to be “survivable”) were rendered relatively hypotensive, using agents such as trimetaphan, specifically with the aim of reducing the risk of rebleeding until surgical control of the aneurysm was possible. During this period, surgical intervention was typically performed between 10 - 21 days post bleed, provided the patient was in an acceptable medical and neurological state. During this period, the mortality of SAH was around 30%, with the predominance of deaths occurring within 7 days.<sup>6</sup>

An important study by Meyer in 1983 demonstrated the “natural” progression of cerebral blood flow over time following SAH.<sup>7</sup> From 1265 inhaled Xe<sup>133</sup> mapping studies in 116 patients, cerebral blood flow

was observed to decrease from a mean of 41 mL/100g/min on presentation to 34 mL/100g/min at day 14, with some restitution in flow to 38 mL/100g/min by day 20. This study was one of the first to demonstrate relative and absolute cerebral oligoemia following SAH in patients where no active intervention to augment systemic blood pressure was conducted.

With advances in neuroimaging and earlier surgical intervention, and increasing awareness of the importance of maintaining adequate cerebral perfusion in the injured brain (particularly following traumatic brain injury), strategies aimed at maintaining or cautiously increasing systemic blood pressure (with the aim of augmenting cerebral blood flow) began to emerge. Origitano highlighted this change in strategy in a case series published in 1990.<sup>8</sup> Using Xe<sup>133</sup> maps, induced systemic hypertension with dopamine resulted in elevations in cerebral blood flow over each of 20 days from admission when compared to Meyer’s cohort. The mortality (n = 43) was 16%, of which 37% had angiographic evidence of cerebral vasospasm. This case series was one of the first to suggest that induced hypertension following SAH may be associated with improved outcomes. Clearly, these small, single-centred, observational studies (using historical “controls”) with high levels of intervention bias do not constitute high-quality scientific evidence, but do provide some insights into the reasons for changes in management over time. Unfortunately, the majority of evidence published to date on the efficacy of induced hypertension is of similar quality.

### Calcium antagonists and vasospasm

The change in priorities of medical management of SAH outlined above saw the emergence of induced hypertension as the vanguard of medical anti-vasospastic therapy. This was accompanied by the use of calcium antagonists, specifically nimodipine and nicardipine. A decade after the publication of the first major study of nimodipine in 1993,<sup>3</sup> the Cooperative Aneurysm Study<sup>2</sup> concluded that whilst nicardipine treatment was associated with a reduced incidence of symptomatic vasospasm, there was no significant difference in outcome (determined at three months) or mortality (17 vs 18%: nicardipine vs placebo). The authors also postulated that, as induced hypertensive treatment was more commonly used in the placebo group of the nicardipine study, “hypertensive/hypervolemic therapy may be effective in reversing ischaemic deficits from vasospasm once they occur”. In many ways, the results of this study conveyed a degree of legitimacy to an emerging trend in medical management of SAH, endorsing the use of both calcium antagonists and hypertensive/hypervolemic treatment.

The results of the Cooperative Aneurysm Study were scrutinised by Solenski in 1995 that provided a different perspective.<sup>9</sup> This report examined the frequency, type, and prognostic factors of medical (non-neurologic) complications from this study. The frequency of at least one life threatening medical complication was 40%, and the proportion of deaths from medical complications was 23%. Specifically, pulmonary oedema occurred in 23% patients and clinically significant arrhythmias in 30%. This value was comparable with the proportion of deaths attributed to the direct effects of the initial haemorrhage (19%), rebleeding (22%), and vasospasm (23%) after aneurysmal rupture. Whilst there was wide inter-institutional variation (total 41 neurosurgical centres) and a non-significant association between “hypertensive/hypervolemic” therapy, Solenski concluded that “meticulous monitoring for (cardiorespiratory), metabolic and haematologic derangements” was mandatory.

