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PRACTICE GUIDANCE FOR CRITICAL CARE MANAGEMENT OF SAH

Hemodynamic Management in the Prevention and Treatment of Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage

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Abstract

One of the most serious complications after subarachnoid hemorrhage (SAH) is delayed cerebral ischemia, the cause of which is multifactorial. Delayed cerebral ischemia considerably worsens neurological outcome and increases the risk of death. The targets of hemodynamic management of SAH have widely changed over the past 30 years. Hypovolemia and hypotension were favored prior to the era of early aneurysmal surgery but were subsequently replaced by the use of hypervolemia and hypertension. More recently, the concept of goal-directed therapy targeting euvolemia, with or without hypertension, is gaining preference. Despite the evolving concepts and the vast literature, fundamental questions related to hemodynamic optimization and its effects on cerebral perfusion and patient outcomes remain unanswered. In this review, we explain the rationale underlying the approaches to hemodynamic management and provide guidance on contemporary strategies related to fluid administration and blood pressure and cardiac output manipulation in the management of SAH.

Keywords: Subarachnoid hemorrhage, Cerebral aneurysm, Cerebral vasospasm, Delayed cerebral ischemia, Triple H therapy

Introduction

Mortality and morbidity remain high after aneurysmal subarachnoid hemorrhage (SAH) despite advances in aneurysm treatment and medical management [1–3]. A significant contributor to disability and death after SAH is delayed neurologic deterioration, referred to as delayed cerebral ischemia (DCI). DCI typically occurs between 3 and 14 days after SAH, clinically manifests as new focal or global neurologic deficits that are often associated with cerebral infarction, and is temporally correlated with luminal narrowing of cerebral vessels [4]. This correlation led to the assumption that cerebral vasospasm and associated perturbations in cerebral hemodynamics were the primary causes of DCI, although more recently, it has become evident that additional mechanisms are in play [4–7]. Nonetheless, the observed association between DCI and cerebral vasospasm led to management strategies centered on improving cerebral blood flow (CBF) through hemodynamic augmentation, approaches that are widely practiced to this day despite the lack of high-level supporting evidence [8–11]. Indeed, several international guidelines recommend some aspects of hemodynamic augmentation for the treatment of DCI based on varying levels of evidence (Table 1) [12–16].

This review discusses the available evidence regarding hemodynamic management for the prevention and treatment of DCI after SAH and offers suggestions based on interpretation of very limited quality data that are not

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Table 1 Guideline statements on hemodynamic management after SAH

Guideline	Recommendation(s)	Level of evidence	Strength of recommendation
Recommendations from the Neurocritical Care Society's Multidisciplinary Conference [12]	The goal should be maintaining euvolemia rather than attempting to induce hypervolemia	Moderate-quality evidence	Strong recommendation
	Consider a saline bolus to increase CBF in areas of ischemia as a prelude to other interventions	Moderate-quality evidence	Weak recommendation
	Patients clinically suspected of having DCI should undergo a trial of induced hypertension	Moderate-quality evidence	Strong recommendation
	The choice of vasopressor should be based on the other pharmacologic properties of the agents (e.g., inotropy, tachycardia)	Moderate-quality evidence	Strong recommendation
	Blood pressure augmentation should progress in a stepwise fashion with assessment of neurologic function at each MAP level to determine whether a higher blood pressure target is appropriate	Poor-quality evidence	Strong recommendation
	If nimodipine administration results in hypotension, then dosing intervals should be changed to more frequent lower doses. If hypotension continues to occur, then nimodipine may be discontinued (low quality, strong recommendation)	Low-quality evidence	Strong recommendation
	If patients with DCI do not improve with blood pressure augmentation, a trial of inotropic therapy may be considered (low-quality evidence, strong recommendation)	Low-quality evidence	Strong recommendation
	Inotropes with prominent β_2 agonist properties (e.g., dobutamine) may lower MAP and require increases in vasopressor dosage	High-quality evidence	Strong recommendation
	Mechanical augmentation of cardiac output and arterial blood flow (e.g., intraaortic balloon counterpulsation) may be useful	Low-quality evidence	Weak recommendation
European Stroke Organization [15]	There is no evidence from controlled studies for induced hypertension or hypervolemia to improve outcome in patients with delayed ischemic deficit	Evidence from uncontrolled studies, case series, case reports, or expert opinion	"Possibly effective, ineffective, or harmful…"

