Neurosurg Rev (2015) 38:399–405
DOI 10.1007/s10143-014-0600-4

REVIEW

Normal perfusion pressure breakthrough theory: a reappraisal after 35 years

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Received: 10 June 2014 / Revised: 3 September 2014 / Accepted: 28 September 2014 / Published online: 9 December 2014

Abstract The intrinsic ability of the brain to maintain constant cerebral blood flow (CBF) is known as cerebral pressure autoregulation. This ability protects the brain against cerebral ischemia and hyperemia within a certain range of blood pressures. The normal perfusion pressure breakthrough (NPPB) theory described by Spetzler in 1978 was adopted to explain the edema and hemorrhage that sometimes occur after resection of brain arteriovenous malformations (AVMs). The underlying pathophysiology of edema and hemorrhage after AVM resection still remains controversial. Over the last three decades, advances in neuroimaging, CBF, and cerebral perfusion pressure (CPP) measurement have both favored and contradicted the NBBP theory. At the same time, other theories have been proposed, including the occlusive hyperemia theory. We believe that both theories are related and complementary and that they both explain changes in hemodynamics after AVM resection. The purpose of this work is to review the current status of the NBBP theory 35 years after its original description.

Keywords Arteriovenous malformation · Perfusion pressure · Perfusion pressure breakthrough · Occlusive hyperemia · Hemorrhage

Introduction

Cerebral pressure autoregulation is the specific intrinsic ability of the brain to maintain constant cerebral blood flow (CBF) over a range of blood pressures. Cerebral perfusion pressure (CPP) autoregulation mechanisms protect the brain against cerebral ischemia that results from hypotension, and against excessive flow (hyperemia) during hypertension, when capillary damage, edema, and hemorrhage might occur [29]. In 1978, Spetzler et al. described the malignant edema or hemorrhage that sometimes occur in the ipsilateral hemisphere of a high-flow arteriovenous malformation (AVM) following resection. They coined the term "normal perfusion pressure breakthrough (NPPB)" to describe this phenomenon [33]. Currently, other theories have been proposed to explain this phenomenon after AVM resection [1]. Recent advances in neuroimaging, CBF, and CPP measurement have at times favored and at other times contradicted the NBBP theory. The purpose of this work is to review the current status of the NBBP theory 35 years after its original description.

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Normal cerebral pressure autoregulation physiology

Under normal circumstances, cerebral pressure autoregulation is a complex process that involves neurogenic, metabolic, and myogenic mechanisms. The neurogenic mechanism occurs through an extensive nerve supply to large- and medium-size vessels. Acute denervation (e.g., neurogenic shock) or activation of α-adrenergic sympathetic nerves shifts the limits of autoregulation toward lower and higher pressures, respectively [13]. The metabolic mechanism occurs in smaller vessels that change according to the local microenvironment [26]. The myogenic component is the intrinsic ability of the vascular smooth muscle to constrict or dilate in response to changes in transmural pressure [25]. The capacity for autoregulation-driven vasoconstriction is much smaller (8–10 % of baseline diameter) than that for autoregulatory vasodilation (up to 65 % of baseline diameter). Therefore, much greater changes in

cerebral blood volume occur with hypotension than with hypertension [29].

Arteriovenous malformation physiology

Results of studies regarding the flow in and around AVMs are controversial. Some propose that AVMs lead to impaired autoregulation, while others believe that loss of autoregulation may be the root cause of AVM formation [16]. AVMs may induce hypotension in the cerebral circulation, probably related to the high bulk flow through the low-resistance conductance vessels drawing flow through the parallel circulation. Feeding AVM artery mean arterial pressures (MAPs) show a 50 % decrease when compared to systemic MAP [17, 32]. MAPs have been recorded during superselective cerebral angiography, and these have revealed that intra-arterial pressure decreases gradually as one proceeds distally out along the arterial tree [11]. Also, there is evidence that areas of normal brain in the hemisphere ipsilateral to the AVM are supplied by arteries showing significant relative hypotension [16]. An AVM appears to result in a "buffering" system; changes in systemic MAP are not transmitted to the circulation nearer to the AVM. Draining venous pressures are considerably higher than central venous pressure. It has also been demonstrated that the MAP of AVM feeders and superficial draining vein pressures have a parallel relation [36]. While pressures are transmitted across the nidus, they are already dampened when they reach the draining vein. This is explained by the buffering effect of the AVM feeding arteries. The feeding MAP is more important than the draining vein pressure in determining the transnidal pressure gradient.