Furthermore, the efficacy of calcium antagonists in reducing vasospasm and improving functional survival remains conjectural. A recent systematic review from the Cochrane Stroke Group Trials Register (2003) examined whether calcium antagonists improve outcome in patients with aneurysmal SAH from 12 trials (n = 2844 patients: 1396 in the treatment group and 1448 in the control group).<sup>10</sup> Collectively, the use of calcium antagonists (nimodipine, nicardipine, AT877 and magnesium) reduced the risk of poor outcome, (relative risk [RR] 0.82; 95% confidence interval [95%CI] 0.72 to 0.93); reduced the clinical signs of secondary ischaemia (RR 0.67; 95%CI 0.60 to 0.76); and CT or MRI confirmed infarction (RR 0.80; 95%CI 0.71 to 0.89). The RR of death on treatment with calcium antagonists was 0.90 (95% CI 0.76 to 1.07). The effects observed on outcome largely depend on a single large trial of *oral* nimodipine, with inconclusive evidence for the other calcium antagonists, suggesting that there is insufficient evidence for the routine use of intravenous nimodipine for aneurysmal SAH on current evidence. These results on reduction of secondary ischaemia are at variance to an earlier meta-analysis of 10 trials (n = 2756 patients).<sup>10</sup> In the analyses for nimodipine only, the RR reduction of angiographically-detected cerebral vasospasm was not statistically significant 0.09 (95%CI, -0.02 to 0.19), as opposed to nicardipine (RR 0.21; 95%CI 0.66 to 0.34). These authors conclude that the intermediate factors by which nimodipine exerts its beneficial effect remain uncertain.

Given strong phase I and phase II data about the potential physiological benefit of calcium antagonists in reversing cerebral vasospasm, where locally applied or systemically delivered calcium antagonists result in transient cerebral arterial vasodilation, the lack of

demonstrable benefit of these agents under clinical and pathophysiological conditions is problematic. This relates to the heterogeneity of patient populations, variation in the timing of the intervention(s), inconsistency and inaccuracies in the measurement of effect and quantification of outcomes and inadequate trial design and statistical power. Considering these issues, the likelihood of demonstrating improved outcomes or reversal of delayed ischaemic neurological deficit using a complex clinical algorithm such as induced hypertension ± haemodilution ± hypervolaemia would appear to be intuitively remote.

### “Triple H” Therapy

As outlined above, the recognition of the importance of maintaining cerebral perfusion in patients with SAH and traumatic brain injury has resulted in the development of haemodynamically-based management strategies. These include induced systemic hypertension, isovolaemic haemodilution and hypervolaemic haemodilution. Together, and in various combinations, these strategies have been termed “Triple-H” therapy, although no standard definition for this exists.<sup>11</sup> Accordingly, “Triple H” therapy will be considered by each component and subsequently as a collective strategy.

### Induced hypertension

Pharmacological augmentation of systemic blood pressure using vasoactive agents, such as catecholamines, is the most common method of induced hypertension. This strategy is predicated on the assumption that elevations in mean arterial pressure will increase cerebral blood flow, particularly in areas of the cerebral penumbra rendered ischaemic by vasospasm. Whilst seemingly intuitive, there are a number of caveats and limitations of this physiologically naïve assumption:

### The cerebral circulation

Under physiological conditions, cerebral blood flow is maintained at relatively constant rates in the presence of fluctuating cerebral perfusion pressures. This autoregulatory protective mechanism is mediated via microvascular fluxes of local vasodilatory and vasoconstrictory mediators, under intense neuro-hormonal control. Access of systemically administered drugs to the cerebral circulation is regulated by the anatomical and metabolic blood-brain barrier.<sup>12</sup> Under pathophysiological conditions such as traumatic brain injury, induced or malignant hypertension or subarachnoid haemorrhage, these autoregulatory functions may be impaired, but not to a predictable and or consistent level.<sup>13,14</sup> Consequently, there is marked intra- and inter-

individual variability in the response to manipulations of the cerebral circulation following pathophysiological perturbations such as aneurysmal subarachnoid haemorrhage.