Table 1 (continued)

Guideline	Recommendation(s)	Level of evidence	Strength of recommendation
Japanese Society Guidelines [13]	Induced hypertension, hypervolemia, and hemodilution (triple H therapy) are reported to be effective at improving CBF in the areas perfused by the vasospastic vessels Although it appears relatively certain that triple H therapy can be useful in reversing deficits once they occur, the data supporting the finding that prophylactic hyperdynamic lessens the incidence of symptomatic vasospasm are considerably weaker Maintenance of cardiac inotropic regulation under normovolemia has also been attempted	Moderate or weak evidence	"Recommended or deserving consideration"
American Heart Association/American Stroke Association guidelines for the management of SAH [14]	Maintenance of euvolemia and normal circulating blood volume is recommended to prevent DCI Induction of hypertension is recommended for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it	Data derived from a single randomized trial or nonrandomized studies	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Korean clinical practice guidelines [16]	Prophylactic triple H therapy is not recommended for the prevention of vasospasm-induced DCI; however, maintaining euvolemia is recommended After the onset of DCI, induced hypertension in accordance with the patient's neurological status is recommended	At least one well-designed controlled trial without randomization	Reasonable or recommended to do

CBF, Cerebral blood flow, DCI, delayed cerebral ischemia, MAP, mean arterial pressure, SAH, subarachnoid hemorrhage

sufficiently rigorous to support guideline-level recommendations [17].

Hemodynamic Management for the Prevention and Treatment of DCI: Historical Perspective

Hemodynamic management of aneurysmal SAH has evolved considerably over the past few decades. Hemodynamic augmentation for prevention or treatment of cerebral vasospasm initially arose in the context of a delayed approach to surgical aneurysm treatment that was common at the time. Because of concerns that surgical conditions would be less favorable early after aneurysm rupture and that surgery could be more dangerous during the period of vasospasm, aneurysm clipping was often delayed for more than 1–2 weeks after the initial hemorrhage [18]. Given the high risk of aneurysmal rebleeding during this period, blood pressure was typically tightly controlled using antihypertensive and diuretic therapy. Also affecting management during this era was the use of fluid restriction to treat hyponatremia, a common occurrence after SAH and historically thought to be due to the syndrome of inappropriate antidiuretic hormone secretion. Yet this strategy of fluid restriction for hyponatremia was ultimately found to be associated with cerebral ischemia [19, 20]. Likewise, decreased intravascular volume, particularly in female patients, was found to be associated with cerebral vasospasm after aneurysmal SAH [21].

The first controlled study to investigate prophylactic fluid management after SAH was published in 1983; 30 patients with aneurysmal SAH were randomized to conventional treatment using diuretics and antihypertensive medications or to an intervention group that underwent pulmonary artery catheterization to facilitate optimized volume expansion combined with antihypertensive therapy [22]. Preoperative angiographic vasospasm and mortality were considerably lower in the intervention group. Cohort studies published in the following decade further supported avoiding fluid restriction in patients with SAH [23, 24]. In addition, case series of varying size reported improvement in vasospasm-associated neurologic deficits with the induction of hypertension and hypervolemia in patients both before and after aneurysm treatment [25–28]. Hemodilution, either intentional or as a byproduct of volume expansion, was eventually added, with the subsequent triad referred to as "triple H therapy" [29], although the support for hemodilution was largely based on theoretical rheologic concepts rather than clinical evidence [30]. After data indicating that hemodilution actually reduced oxygen delivery were reported [31], the practice fell out of favor. Thus, current hemodynamic augmentation largely centers around manipulation of intravascular volume, blood pressure, and cardiac performance.

The International Cooperative Study on the Timing of Aneurysm Surgery, published in 1990, reported that early surgery was not more technically difficult than surgery performed later and resulted in 6-month outcomes comparable to those from delayed surgery [18]. In a secondary analysis, limited to North American centers, outcome was better when surgery was planned between days 0 and 3 after SAH [32]. This eventually led to early surgery becoming the standard; aneurysm repair within 24 h is currently recommended (American Heart Association guidelines) [14]. This practice change provided the opportunity for more widespread and earlier application of hemodynamic augmentation for prevention and treatment of cerebral vasospasm [24]. The development of endovascular approaches to aneurysm treatment also contributed to earlier application of hemodynamic augmentation after SAH [33]. Although reports published before the 1990s are no longer relevant to today's practice, they reveal the deleterious effects of hypovolemia and highlight the importance of hemodynamic optimization. Thus, the remainder of this review will focus on evidence from the 1990s onward.

