Risk Factors and Medical Management of Vasospasm After Subarachnoid Hemorrhage

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KEYWORDS

• Vasospasm • Aneurysmal subarachnoid hemorrhage
• Triple-H therapy • Cerebral blood flow

Aneurysmal subarachnoid hemorrhage (aSAH) comprises 5% of all strokes and affects as many as 30,000 Americans each year.[1,2] Commonly, it involves a younger population. In fact half of the patients are younger than 55 years[3]; as a result, the loss of productive life years approaches that for ischemic stroke and intracerebral hemorrhage.[4] About 10% to 15% of patients die from the initial rupture and never make it to the hospital.[5,6] For the survivors, rebleeding becomes an immediate concern, with an incidence of 4% to 15% in different series in the first 24 hours, carrying very high mortality and morbidity.[7,8] Prevention of rebleeding with prompt exclusion of the ruptured aneurysm from the circulation has become the standard of care for most patients; also, interest in the use of short-term antifibrinolytics has reemerged.[9,10] After this first phase of the disease, patients may deteriorate secondary to hydrocephalus, delayed ischemic neurologic deficits (DIND) (also called delayed cerebral ischemia [DCI]), and multiple medical complications including cardiomyopathy and nosocomial infections. In addition, there is increasing recognition and understanding of the mechanisms of early brain injury (EBI) as a major contributor to poor neurologic outcomes.[11,12] DIND has been classically associated with angiographic vasospasm, especially when manifested with clinical symptoms referable to the vascular territory of the involved vessel. Treatment consists of a combination of interventional procedures, such as mechanical and/or chemical angioplasty for amenable lesions[13] and medical therapy summarized under the term triple-H (hypertension, hypervolemia, hemodilution) therapy. This approach is considered the standard of care by many despite the absence of high-quality evidence on the effectiveness of these interventions.[14] In recent years, several investigators have challenged the traditional presumption linking DIND and DCI exclusively with angiographic vasospasm. Alternative mechanisms have been proposed, including microvascular spasm with cerebral blood flow (CBF) autoregulatory failure, microthrombosis and microembolism, cortical spreading depolarizations and ischemia, and delayed neuronal apoptosis triggered by EBI.[15–18] In this article,

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the known risk factors, prevention, and current medical management of DIND are reviewed.

RISK FACTORS

Angiographic vasospasm is seen in 30% to 70% of patients post aSAH[19,20]; typically it can be expected to start after postbleed day 3, although hyperacute or early vasospasm has been reported.[21,22] Symptoms of cerebral ischemia with high risk for debilitating stroke and mortality are experienced by 20% to 30% of patients. The presence and the amount of oxyhemoglobin in the subarachnoid cisterns is believed to be the major trigger of the phenomena that ultimately cause smooth muscle spasm, narrowing of the arterial lumen, and impaired blood flow autoregulation.[23,24] In their seminal paper, Fisher and colleagues[25] found a strong correlation linking thick cisternal clot with angiographic and clinical vasospasm. The Fisher computed tomographic (CT) rating scale is widely used by neurointensivists and neurosurgeons and has been recently modified to incorporate intraventricular hemorrhage as a significant predictor for vasospasm and also to denote increasing risk as the grade increases.[26,27] Techniques to remove blood or increase clearance of blood from the basal cisterns with either intracisternal[28] or intrathecal lysis, head shaking,[29] and lumbar drainage[30] have been attempted with variable results. Other potential risk factors include poor clinical grade, early angiographic spasm, history of hypertension, and admission mean arterial pressure (MAP).[27] There have been conflicting reports regarding age as a predictor, with one study identifying age less than 35 years as a risk factor,[31] although this finding was not confirmed by others.[32,33] One prospective study of 70 patients demonstrated that apart from thick subarachnoid clot, a history of smoking was independently associated with development of symptomatic spasm.[32] Volume status of the patient with aSAH is considered critical, and a large part of critical care in this disease centers on its regulation. Hypovolemia is believed to be a potentially significant contributor to DCI and can be common if not prevented, especially in the presence of natriuresis secondary to cerebral salt-wasting syndrome (CSWS).[34]