#### Measurement of the cerebral circulation

Assessing fluctuations in cerebral blood flow to augmentation of systemic blood pressure is critically dependent on the methods of measurements of both parameters. To date, there is no reliable, bedside, real-time measurement of cerebral blood flow, and researchers and clinicians alike are dependant on indirect or surrogate measurements. Under controlled research conditions, assessments of the changes in cerebral blood flow under conditions of induced hypertension have produced varied results.<sup>15</sup> Under physiological conditions, infusions of vasoactive agents such as adrenaline, noradrenaline and dopamine have been demonstrated to produce corresponding increases in cerebral blood flow at extreme levels of induced hypertension (eg mean arterial pressure > 160-180mmHg). Using a variety of direct measurements of cerebral blood flow such as implanted Doppler flowmeters, radiolabelled microspheres and PET scans, the "breakpoint" at which the "upper" autoregulatory threshold occurs is extremely variable, both within and between species. Under simulated pathophysiological conditions, autoregulatory thresholds are more variable,<sup>16,17</sup> and depend on the nature of the primary insult and measurement technique.

Translating the results of animal data into humans is more problematic, primarily because of the reliance of indirect and intermittent measurements of cerebral blood flow. Of these, transcranial Doppler and intermittent neuroimaging such as Xe<sup>133</sup> or PET scan have been most commonly used. Limited studies on the utility of assessing augmentation of cerebral blood flow have produced conflicting and inconsistent results, with the majority of studies using reproducible and operator-independent techniques (such as Xe<sup>133</sup> or PET) showing minimal or inconsistent changes in cerebral blood flow. For example, an observational study analysing 212 cerebral blood flow maps using Xe<sup>133</sup> labelled CT demonstrated that in a cohort of patients with SAH, induced hypertension (using dopamine), produced equivalent increases cerebral blood flow in a minority (30%) of ischaemic and non-ischaemic areas of the brain.<sup>18</sup> However, only 15% of territories were shown to be ischaemic, of which the majority had evidence of infarction. By contrast, dopamine produced reductions in cerebral blood flow in non-ischaemic areas to a similar degree.

The use of transcranial Doppler as a surrogate measurement of cerebral blood flow has attained

popular use primarily because of its non-invasiveness and ease of access. Insonation through naturally occurring acoustic windows allow determination of changes in systolic, diastolic and mean velocities through large cerebral vessels and distinct patterns and indices associated with normal, hyperaemic, vasospastic and absent flow are recognised.<sup>19</sup> However, these indices do not provide assessment of altered flow through cerebral arterioles or microvascular regions, where cerebral vasospasm is most likely to occur. Further, transcranial Doppler is a markedly operator-dependent technique, especially when intermittent measurements are used. Studies analysing the agreement between "vasospasm" identified by transcranial Doppler and other neuroimaging techniques (SPECT, CT and angiography) have produced conflicting results.<sup>20</sup> Given these limitations, transcranial Doppler cannot be recommended as a sole measurement tool for the determination of cerebral vasospasm.

Cerebral angiography remains the "gold standard" for the clinical diagnosis of vasospasm. Although intermittent, angiography provides unequivocal imaging of vasospastic vessels to arteriolar levels, and the response to locally administered vasodilators such as papaverine may be assessed immediately. However, catheter-induced vasospasm may produce artefactual false positives, and whilst angiographic evidence of vasospasm may be apparent, this may not correlate with functional cerebral ischaemia resulting in delayed ischaemic neurological deficits.

#### Measurement of the systemic circulation.

Given the accepted difficulty of assessing and quantifying changes in the cerebral circulation to induced hypertension, most clinicians have adopted a pragmatic approach using a systemic haemodynamic target, with the assumption (or hope) that this will translate into improved cerebral perfusion.

In a conscious patient, this is an acceptably pragmatic approach, and a "target" blood pressure should be that which accords with the patient's pre-morbid blood pressure, and that at which the patient has the best neurological function. Clearly, the lowest blood pressure to attain these indeterminate parameters should be attained.