Management of Fluids and Intravascular Volume in the Prevention and Treatment of DCI: Available Evidence

As the practice of fluid restriction and diuretic administration after SAH was abandoned, management shifted toward hypervolemia as a component of triple H therapy to prevent or treat cerebral vasospasm and ultimately DCI [29], with calls for randomized trials to investigate triple H therapy appearing as early as 1991 [30]. Given that hypervolemia was typically combined with augmentation of blood pressure and/or cardiac output, the individual contribution of each component to outcomes or complications is difficult to ascertain. To this date, the evidence supporting any component of triple H therapy for the prevention and/or treatment of vasospasm/DCI is generally of low quality, composed largely of case series of varying size.

Initially, hypervolemia was generally achieved by using invasive cardiovascular monitoring and targeting a supraphysiologic pulmonary capillary wedge pressure and/or central venous pressure [34–36]. In an uncontrolled cohort of 43 patients with SAH, Origitano et al. [34] found that CBF increased with prophylactic triple H therapy, and 84% of patients were functionally independent at discharge. In a small single-center study of potential complications from volume expansion and phenylephrine-induced hypertension in a closely monitored population, Miller et al. [37] found no instances of pulmonary edema,

and 88% of patients had improvement in neurologic status. On the other hand, study participants in the placebo arm of a multicenter randomized trial of intravenous nicardipine for the prevention of cerebral vasospasm had a 40% incidence of medical complications, some of which were attributable to hypertensive, hypervolemic therapy, and/or associated invasive monitoring [38]. The proportion of deaths attributable to medical complications was 23%. One quarter of the patents developed pulmonary edema, although the association with hypertensive hypervolemic therapy was not significant.

In addition to the concerns about medical complications associated with triple H therapy, a series of small randomized controlled trials and cohort studies raised some doubt about the effectiveness of hypervolemia in affecting intravascular volume or CBF. In a small study, 43 patients were randomized to either hypervolemic or normovolemic fluid administration [39]. Despite receiving more fluids and 5% albumin, both groups had similar intravascular volume. In a subsequent study, the same group investigated the impact of hypervolemic therapy on CBF by randomizing 82 patients with SAH to hypervolemic or normovolemic management [40]. Again, overall fluid balance and blood volume were not affected by hypervolemic management, and CBF measured by ^{133}Xenon clearance and symptomatic vasospasm did not differ between groups. Similarly, Egge et al. [41] found no differences in regional CBF measured by single-photon emission computerized tomography (SPECT), clinical vasospasm, or Doppler-detected cerebral vasospasm in patients randomized to triple H therapy vs. normovolemic management; furthermore, in this study, the triple H group had more medical complications. A randomized controlled pilot study used a factorial design that included randomization to normovolemic vs. hypervolemic fluid therapy (and normotension vs. hypertension) [42]. Despite an approximately 2-L daily fluid intake difference between groups, there was no difference in the 6-month modified Rankin score, and increased sodium losses were observed in the hypervolemia group [43]. In a cohort study of 58 patients after SAH, Gura et al. [44] found that combining induced hypertension with hypervolemia added no additional benefit when compared to normovolemia. Finally, in a prospective cohort study, Tagami et al. [45] found that despite receiving more fluid and having higher blood pressure, patients who received prophylactic triple H therapy did not have a lower incidence of DCI than those not receiving triple H therapy.

It is possible that volume expansion may have at least transient effects on CBF that could translate into a reduction in DCI-related symptoms. Jost et al. [46] used positron emission tomography to assess CBF in six patients with cerebral vasospasm after SAH and observed an immediate increase in CBF after a saline bolus in brain regions with low (ischemic range) baseline CBF in association with expected increases in blood pressure and cardiac output. However, the duration of the response was not assessed in this study. The transient hemodynamic optimization associated with a fluid bolus may account for some of the clinical observations of neurologic improvement associated with fluid administration in patients with DCI.