PREVENTION AND VOLUME MANAGEMENT

Current guidelines advise maintenance of normal circulating blood volume instead of prophylactic hyperdynamic, hypervolemic therapy.[35] Lennihan and colleagues randomized patients with aSAH into hypervolemic versus normovolemic regimens based on the measurements of pulmonary artery diastolic pressures (PADPs) for the first 3 days and central venous pressure (CVP) measurements thereafter, and until day 14, they measured CBF using xenon (Xe) washout. There was no difference between the 2 groups in mean global CBF, rate of symptomatic spasm, or functional outcome.[36] Subsequently, Egge and colleagues[37] published similar results in their randomized prospective trial that compared hypervolemic to normovolemic approaches, finding no difference in the occurrence of vasospasm, TCD ultrasonography recordings, or SPECT (single-photon emission computed tomography) CBF measurements. These studies, despite the small number of patients, suggest that euvolemia should be the goal because extra volume translates neither to an increase in CBF nor to improved outcomes. Importantly, fluid management should also take into account the not-uncommon presence of cardiomyopathy[38,39] and neurogenic pulmonary edema.[40] Even moderate volume overload can lead to further lung[41] and cerebral edema in these patients, and positive fluid balance has been associated with increased mortality in neurologic and general critical care populations.[42,43] This discussion raises the question of volume assessment to guide therapy. It is common practice to calculate daily fluid balance (DFB) as a measure of the need for more or less fluid administration, but the correlation of DFB with actual circulating blood volume as measured by integrated pulse spectrophotometry and pulse dye densitometry has been shown to be poor.[44,45] As a consequence, several institutional protocols for the management of aSAH call for insertion of central venous and/or pulmonary artery catheters for the measurement of CVP, PADP, and pulmonary artery occlusion pressures (PAOPs) as measures of right and left heart preload and also for cardiac output (CO) estimations. The major limitation of this approach, apart from its being invasive, relates to the inaccuracy of extrapolating cardiac filling pressures to volumetric assessments. This inaccuracy is accentuated when cardiac compliance is altered, as may be seen with neurogenic stunned myocardium. The failure of these static pressures to predict volume responsiveness has been demonstrated across the spectrum from healthy volunteers to critically ill mechanically ventilated (MV) patients with sepsis; accordingly, dynamic parameters, such as systolic pressure variation and pulse pressure variation for MV patients, are recommended.[46–48] An alternative for advanced

hemodynamic monitoring is a device that combines single indicator transpulmonary thermodilution technique and pulse contour continuous CO measurements (PiCCO, PULSION Medical Systems AG, Munich, Germany).[49] This device has been used extensively to guide management of different populations of critically ill patients, including those with conditions such as septic[50] and cardiogenic[51] shock and acute respiratory distress syndrome,[52] and it has been used for management in the operating theater. The potential theoretical benefits are direct volumetric measurements of intrathoracic blood volume (ITBV), global end diastolic volume (GEDV), and extravascular lung water (EVLW) volume and also continuous dynamic volume responsiveness parameter (stroke volume variation [SVV]) and CO monitoring. It does require positive pressure MV and minimal spontaneous breathing efforts. The device has been used in patients with aSAH and was found to be a useful tool for volume and hemodynamic augmentation (HA) management.[53–55] The authors also use PiCCO for selected patients and to target normovolemia goals (GEDV index, 680–800 mL/m^2; ITBV index, 850–1000 mL/m^2; SVV $\leq$ 10%; and EVLW index $\leq$ 10 mL/kg). It remains to be seen in a prospective trial if this device proves more useful over traditional measures such as DFB and cardiac filling pressures in patients with aSAH. A last comment on the prevention of hypovolemia concerns the occurrence of CSWS. Despite an incomplete understanding of the pathophysiology of the syndrome, it is considered when large urinary output is accompanied by hyponatremia. A similar clinical picture can be seen secondary to iatrogenic reasons such as overzealous fluid administration and the use of natural diuretics, such as hypertonic saline (HTS).[56] Fludrocortisone is often used as an adjunct to volume and sodium replacement in CSWS. It has been evaluated in 2 randomized controlled trials (RCTs) as a means to prevent hyponatremia and volume contraction, with mixed results.[57,58] An alternative or supplementary fluid management technique is to use colloids, such as 5% albumin, not only as a volume expander but also to potentially prevent sodium and fluid losses associated with CSWS.[59]