However, in patients with altered consciousness, neurology becomes more difficult to determine, and in an unconscious patient, impossible. Under these conditions, a "target" blood pressure is often prescribed. There are no evidence-based guidelines or definitive studies to assist in the selection of such a target and consequently, there is marked inconsistency in the level, parameter and method of measurement of systemic blood pressure. From a physiological perspective, flow

and pressure have a relationship that is dependent on a number of variables including the pressure gradient across the brain, vessel diameter and blood viscosity. Of these the pressure gradient is the most important factor, and this correlates with the mean or average flow across the vascular system. Accordingly, mean arterial pressure is the systemic pressure that best correlates with flow, and should be used as the "target" parameter. Further, measurement of mean arterial pressure through an arterial catheter reduces the potential for error that occurs when systolic and diastolic pressures are determined. However, many clinicians continue to use *systolic* blood pressure as the "target" pressure in these conditions, on the basis of familiarity and the delusion that systolic pressure is the "driving" force across the vasculature. When compounded by potential errors of measurement (such as transducer and catheter calibration, damping, arterial diameter and inconsistencies in reference levels), and the reliance of non-invasive sphygmomanometers, this practice is largely guesswork.

The level of target pressure is another clinical area of inconsistency, with systolic targets ranging from 120-200 mmHg and mean arterial pressures between 90-140 mmHg. Again, there is no evidence upon which to base these targets, but given the limited relationship between systemic blood pressure and augmentation of cerebral blood flow, prescription of targets that would be regarded by many physicians as severe hypertension, particularly in patients with an acute intracranial haemorrhage. Consequently "blind" application of these algorithms must be regarded with circumspection and caution.

### Selection of vasoactive agent

The catecholamines, adrenaline, noradrenaline and dopamine, are the most commonly used agents in this context. Within Australia, noradrenaline is regarded by many as the agent of choice, although there is a paucity of evidence to support this practice. Under physiological conditions, catecholamines do not cross the blood-brain barrier, and catecholamine-induced hypertension may be assumed to result in minimal direct effect on the cerebral circulation. This hypothesis has been confirmed in a number of animal studies, although at extreme levels of induced hypertension, blood-brain barrier permeability is altered, and direct cerebrovascular effects, such as cerebral hyperaemia may result, particularly with dopamine.<sup>15</sup> Under conditions where blood-brain barrier permeability is altered, exogenous catecholamines exert a more pronounced cerebral vasodilatory effect on the cerebral circulation in a dose-dependent manner, most pronounced by dopamine.<sup>16,21</sup> However, whether this translates into

clinically important increases or reductions in flow through ischaemic areas of brain, particularly following SAH is unknown.

On balance, noradrenaline may be regarded as the agent of choice, as it has a lower metabolic side-effect profile to adrenaline. Increasing concerns of cerebral hyperaemia and neuroendocrine and immunomodulatory side effects of dopamine have resulted in a decrease in its use,<sup>22</sup> although dopamine remains a first line agent in parts of Europe and North America.

### Hypervolaemic haemodilution

Together, induced hypervolaemia and isovolaemic or hypervolaemic haemodilution form one of two "H's" in "Triple H" therapy.

### Hypervolaemia

The intended purpose of induced hypervolaemia is to increase regional cerebral blood flow throughout the brain, but particularly in areas that have impaired myogenic autoregulation. As outlined above, cerebral autoregulatory processes are under complex neuro-hormonal control, and it is counter-intuitive that a simple manoeuvre such as administration of large volumes of intravenous fluid would any prolonged effect on regional or microvascular flow.

The injudicious use of fluid loading is associated with highest incidence of medical side effects, particularly pulmonary oedema and cardiac ischaemia.<sup>9</sup> As many patients with SAH have associated cardiorespiratory disease, aggressive fluid loading to arbitrary parameters is a hazardous practice, even under "intensive", but often misleading monitoring from pulmonary artery catheters. In patients with intact renal and preserved cardiac function, it is often impossible to attain a "hypervolaemic" state. The administration of large volumes of intravenous colloids or crystalloids invariably results in a polyuric state, often complicated by electrolyte disturbances such as hypokalaemia and hypomagnesaemia and the associated arrhythmogenicity. Hypervolaemia-induced polyuria in SAH patients is frequently termed "cerebral salt wasting", when in most circumstances is entirely iatrogenic.