Autoregulatory dysfunction is generally agreed to be important in AVM physiology. The possibility of loss of autoregulation in the hypotensive territories adjacent to AVMs has been proposed. Young et al. measured the CBF in normal brain tissue adjacent to the AVM and found that an increase in MAP did not increase CBF in these hypotensive vascular territories, suggesting that chronic hypotension does not necessarily result in impaired autoregulation [38]. Instead, the lower limit of autoregulation is displaced in affected vascular territories by a shift of the autoregulatory curve to the left [16, 38, 41]. Capillaries may also play a structural role in autoregulation. Capillary proliferation has been observed in the AVM rat model as a result of neovascularization; however, these small vessels partially lack an astrocytic foot process layer, making them prone to mechanical weakness and instability [31].

Pathophysiology of edema and hemorrhage after AVM resection: the two theories

Normal perfusion pressure breakthrough theory

In the original description of the NPPB theory, the authors' results indicated that CO_2 reactivity and autoregulation were abolished. The mechanism can be appreciated when an AVM is considered a large arteriovenous conduit with no resistance to flow, compared with small vessels with high resistance in the surrounding hemisphere. The normal vessels remain maximally dilated in order to maintain flow to normal brain. This chronic dilatation in the presence of ischemia could lead to loss of autoregulation. After AVM resection, the blood flow is redirected to these chronically dilated low-resistance vessels. The usual mechanisms of autoregulatory control, which possibly occur at the arteriolar level, cannot increase the resistance to the new perfusion pressure to protect the capillaries. These events cause edema or hemorrhage. Since the original description, several studies support the NPPB hypothesis [4, 6, 8, 10, 18, 23, 27, 39, 40]. Using angiography and transcranial Doppler, autoregulation in AVM feeding vessels was demonstrated to be impaired in response to hyperventilation [10]. Similarly, with the use of transcranial Doppler ultrasound in conjunction with acetazolamide and CO_2 to challenge vessel reactivity preoperatively, vasomotor paralysis was observed in only 2 of 35 patients; however, these 2 patients developed edema and hemorrhage after AVM resection [8]. Using orthogonal polarization spectral imaging, arteriolar pulsatility has been found to decrease after AVM resection, and at the same time, microvascular flow at the perinidal brain parenchyma was significantly increased [27]. AVM specimens have been tested in vitro with vasoactive substances and some of them have shown lack of spontaneous activity and therefore were considered nonreactive. These specimens belonged to patients who developed edema and hemorrhage after AVM resection [23]. Even though these previous studies support the NPPB theory, several recent studies have contradicted it. For instance, the CO_2 reactivity has been shown to be normal or impaired before AVM resection. There is almost unanimous agreement that the CO_2 reactivity after AVM resection is restored to normal [4, 6, 15, 33, 39, 40]. In most of these studies, the CO_2 reactivity was measured at different times during surgery. Similarly, there is evidence that vasoreactivity is intact and may be enhanced in patients developing a NPPB syndrome [5–7, 37]. Young and colleagues have demonstrated in both groups of patients (i.e., those with and without postoperative edema or hemorrhage) improved perfusion in the ipsilateral hemisphere following AVM resection, but no change in CBF after increasing blood pressure, suggesting intact autoregulation [37]. With these observations, the authors postulated that adaptive autoregulation could be a possible explanation for

the hemodynamic alterations seen in AVM patients [37, 38, 40]. Another important aspect of the NPPB is that edema and/or hemorrhage are localized to the adjacent brain parenchyma to the AVM. However, it has been well demonstrated that a global increase in CBF occurs after AVM resection [35] and that the worst vascular steal effect occurs 2–4 cm distal to the AVM (Fig. 1) [4]. There are no objective data demonstrating the relation of NPPB and AVM grade. However, the majority of NPPB cases have been on patients with Spetzler-Martin grade III or higher.

Occlusive hyperemia theory

In 1993, Al-Rodhan et al. [1] proposed the occlusive hyperemia theory as an alternative explanation to the edema and hemorrhage seen after AVM resection. This theory involves two separate but interrelated mechanisms involving arterial feeders and venous drainage. These mechanisms include the stagnation of arterial flow in former AVM feeders and their branches to normal brain with worsening of the existing ischemia with subsequent edema and hemorrhage, and the obstruction of draining veins of adjacent normal brain with subsequent engorgement, hyperemia, and further arterial stagnation. Arterial stagnation has been also described by others [14, 15, 28]. Factors related to arterial stagnation include increased resistance to flow, vessel architecture remodeling due to mechanical stress [21], and an arterial vasoconstriction reflex that compensates for normal or increased perfusion in the face of normal autoregulatory mechanisms. Venous obstruction in preoperative AVM has been reported. Yaşargil reported a 30–100 % incidence of venous drainage anomalies in AVMs, which includes agenesis, stenosis, and occlusion. Irregularities of vein of Galen and occlusion of the deep venous systems have been found in patients with AVM [34]. The number of draining veins has also been correlated with the risk of hemorrhage [2]. Risk factors for occlusive