NEUROPROTECTION

Nimodipine administration from the time of admission and for 21 days is considered the standard of care and is the only recommendation carrying a class I, level A evidence grade in current guidelines.[35] A recent Cochrane review analyzed a total of 12 studies on calcium antagonists (heavily weighted by a single large trial of nimodipine[60]) and found an outcome improvement with a relative risk reduction of 18% (95% confidence interval [CI], 7%–28%) and an absolute risk reduction of 5.1%.[61] Treatment with nimodipine may prevent 1 poor outcome in every 13 patients with aSAH.[62] However, the medication does not prevent vasospasm[63] and is believed to improve outcome through a neuroprotective mechanism. Alternative explanations have been proposed to explain this beneficial effect, including enhanced fibrinolysis[64] and the observation that nimodipine transforms cortical spreading ischemia back to cortical spreading hyperemia.[65] In recent years, many centers have incorporated the use of HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors such as ''statins'' in their standard armamentarium in the treatment of patients with aSAH. A meta-analysis by Sillberg and colleagues[66] included 3 double-blind RCTs of statin versus placebo and found significantly reduced incidence of vasospasm (relative risk [RR] 0.73; 95% CI, 0.54–0.99, number needed to treat [NNT] 6.25), delayed ischemic deficits (RR 0.38; 95% CI, 0.17–0.83, NNT 5), and mortality (RR 0.22; 95% CI, 0.06–0.82, NNT 6.7). All 3 trials have included small numbers of patients, and there is heterogeneity in regards to primary end points. Furthermore, 2 large retrospective studies have reported no benefits from statin use in vasospasm incidence or clinical outcomes.[67,68] The potentially favorable benefit-risk ratio of statins makes them attractive for wide use in aSAH; the authors hope that future large RCTs such as STASH, which is a multicenter placebo-controlled double-blinded phase 3 trial assessing the clinical benefit of SimvaSTatin in Aneurysmal Subarachnoid Hemorrhage, will provide a definitive answer. The hypothesis is that simvastatin 40 mg given within 96 hours of ictus over 3 weeks reduces the incidence and duration of DCI after aSAH when compared with placebo (Dr Peter Kirkpatrick, chief investigator, University of Cambridge, UK).

As mentioned earlier, DIND seems to be the end result of multiple cooperating mechanisms, and relieving angiographic vessel narrowing does not necessarily translate to clinical improvement. The endothelin receptor-A antagonist (clazosentan) studies may provide another valuable clue in dissociating angiographic vasospasm, clinical outcomes, and DCI. CONSCIOUS-1 was a randomized, double-blind, placebo-controlled phase 2 dose-finding trial of intravenous clazosentan with the aim of preventing vasospasm in patients with aSAH. Clazosentan significantly

decreased moderate and severe angiographic vasospasm in a dose-dependent manner; nevertheless, no significant benefit on any morbidity or mortality end points was observed.[69] It is possible that the study was underpowered, and a phase 3 clinical trial (CONSCIOUS-2) is designed to focus on clinical outcomes in patients undergoing aneurysm clipping receiving placebo or 5 mg/h of clazosentan.[70] This lack of a clinical effect has led certain investigators to further challenge conventional notions and question if angiographic vasospasm is no more than an epiphenomenon.[16]

Other medical therapies that have been evaluated for the prevention of vasospasm and poor outcomes include the nonglucocorticoid 21-aminosteroid tirilazad, magnesium, aspirin, low molecular weight heparin, nitroglycerin, and nitric oxide donors. Meta-analysis of the tirilazad mesylate study included 3797 patients and found no effect on clinical outcome despite a decrease in symptomatic vasospasm.[71] Magnesium therapy has been studied in a large placebo-controlled trial of continuous intravenous infusion for 14 days with promising results (Magnesium and Acetylsalicylic acid in Subarachnoid Hemorrhage [MASH]). Van den Bergh and colleagues[72] noticed a reduction in poor outcomes at 3 months by 23%, and the RR of a good outcome was 3.4 (95% CI, 1.3–8.9) for treated patients. A (MASH II) phase 3 clinical trial is currently under way with an aim to include 1200 patients before 2010 to further define the role of intravenous magnesiun infusion in patients with aSAH.[73]

DIAGNOSIS AND MULTIMODALITY NEUROMONITORING

Before the discussion of HA as the mainstay of medical management, the diagnosis and neuromonitoring of vasospasm and DCI are reviewed. The gold standard for detection of angiographic vessel narrowing is conventional digital-subtraction angiography (DSA). When clinical symptoms correlate with an area of narrowing on DSA, the diagnosis of clinical vasospasm is made. It should be noted that the presence of large vessel narrowing is not necessary for DCI to occur; in fact, Rabinstein and colleagues[74] reported that the presence and location of angiographically demonstrated vasospasm failed to correlate with areas of cerebral infarction in as many as one-third of their cases. Transcranial Doppler (TCD) ultrasonography is commonly used on a daily basis in the neurocritical care unit to follow patients with aSAH and with moderate to high risk for DCI.