Despite this caveat, the weight of evidence suggests that liberal fluid administration is detrimental. A retrospective review of 142 patients found an association between positive fluid balance over the first 7 days and risk of poor outcome [47]. A prospective observational study of a protocol-based restrictive approach to fluid administration reported lower cumulative fluid balance and a lower incidence of hypoxemia at days 3 and 7 after SAH [48]. In addition to hypoxemia as a complication of hypervolemic therapy [48], there were trends toward higher frequency of pulmonary edema in the hypervolemic arms of all four randomized controlled trials previously mentioned [39–42], in the hypervolemic arm of the cohort study by Gura et al. [44], and in the placebo arm of the intravenous nicardipine study [38]. The consistent signal across studies lends support for the notion that hypervolemic therapy increases the risk of pulmonary complications.

Transpulmonary thermodilution, a technique that requires both a central venous catheter and a large-bore femoral arterial catheter, has been used in more recent studies as part of a protocolized approach to hemodynamic management [49–54]. In general, these studies and others suggest that protocolized hemodynamic management can result in less fluid administration with similar or improved outcomes compared to a conventional management approach [55]. Two randomized controlled trials used transpulmonary thermodilution as part of goal-directed hemodynamic therapy (GDHT) protocols to guide fluid and cardiovascular management [51, 52]. Mutoh et al. [51] compared early goal-directed fluid therapy using a transpulmonary thermodilution-based algorithm to standard management. Although there were no significant differences in DCI or other outcomes in the entire cohort, the authors reported that the subgroup with poor clinical grade (World Federation of Neurological Surgeons grades IV and V) had reduced DCI, more favorable modified Rankin scores at 3 months, and a trend toward less pulmonary edema. However, when these data are analyzed using more conservative statistical testing (relative risk calculation), the differences between groups were not significant. In a subsequent randomized controlled trial of GDHT vs. conventional management in 108 patients, Anetsberger et al. [52]

reported a lower incidence of DCI and reduced disability at 3 months in the GDHT group and a trend toward lower risk of pulmonary edema with GDHT.

In summary, the weight of the evidence suggests that a fluid administration strategy targeting euvolemia after SAH results in similar or better outcomes and fewer pulmonary complications than an approach targeting hypervolemia. The evidence supporting hypervolemia as a hemodynamic treatment target comes almost exclusively from older studies whose interpretation is affected by delayed aneurysm treatment. Clinical guidelines are generally consistent in recommending euvolemia as a target for fluid management after SAH (Table 1) [12–17]. The method for assessing and achieving euvolemia remains unclear, although recent work suggests that protocolized goal-directed fluid management may result in reduced fluid administration and improved clinical outcomes. However, there is a dearth of quality evidence in the form of large randomized controlled trials in this area, and it is furthermore difficult to disentangle the intertwined effects of fluid management and blood pressure and/or cardiac output augmentation in the prevention and treatment of DCI.

Management of Blood Pressure and Cardiac Output in the Prevention and Treatment of DCI: Available Evidence

Induced hypertension in patients with symptomatic vasospasm can be traced to the early 1980s when small single-center studies suggested that induced arterial hypertension, with or without intravascular volume expansion, may improve neurologic deficits [26, 56]. However, these retrospective single-center case series are limited by poor methodologic rigor, at least by current research standards. Even as these treatments were being introduced, they were known to be associated with risk. Induced hypertension shared several complications observed with hypervolemia, including pulmonary edema, hyponatremia, aneurysm rebleeding (before securement of the ruptured aneurysm), coagulopathy, hemothorax, and myocardial infarction.

The rationale for augmenting cardiac output and/or blood pressure is based on the argument that these interventions improve CBF and thus oxygen delivery, thereby potentially reversing DCI, and the rationale further works under the assumption that DCI is largely due to hypoperfusion and can be reversed by improving oxygen delivery. Furthermore, this approach assumes some degree of impairment of autoregulation for a rise in blood pressure to improve oxygen delivery. Lastly, under normal conditions, cardiac output has little impact on CBF, although this may not be the case when there is ongoing cerebral ischemia.

A growing understanding of the pathophysiology of SAH and DCI demonstrates that multiple pathophysiologic processes, including vessel constriction, impaired cerebral autoregulation, disruption in the blood–brain barrier, microthrombosis, cortical spreading depolarizations, and neuroinflammation, may all play a role in the development of DCI [57]. These multifactorial mechanisms may in part explain why studies of hypertension and hypervolemia in symptomatic vasospasm have yielded mixed results.

The body of evidence regarding induced hypertension and cardiac output augmentation is further complicated by the heterogeneity in the outcome measures employed. Although quantifiable improvement in patient outcomes (mortality, measures of cerebral vasospasm, functional outcome scales, complications) is required for clinical practice guidelines, studies using physiologic end points can provide insight into the mechanisms and impact of these interventions.