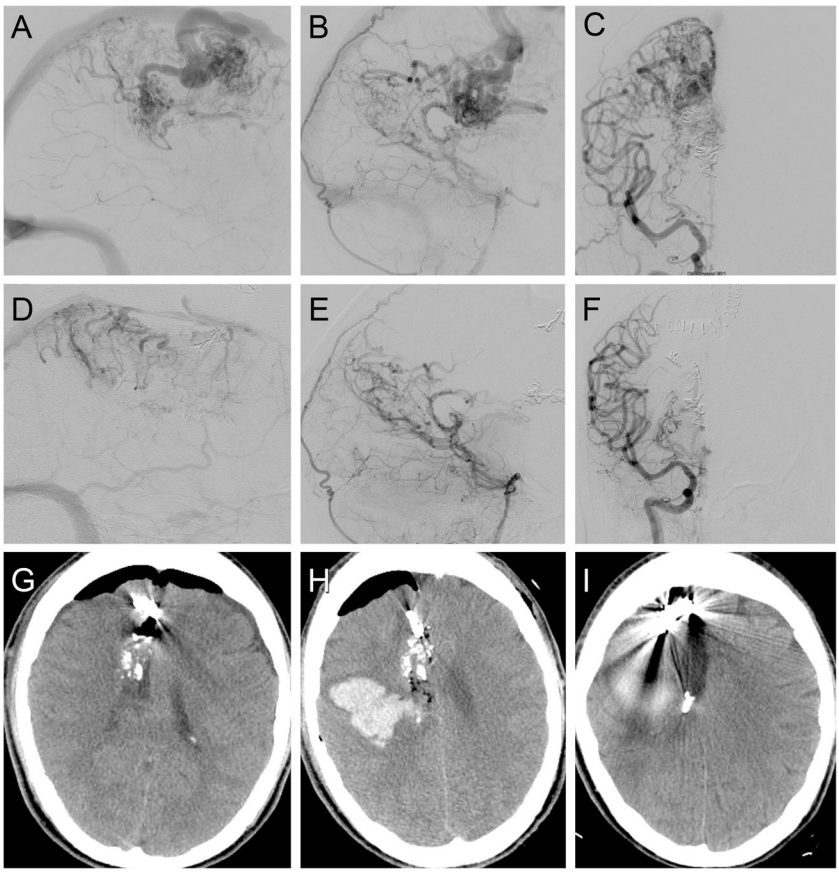

Fig. 1 A 20-year-old man with a right frontoparietal Spetzler-Martin grade III unruptured arteriovenous malformation (**a**–**c**). It was previously treated with radiation therapy. The recommendation was surgical resection. He underwent preoperative endovascular embolization followed by right frontoparietal craniotomy and microsurgical resection. Both procedures were uneventful. A postoperative cerebral angiogram showed complete AVM resection with no evidence of residual (**d**–**f**). After surgery, patient remained neurologically intact with a normal computed tomography (CT) scan of the brain (**g**). Seventy-two hours later, he complained of severe headache and had a tonic-clonic seizure episode. A brain CT (**h**) showed a large intraventricular and intraparenchymal hemorrhage adjacent to the surgical cavity. Patient was taken back to the operating room for hematoma evacuation. After hemorrhage, he had severe left hemiparesis. Two weeks later, the patient was discharge to rehabilitation (**i**). Clinical follow-up at 1 year, the patient has improved remarkably. He was able to ambulate with a cane and had some fine-motor difficulties with left hand. Used with permission from Barrow Neurological Institute

hyperemia include preoperative evidence of steal, location of the AVM in a watershed zone (increased risk of hypoperfusion and ischemia), large and high-flow AVMs, long and tortuous feeders subject to retrograde thrombosis [20], surgical alteration of venous flow velocity (high-flow to low-flow veins) [4, 24], preexisting venous anomalies (narrowing or occlusion) [34], small number of draining veins, and draining vein endothelial damage due to pressure and shearing stress [12]. Although the occlusive hyperemia makes sense and could explain the phenomenon after AVM resection, more recent data contradict this theory. Arterial stagnation with secondary hypoperfusion and ischemia in the surrounding brain parenchyma is part of the occlusive hyperemia theory. However, it is common to observe arterial stagnation following AVM resection, often in former feeding arteries but not in their branches. Slow transient flow within vessels reflects a reduction in flow velocity rather than a linear reduction in blood flow [19]. Meyer et al. have shown higher levels of oxygenation in postoperative brain tissue in patients with excessive angiographically confirmed stagnation of flow, including on patients with postoperative hyperemic complications [3, 19]. These findings were statistically significant enough to dispute the possibility of a venous mechanism for postoperative hemorrhagic complication.