The American Academy of Neurology expert committee has given a Type A, Class II level of evidence supporting the use of TCD ultrasonography in diagnosis of severe spasm.[75] A meta-analysis of 7 trials out of 26 reports evaluated the accuracy of TCD ultrasonography as compared with DSA. For the middle cerebral artery (MCA), sensitivity of TCD ultrasonography was 67% and specificity was 99%, with a positive predictive value of 97% and negative predictive value of 78%. The accuracy of TCD ultrasonography was considerably less for detecting spasm in vessels other than the MCA.[76] The noninvasiveness, ease, and wide availability have made TCD ultrasonography the most common neuromonitor for patients with aSAH. As cautioned before and in relation to DSA, Minhas and colleagues observed no correlation between positron emission tomography (PET) and TCD ultrasonography among patients who developed delayed neurologic deficits after aSAH. They concluded that TCD ultrasonography–derived indices correlate poorly with cerebral perfusion values.[77]

TCD ultrasonography, apart from measurement of flow velocities, can also be used to characterize the state of pressure autoregulation, which has been shown to be deranged in patients with aSAH.[78,79] Soehle and colleagues calculated and followed the moving correlation coefficient between slow changes of arterial blood pressure (ABP) and mean (Mx) or systolic flow velocity. The investigators demonstrated an increase in Mx during vasospasm reflecting a derangement of cerebral pressure autoregulation.[80] The authors have mentioned earlier the potentially beneficial effect of statins in preventing DCI and improving outcomes. A plausible explanation of this effect was published by the Cambridge group and it relates to an improvement in the state of pressure-flow autoregulation as measured by the transient hyperemic response test (TCD ultrasonography derived).[81]

Using brain tissue oxygen ($PtiO_2$) as a surrogate for CBF, Jaeger and colleagues found deranged CBF-autoregulation that does not improve after aSAH-ictus to be closely associated to the development of DCI. They calculated ORx (oxygen reactivity index), which is the moving linear (Pearson) correlation coefficient between the values of cerebral perfusion pressure (CPP) and $PtiO_2$ and varies between -1 and $+1$. The more positive, the more it indicates a passive relationship between CBF and MAP/CPP, meaning a pressure-passive nonreactive vascular bed. Of note, $PtiO_2$ alone was not different between the DCI and non-DCI groups.[82] The investigation of vascular reactivity and pressure autoregulation indices in patients with aSAH

is fascinating and potentially it may yield an early marker for detection of DCI before clinical symptoms ensue. The investigation also provides alternative mechanisms and therapeutic targets for DCI, placing the focus from the proximal segments of the circle of Willis to the microcirculation responsible for CBF regulation.

Microdialysis (MD) is increasingly used in the neuromonitoring of patients with severe TBI and aSAH. A consensus meeting on MD based on the available literature noted that glutamate was found to be the earliest marker of the onset of vasospasm followed over time by lactate, the lactate/pyruvate (L/P) ratio, and glycerol.[83] Sarrafzadeh and colleagues[84] compared MD with PET in 15 patients with aSAH and found glutamate to have the closest correlation with regional CBF (rCBF). Lactate, L/P ratio, and glycerol were significantly higher in symptomatic patients. It is also of interest to note that in this same study and in most symptomatic patients the measured PET-rCBF values were higher than the accepted critical thresholds of ischemia. In an earlier comparison of MD with TCD ultrasonography and DSA by the same group of investigators, MD was shown to be more specific but less sensitive as a diagnostic tool for DIND.[85] Brain tissue oxygenation is actively being researched, especially in TBI, and several centers use it routinely to prevent, detect, and treat secondary brain insults. Retrospective data from a prospective database of patients with aSAH were reported. The investigators observed an association of lower $PtiO_2$ with mortality. More specifically, low $PtiO_2$ on the first day of monitoring, lower mean daily $PtiO_2$, lower mean minimum $PtiO_2$, and longer cumulative duration of compromised $PtiO_2$ tend to be associated with an increased mortality rate at 1 month after aSAH in this cohort.[86] Finally, perfusion imaging in patients with aSAH using PET, SPECT, MRI, and CT methodologies is actively investigated. CT can provide expediently combined computed tomography angiogram and dynamic computed tomographic perfusion (CTP) scans and is becoming increasingly used for the diagnosis of DCI. CTP is based on the central volume principle, which states that the CBF value is the ratio of the blood volume within all blood vessels in a given volume of tissue (cerebral blood volume [CBV], which is measured in milliliters per gram) to the mean transit time (MTT, measured in seconds) of the contrast agent, from the arterial input to the venous drainage, within the volume being evaluated (CBF = CBV/MTT).[87] Recent articles are finding MTT to be an early predictor for DCI and angiographic vasospasm in animal models and human subjects.[88,89] In addition, relative CBF and MTT values have correlated well with estimated rCBF as measured by SPECT in patients with vasospasm after aSAH.[90]