Clinical outcome after induced hypertension was addressed in two very small randomized controlled trials. In 32 patients, Egge et al. [41] compared prophylactic hypertensive hemodilution to normovolemia and found no difference in functional outcome. Gathier et al. [58] randomized 41 patients to induced hypertension or normotension and reported no difference in functional outcome but more adverse events in the hypertension group. Admittedly, both these trials lacked sufficient statistical power to be deemed conclusive. In a low-quality retrospective review of 300 patients, Haegens et al. [59] reported improved outcome in those treated with hypertension compared with those who were not.

Rondeau et al. [60] studied the impact of augmentation of cardiac output on clinical outcome in a randomized controlled trial comparing prophylactic dobutamine-induced rise in cardiac index to norepinephrine-induced hypertension to prevent vasospasm; they found no difference in outcome or complications [60]. The lack of a placebo group limits interpretation of this study.

In addition to its role in intraarterial therapy, the use of milrinone for its inotropic properties in the prevention and treatment of DCI has become increasingly popular over the past decade, but as with other methods of hemodynamic augmentation, the lack of high-quality evidence hampers the interpretation of its efficacy [61]. The literature on milrinone is further clouded by a large variation in treatment protocols, some of which include a combination of intraarterial injection plus continuous infusion. In the single reported randomized controlled trial of milrinone for the treatment of cerebral vasospasm after SAH, Soliman et al. [62] randomized 90 patients to

milrinone at a continuous infusion rate of 0.5 μg/kg/minute or magnesium infusion (500 mg/day). They reported a lower incidence of subsequent Doppler-assessed cerebral vasospasm in the magnesium group. Unfortunately, this study did not report the incidence of DCI or long-term functional outcomes and did not include a placebo group, making interpretation limited. A more recent observational study compared 41 patients who received intravenous milrinone infusion at 0.5–1.5 μg/kg/minute plus induced hypertension to a group of historical controls from several years earlier who received induced hypertension alone [63]. Milrinone administration was associated with improved functional outcomes at 6 months as well as a lower rate of endovascular intervention for vasospasm than in historical controls. Further data are needed to allow conclusions on the efficacy of intravenous milrinone for the prevention or treatment of DCI.

Other studies have examined the impact of increased blood pressure and/or cardiac output on surrogate outcome measures, with mixed results. As long ago as 1986, Muizelaar and Becker [64] demonstrated an increase in CBF (and clinical improvement) in four patients with symptomatic cerebral vasospasm who were treated with phenylephrine-induced hypertension. In a cohort of ten patients, Muench et al. [65] reported that induced hypertension resulted in an increase in regional CBF and brain tissue oxygenation ($PbtO_2$). Volume expansion was less effective. In contrast, in a small randomized controlled trial comparing induced hypertension vs. normotension, Gathier et al. [66] found no difference in CBF between groups. In a randomized study of the effects of simvastatin on autoregulation in SAH, Diringer et al. [67] reported that raising blood pressure by 15% in patients with DCI or at high risk of developing DCI did not acutely change regional CBF measured by positron emission tomography (PET), even in regions with baseline ischemia and regardless of the administration of simvastatin. Joseph et al. [68] measured the impact of increases in cardiac output with dobutamine on CBF and reported that elevating cardiac output reversed flow deficits independent of blood pressure. In a retrospective review of 45 patients, Raabe et al. [69] correlated blood pressure to $PbtO_2$ to study the effects of hypertension and hypervolemia in patients with DCI. Results were mixed, with moderate hypertension modestly improving cerebral oxygenation in normovolemic poor-grade patients. In an observational cohort study of 60 patients, Rass et al. [70] found no relationship between hemodynamic profiles and $PbtO_2$. Fluid boluses did not influence $PbtO_2$ for the whole cohort but appeared to slightly improve $PbtO_2$ in those who had baseline brain hypoxia (though without raising $PbtO_2$ above the ischemic range).