Recognition, prevention, and management

In the original description of NPPB, Spetzler et al. suggested that patients who might potentially suffer this complication after AVM surgery can be identified by the presence of preoperative ischemic symptoms, radiographic evidence of a large AVM with poor filling of the normal hemisphere branches, or both. They proposed two management strategies: a gradual increase in perfusion to the ischemic hemisphere by staged ligation/embolization of the feeding arteries, and lowering the blood pressure after surgical AVM resection [33]. Currently, staged embolization to allow a gradual increase in perfusion to normal brain is still recommended. We have observed that lowering the blood pressure during and after surgical AVM resection may have detrimental consequences. In our practice, we maintain constant normal blood pressure during and after resection. In 1982, Day et al. [9] reported the successful treatment of NPPB in three patients. Their management included intraoperative and postoperative hypotension, barbiturate coma, hyperventilation, mannitol, and steroids. Similarly, these maneuvers are no longer used and/or are contraindicated. Residual AVM should always be ruled out first as a cause of hemorrhage. Intraoperative and/or immediate postoperative cerebral angiography is always recommended. While intraoperative use of indocyanine green angiography is a quick and safe method for mapping angioarchitecture of superficial AVMs, it is less valuable for deep-seated lesions. It has not been shown to improve identification of residual AVM; therefore, its intraoperative findings in terms of residual AVM should be interpreted with caution [42].

In summary, there are no specific guidelines or algorithm for the management of this rare complication. We advocate the maintenance of normal blood pressure in the postoperative period on patients undergoing brain AVM resection, regardless of whether embolization was used preoperatively or not. Certain strategies have been implemented in the restoration of impaired cerebral autoregulation in similar neurovascular injuries such as traumatic brain injury [29]. *Hyperventilation* improves autoregulation but is neither homogenous nor long lasting. The mechanisms include an improved CPP, alteration in the pH value of cerebrospinal fluid, and increased vascular tone [22]. *Hyperoxia* has been shown to restore cerebral autoregulation, but its effect is limited. Hyperoxia decreases the CBF, intracranial pressure, and flow velocity secondary to vasoconstriction [30]. *Nitric oxide* (*NO*) plays a role in several physiological processes in the brain, including basal vasomotor tone. Under pathological conditions, both excesses and deficiencies of NO may have deleterious effects. Depletion of NO produced by endothelium could result in inadequate cerebral perfusion. Administration of L-arginine, the precursor of NO, has been shown to improve CBF and neurological outcome [29]. However, the degree to which these various factors contribute to the microenvironment around and within the AVM, and their influence on subsequent risk of hemorrhage, are unclear.

It may well be that there are two or more pathophysiological pathways at work in perioperative brain swelling and hemorrhage in AVM patients. For the individual patient, determining which is most likely at work is still not a trivial matter. Further work is needed at both the physiological level (e.g., in terms of AVM bed hyperemia vs normal flow, oxygen extraction, and vascular resistance responsiveness) and at the microenvironment level to determine a rational strategy for anticipating and treating NPPB-like reactions. This is an area worthy of more research, both for the illumination it will provide of the underlying pathology and to spare patients from devastating neurological outcomes.

Conclusion

Since the original description of the NPPB hypothesis in 1978, other theories supporting or contradicting it have been proposed. The underlying pathophysiology of edema and hemorrhage after AVM resection remains controversial. We believe that both the NPPB and the occlusive hyperemia theories, are related and complementary, and that they both explain changes in hemodynamics after AVM resection. We

advocate maintaining normal blood pressure on the postoperative period on patients undergoing AVM resection. Further studies are still necessary to completely elucidate the mechanisms of this phenomenon.

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Comments

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In this review, Rangel-Castilla and colleagues provide an overview of the basic principles supporting normal perfusion pressure breakthrough (NPPB) and occlusive hyperemia (OH) proposed to explain postoperative edema and hemorrhage following resection of arteriovenous malformations (AVMs). Supportive and disputing studies for both theories are discussed and an updated perspective that consolidates the complementary roles of both theories is presented.