TREATMENT: HEMODYNAMIC AUGMENTATION

The traditional approach to the medical treatment of cerebral vasospasm after aSAH for the prevention of DCI is summarized under the terms of triple-H therapy. The rationale behind this therapy is the enhancement of CBF by an increase in the circulating blood volume, increase in CPP, and improved rheologic properties via hemodilution. It is interesting that this management is considered as the standard of care despite the paucity of well-conducted RCTs. In the following paragraphs the authors review the available literature and describe current thinking under the term HA. Transluminal balloon angioplasty of affected segments combined with intra-arterial vasodilators may be considered in addition to HA in patients with symptomatic vasospasm refractory to triple-H therapy, whereas other proponents of its use suggest using HA merely as a bridge to the more definitive endovascular intervention; this methodology is the subject of discussion in another article (See the article by McGuinness and Gandhi elsewhere in this issue for further exploration of this topic.).

The first report in relation to triple-H therapy is credited to Kosnik and Hunt[91] (1976) when they described 7 patients post clipping for aSAH who developed delayed neurologic deficits. The investigators treated these patients successfully with phenylephrine for blood pressure augmentation and colloids for volume expansion. Shortly after this first report, Kassell and colleagues[92] published their cohort of 58 patients who developed angiographic and clinical spasm post clipping. Treatment with a hypervolemic-hypertensive regimen was able to reverse clinical symptoms in 47 patients. Most publications that followed consist of case reports, series, retrospective data, and noncontrolled studies. Treggiari and colleagues[93] reviewed the literature on the prophylactic application of triple-H therapy and found only 2 RCTs. The investigators commented on the great variability of study protocols and prophylactic regimens used and concluded that there is insufficient evidence to make any recommendations. The issue of prophylactic euvolemia versus hypervolemia has been discussed earlier, and currently the consensus is against prophylactic hypervolemia.

When a patient develops neurologic deficit, volume status should be quickly optimized. In a study of 6 euvolemic patients who developed

DIND and were imaged via PET scanning, Jost and colleagues were able to demonstrate an enhancement of rCBF after a normal saline bolus. Importantly, areas with ischemic level of CBF increased to nonischemic levels with volume expansion. It is notable that the bolus did not increase ABP, CO, or cardiac filling pressures as measured by central venous and pulmonary artery catheters.[94] The number of patients investigated is small and there are no outcome data; nevertheless, this elegant study shows the beneficial potential of volume loading in enhancement of CBF in ischemic brain regions. Subsequently, the Cambridge group has researched the effect of 23.5% HTS infusion on CBF as measured by Xe-CT and on cerebral autoregulation as measured by TCD ultrasonography and by waveform cross correlation of continuous ABP, intracranial pressure (ICP), and CPP monitoring.[95] Subjects for this study were 35 patients with low-grade aSAH. HTS administration significantly increased ABP and CPP at 30 minutes post infusion followed by a decrease in ICP, and also there was a dose-dependent effect of CBF increments on favorable outcome (mRS [modified Rankin scale] at hospital discharge). In this study, CBF augmentation by HTS was independent of baseline levels. Transient autoregulatory impairment was seen with HTS administration likely secondary to vasodilation with an eventual increase in CPP. A significant contribution to the literature on HA is the article by Muench and colleagues.[55] This is a combined experimental animal and clinical intervention study involving 10 patients with aSAH. For both parts of the study, advanced hemodynamic monitoring with a central venous catheter and the PiCCO device and advanced neuromonitoring with intraparenchymal ICP monitor, $PtiO_2$ probe, and thermal diffusion rCBF microprobe were used. The aim of the study was to investigate the influence of the 3 components of triple-H therapy on rCBF and brain tissue oxygenation in healthy animals with intact pressure autoregulation and in patients with aSAH with potentially deranged autoregulation. Their findings have important implications. Specifically, in the animal experiment, neither induced hypertension nor hypervolemia altered ICP, $PtiO_2$, or rCBF. In patients, who all had deranged autoregulation from day 1, induced hypertension resulted in significant increase of rCBF and $PtiO_2$. This benefit of ABP augmentation was lost when it was combined with hypervolemic hemodilution, which led to a decrease in $PtiO_2$ likely due to an adverse effect on oxygen delivery. State of autoregulation and oxygen carrying capacity of the blood should be critically considered during HA application.