Given the physiological improbability of attaining a hypervolaemic state in the majority of patients, and the equal improbability that it will improve regional cerebral ischaemia, induced hypervolaemia should be done with great circumspection (if at all) and not blindly administered to standard haemodynamic parameters such as right atrial pressure or derived variables such as PAOP, ITBV and EVLW.<sup>23</sup>

### Haemodilution

Reduction in blood viscosity will alter rheological

properties of blood and theoretically improve flow through ischaemic regions, thereby improving substrate delivery. The optimal rheology for the cerebral circulation is considered to be 0.31, although the basis of this determination is limited. Given the complexity of regional autoregulation, it is improbable that modest reductions in viscosity (induced by isovolaemic reduction in red cell mass or induced hypervolaemia) will result in significant improvements in regional blood flow over and above those that normally occur in acute illness.

There is little evidence regarding the target haematocrit required to achieve improved flow in patients with SAH-induced vasospasm, nor robust methods of measuring efficacy of induced haemodilution. Given the increasing trend by clinicians to accept lower haemoglobin levels in patients with critical illness, relative haemodilution is a state that occurs in the majority of patients regardless of intention.

However, as a deliberate anti-vasospastic strategy, it remains difficult to implement and unproven.

#### The evidence for "Triple H" therapy.

Despite prominence in neurosurgical and neurocritical practice, the evidence on the efficacy of "Triple H" therapy in improving cerebral vasospasm and improving outcome is limited, and on current data cannot be regarded as routine or proven treatment.

Given the discourse above, there is a flimsy physiological basis upon which to base "Triple H" therapy as an effective treatment. This is compounded by marked variations in the application, interpretation and utilisation of this strategy, so that comparative studies are limited by inadequate power, variations in the definitions and applications of the components of "Triple H", inadequate trial design and follow-up.

This was highlighted in a recent systematic review of the prevention of delayed ischaemic neurological deficits with "Triple H" following SAH published in 2003.<sup>24</sup> From 465 reports on "Triple H" screened between 1996-2001, 16 prospective studies on "Triple H" were identified from which 4 were had a control group and 2 had adequate allocation concealment. There were high levels of inadequate internal and external trial validity in the 4 "higher" quality trials and a total patient sample of 224 patients. This meta-analysis concluded that compared with no prevention, "Triple H" therapy was not associated with a reduced risk of delayed ischaemic neurological deficit (RR 0.54; 95%CI 0.2 to 1.49) and that the risk of death was higher (RR 0.68; 95%CI 0.53 to 0.87).

Of these trials, the only (and largest, n = 82) prospective, randomised, concealed and standardised trial that used an objective measurement of cerebral

blood flow, with adequate follow-up demonstrated no increase in cerebral blood flow by induced hypertension and hypervolaemia despite attaining increases in cardiac pressures, no difference in symptomatic vasospasm (20% in both control and intervention) and no differences in functional outcomes.<sup>25</sup>

#### Conclusions

The contribution of cerebral vasospasm to attributable morbidity and mortality from aneurysmal subarachnoid haemorrhage remains conjectural albeit real, and whilst medical anti-vasospastic therapies should be considered in vulnerable patients, they should be used with circumspection and caution.

There is little or no evidence to justify the aggressive use of anti-vasospastic therapies as a preventative manner with exception of oral nimodipine in patients with low-grade aneurysmal subarachnoid haemorrhage.

Concomitant use of induced hypertension/hypervolaemia/haemodilution cannot be recommended on current evidence, but if employed should be done on an individualised basis, considering the patients underlying neurological condition, cardiopulmonary reserve, adequacy of systemic and neurological monitoring and access to expert neuroradiological, neurosurgical and neurocritical care services.

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