Since the NPPB hypothesis was first introduced by Spetzler in 1978, multiple studies have been conducted to validate or dispute its principles (3). While studies supportive of NPPB involved preoperative and postoperative assessments of autoregulation using physiologic or pharmacologic challenges such as hyperventilation and acetazolamide, contradicting studies showed restored reactivity to hyperventilation after AVM resection and preserved autoregulation.

Similarly, Al-Rhodan and colleagues first postulated the OH theory in 1993, and since then, the concept of arterial stagnation has been supported by several studies (1). Venous outflow obstruction, the second principle of OH, has also been extensively documented by others and has provided further tools for potential identification of patients at risk. Larger observational series, however, still fail to explain the absence of OH in patients presenting with both arterial stagnation and venous outflow obstruction.

Clearly, these theories are not mutually exclusive, and the contributing influences of abnormal autoregulation, arterial stagnation, and altered venous outflow can be incorporated in patients exhibiting postoperative complications. The extent to which each factor contributes to increase the risk of postoperative complications remains uncertain, and additional physiological and biological studies that correlate radiographic findings, anatomical variations, adaptive responses, and postoperative outcomes are clearly needed.

Using a combined approach, preoperative identification of these patients can be pursued, and individualized postoperative plans can be tailored to prevent NPPB/OH. Staged preoperative embolization of large lesions and strict postoperative targeted normotension have emerged as accepted strategies to prevent NPPB/OH onset, although its efficacy remains to be demonstrated in a systematic fashion (2). The value of postoperative hyperventilation, hyperoxia, nitric oxide donors, and other experimental therapies after NPPB/OH onset is anecdotal at best.

Ongoing controversies on the benefits of treatment of unruptured AVMs will likely impact our ability to treat these patients in a proactive fashion. Differences in incidence of NPPB/OH for patients with unruptured versus ruptured AVMs are unknown, but the hemodynamic stress resulting in ruptures is likely to contribute to more severe forms of NPPB/OH, which develop in patients with less theoretical reserve to tolerate these events.

We commend the authors on an updated and inclusive perspective on this challenging topic and hope that their review stimulates new research in this fascinating phenomenon.

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The theory of normal perfusion pressure breakthrough (NPPB) was originally proposed by Spetzler et al. [1] in 1978 to describe the phenomenon of the malignant edema or hemorrhage that sometimes occurs in the ipsilateral hemisphere of a high-flow arteriovenous malformation (AVM) following resection. In the original description of NPPB, those authors suggested that patients who might suffer this complication after AVM surgery could be recognized by the presence of preoperative ischemic symptoms and/or radiographic evidence of a large AVM with poor filling of the normal hemisphere branches. To tackle the complications, they proposed two management strategies: (1) a gradual increase in perfusion to the ischemic hemisphere by staged ligation or (2) embolization of the feeding arteries and lowering of the blood pressure after surgical AVM resection.

The current understanding of AVM pathophysiology has changed, and an occlusive hyperemia theory was proposed by al-Rodhan et al. [2] in 1993. This theory was based on venous occlusion and stasis of flow in the arteries associated with a previously resected AVM. Together, these characteristics were found to be responsible for ischemia and hemorrhage following AVM treatment.

With modern technology, endovascular embolization of AVM is safer and controlled, compared with the early embolization experience. The authors of this NPPB theory reappraisal article have rightly recommended staged embolization for high-grade AVMs. This approach allows a gradual increase in perfusion to normal brain. In fact, they no longer recommend hypotension perioperatively or postoperatively. This marks a paradigm shift in AVM management, as strict blood pressure control was the standard. Management strategies continue to evolve with time, based on better understanding of disease processes and evidence arising from trials.

It is interesting to address the issue of "disruptive innovations" in neurosurgery. Endovascular coiling of aneurysms is gradually replacing the standard of aneurysm clipping. Contemporary literature is suggestive of complete cure of low-grade AVMs (Spetzler-Martin [SM] grade [3] of III or less) with embolization alone [4]. What is important is to know if there is a role for partial embolization of brain AVMs in decreasing the risk of hemorrhage or whether this approach increases the chances of hemorrhage. This question has become more important because most SM grade >III AVMs are treated with staged therapy with embolization and microneurosurgery [5, 6]. More trials and studies are needed to understand the phenomenon of postoperative ischemia and hemorrhage following AVM treatment and for the development of an appropriate management protocol.

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