Hemodilution conceptually leads to decreased blood viscosity and improved rheology. Ekelund and colleagues showed that isovolemic hemodilution to a hematocrit value of 0.28 from 0.36 does increase CBF, but it comes with a pronounced reduction in oxygen delivery capacity, translating to an overall increase in the volume of ischemic brain regions. In addition, hypervolemia conferred no benefit, further suggesting that there may be a hemoglobin (Hgb) threshold that should not be exceeded irrespective of volume status.[96] Kramer and colleagues have published a retrospective cohort study of 245 patients with aSAH. Anemia (Hgb <10 g/dL) and use of transfusions were both associated with worse outcomes; with both variables entered into logistic regression, only transfusion remained significantly predictive. Transfusion-related outcome worsening was stronger among patients without vasospasm.[97] Cause and effect are impossible to decipher from such a retrospective design in which there may be uncontrolled confounders. Other reports have shown an association of higher Hgb levels with improved outcome after correction for other clinical predictors.[98] The authors agree with the investigators of the previously referenced studies that a liberal versus a restrictive transfusion strategy trial is justified in patients with aSAH and that extrapolations from the literature on non–brain injured patients are not appropriate. Further understanding of the optimal Hgb level and transfusion triggers could be guided by advanced neuromonitoring. Recently, the Penn group has reported their findings from monitoring brain tissue oxygenation and MD metabolic parameters in patients with poor-grade aSAH who received blood transfusions. They found the incidence of brain hypoxia and cell energy dysfunction to increase significantly when Hgb level was less than 9 g/dL. This finding was independent of other relevant physiologic variables (such as CPP, CVP, Pao_2/Fio_2 ratio [partial pressure of arterial oxygen to fraction of inspired oxygen ratio]) and from the presence of clinical vasospasm.[99] Significant limitations are again the small sample size and the lack of correlation with clinical outcomes. The optimal Hgb level is currently unknown and most experts maintain a level close to 10 g/dL, especially during the peak vasospasm period and in symptomatic patients.

The previously discussed studies serve as a proof of concept for cautious volume expansion, with attention to Hgb levels and oxygen delivery, in the euvolemic patient with neurologic deterioration during the vasospasm period, and this is the first step that the authors take in the management of

such patients. Advanced hemodynamic monitoring often becomes necessary to guide fluid administration. CVP and PADP/PAOP measurements are most commonly used, we have mentioned the possible caveats with their use in the patient with aSAH. It will be interesting to see if ITBV and GEDV prove to be more sensitive indices and if the assistance of knowing EVLW can help optimize volume with avoidance of pulmonary edema.