In addition to the lack of convincing evidence of the benefit of hemodynamic augmentation for the prevention or treatment of DCI, there is no consensus on appropriate hemodynamic targets. International guidelines are not prescriptive regarding specific hemodynamic goals. Moreover, they make no recommendations on whether to target systolic or mean arterial pressure. Clinical studies have used both, and clinical practice is likewise varied. In a survey of members of the Neurocritical Care Society, clinicians were split approximately 50:50 on using mean or systolic blood pressure goals, and a very broad range of blood pressure targets was reported [71]. In a similar survey of European physicians, roughly equal numbers of respondents targeted mean arterial pressure of greater than 90, 100, or 110 mmHg in patients with symptomatic vasospasm [11]. Physiologic arguments exist to support the use of either mean arterial or systolic blood pressure targets. Additionally, different devices (arterial line vs. noninvasive cuff) can produce differing results, especially for systolic blood pressures. This not only complicates defining targets but can also lead to management errors when comparing or transitioning from one device to another without calibration.

In addition to the previously described medical complications associated with hypertensive hypervolemic therapy, there are several reports of posterior reversible encephalopathy syndrome (PRES) in association with induction of hypertension in patients with aneurysmal SAH and cerebral vasospasm [72–78]. Although PRES in this context appears to be uncommon, an incidence of 1.7–7% has been reported [72, 74], and PRES appears to be associated with the magnitude and duration of blood pressure elevation. Symptoms and signs associated with PRES (encephalopathy, seizures, focal neurologic deficits) typically resolve with reduction of blood pressure; it is important to keep this entity in mind when unexplained neurologic changes occur in the context of induced hypertension.

Taken together this body of evidence provides few clear answers. Little progress has been made on clarifying the pathophysiological assumptions required for these interventions to be effective. The quality of the randomized controlled trials is significantly limited by factors such as lack of adequate controls and, in all cases, small sample size. The retrospective studies suffer from selection bias, limited power, and use of surrogate measures that may show statistically significant changes that are of uncertain clinical significance. Interventions that improve CBF or $PbtO_2$ may not result in better functional outcomes and are known to put patients at risk for complications. The one consistent and clinically relevant signal is that hemodynamic augmentation is not without risk and that both

hypervolemia and induced hypertension are associated with medical complications.

Practice Guidance

Investigations on the topic of hemodynamic management in patients with SAH are challenging to interpret because of variability in the management approaches investigated. All studies included are significantly limited by methodologic flaws and risk of bias in addition to widely different monitoring approaches and management strategies [17]. Further, the benefit of hemodynamic augmentation has not been demonstrated, and these interventions cause serious harm. When reviewing the available evidence with the rigor that is required for current guideline development, the Neurocritical Care Society guideline panel recommended against hypervolemia but could not make a recommendation for or against blood pressure or cardiac output augmentation for the prevention or treatment of DCI [17]. Yet many practitioners have appreciated neurologic improvement in individual patients when treating DCI with induced hypertension and may be dismayed by the discordance between the evidence and their own clinical experience. Because it appears that inducing hypertension in symptomatic DCI may be helpful in some patients, at least in the short term, it remains to be determined how to select the appropriate patients, what vasoactive agents should be used, and how hemodynamic indices should be targeted and adjusted.

Thus, the question about the value of augmenting blood pressure and/or cardiac output to prevent (or even to treat) DCI remains unanswered. Addressing this issue is particularly important and challenging given that hemodynamic interventions are routinely employed in many centers. Guiding principles integrating the data and clinical experience of the writing group produced the following practice guidance:

1. In all cases, care must be individualized and take into consideration the entire medical profile of the patient.
2. Interventions should be employed to prevent or correct hypovolemia, hypotension, and/or low cardiac output states, especially in poor-grade patients during the DCI window. However, induced hypervolemia should be avoided because of the lack of benefit and risk of complications.
3. In euvolemic normotensive patients who develop a deficit attributed to DCI, a trial of induced hypertension or cardiac output augmentation is reasonable when reliable examinations can be performed to determine whether the intervention reverses the deficit. No guidance can be offered on specific hemodynamic targets or on how to use these interventions in patients who do not have a reliable clinical examination.
4. When treating with induced hypertension and/or cardiac output augmentation, patients should be closely monitored for complications and cared for by a team with expertise in the management of hemodynamics and SAH.

Future directions

Further research into the pathophysiology of DCI is needed to determine whether hemodynamic interventions can prevent or ameliorate DCI and it's associated complications. Studies into the pathophysiology of DCI using surrogate end points can be useful when designing early-phase studies, but ultimately, appropriately powered phase 3 trials need to be performed to demonstrate efficacy and safety using patient-centered outcomes.

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