To directly increase CBF, manipulation of ABP and CO become the major tools. ABP augmentation is achieved with the use of vasopressors such as phenylephrine, dopamine (DA), and norepinephrine (NE). The target blood pressure is titrated according to clinical neurologic examination, direct rCBF measurements, and tissue oxygen and metabolic parameters when available, and to adverse effects related to end-organ damage. Neurogenic stunned myocardium and cardiomyopathy as well as cardiogenic and noncardiogenic pulmonary edema must be taken into account. There are no comparative studies between vasopressor agents in the setting of HA for aSAH. The choice depends on comorbidities such as cardiac function and patient tolerance. Miller and colleagues treated a cohort of 24 patients with aSAH with phenylephrine for the prevention of DCI; two-thirds of them had vascular risk factors but normal cardiac index before augmentation. There were no clinically significant episodes of pulmonary edema or myocardial infarctions and no extracardiac toxicity. Phenylephrine was discontinued in only 1 patient, and 88% of the patients exhibited neurologic improvement.[100] The effect of CPP augmentation with DA as compared with NE on brain tissue oxygenation and MD parameters was studied by Johnston and colleagues in a small number of patients with severe TBI. Although TBI has a potentially different pathophysiology from that of aSAH, the investigators noted no significant differences between the 2 agents on cerebral oxygenation or metabolic parameters. DA leads to a significantly higher cardiac index without a difference in MAP. Overall, there were no large differences observed in terms of CBF or $CMRO_2$ (cerebral metabolic rate of oxygen). CPP augmentation with NE significantly reduced $AVDO_2$ (arteriojugular venous difference of oxygen) and increased $PbtO_2$ (brain tissue partial pressure), and the response was more predictable than with the use of DA.[101] The same group had similar results when DA was compared with NE using TCD ultrasonography FVm (mean flow velocity) as a surrogate for CBF. Their conclusion was that NE may be more reliable and efficient for CPP augmentation in patients with TBI.[102] The authors use NE or phenylephrine as a first choice in patients with preserved cardiac function. If there is any cardiac compromise, a combination of NE with dobutamine or milrinone is considered, or DA.

Kim and colleagues treated 16 patients with vasospasm post aSAH and assigned them to 3 different groups for HA. One group received hypervolemia only, the second group received MAP augmentation with phenylephrine, and the third one received CO augmentation with dobutamine. CBF was measured with Xe-CT, and all 3 groups had similar baseline values. The important finding of this study is the direct effect of increased CO to an increment of CBF independent of MAP.[103] CO augmentation is an alternative and complementary method for HA, and as the investigators argue, it may be safer than induced hypertension. Of note, hypervolemia alone had no effect on CBF in this study. Milrinone is another potentially useful agent for CO augmentation in the setting of aSAH. Naidech and colleagues[104] suggested that dobutamine and milrinone could be equal choices for patients with moderate MAP and systemic vascular resistance, but dobutamine may be superior in hypotensive patients or patients with low systemic vascular resistance. Apart from CO augmentation in the setting of HA, CO augmentation may be required secondary to a neurogenic stunned myocardium or to a so-called takotsubo cardiomyopathy.[105,106] Patients may develop cardiogenic shock, and a few case reports and case series describe rescue therapy with employment of an intra-aortic balloon pump (IABP) in patients with aSAH.[107,108] In fact, the common use of vasopressors may not be appropriate in the presence of takotsubo cardiomyopathy in view of the proposed pathophysiology of the syndrome, meaning catecholamine excess. Tung and colleagues[109] in a multivariate model examining predictors of neurocardiogenic injury found the use of phenylephrine, a pure alpha agonist, to be independently associated with higher levels of troponin release. This was not a result of the higher systolic blood pressure achieved with phenylephrine, suggesting direct toxicity of this pressor to the myocardium. In this scenario, mechanical circulatory support in the form of an IABP may be the more appropriate therapy instead of increasing doses of vasoactive medications, as suggested for patients with myocardial stunning caused by sudden emotional stress.[110] As a last comment on IABP use, the authors refer to the study by Spann and colleagues because this is the only study administering IABP therapy in a prospective fashion in 6 patients with aSAH who were deemed by them at high risk for DCI but before they developed any vasospasm or

cardiac dysfunction. The objective was to measure the effect of IABP on CBF, which is measured after administration of Xe-133. This study provides evidence of the beneficial effect of IABP on CBF even in patients with apparently not severely compromised cardiac function.[111]

SUMMARY

The understanding of DIND pathomechanisms is evolving. Arterial vessel narrowing is neither necessary nor always sufficient to cause DCI. Advanced hemodynamic monitoring and neuromonitoring hold promise in prevention, early detection, and therapy guidance. Knowledge of the state of pressure autoregulation, vascular reactivity, local CBF, and tissue oxygen and metabolic parameters could potentially lead to targeted interventional and medical manipulations. The aim is to reduce the toll of DIND on patients with aSAH and to minimize complications of applied therapies.

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