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The Triple Effort of Cerebral Vasospasm Management

Eelco F. M. Wijdicks*

"From the figures given, it seems fair to conclude that arterial spasm bears some relation to a bad prognosis" is what Alcock and Drake concluded in their early 1960s articles [1, 2]. Their remedy was as follows:

> Operation is postponed for 7-10 days after a bleeding, or longer if spasm is still present. During this time, the patient is kept mildly hypotensive with the idea of minimising the risk of a further haemorrhage. This may aggravate the effects of any spasm present, but it is felt that this theoretical disadvantage is outweighed by the possibility of a disastrous recurrent haemorrhage. The systolic blood pressure is lowered to 80 mm Hg during the dissection of the aneurysm.... If the obliteration is satisfactory, the patient's blood pressure is maintained postoperatively at a level at or above the normal range. Liberal supplies of ethyl alcohol and more enthusiastic administration of carbon dioxide are being tried as a preventative and treatment of spasm [1].

Already in the early days, when neurosurgeons tried to grasp the immediate and later consequences of aneurysmal rupture, the development of cerebral vasospasm seen on angiogram was recognized as a major cause of deterioration [2]. The mechanism of cerebral vasospasm remained unsatisfactorily explained and experimental studies assessing the effects of "spasmolytic" drugs in animal models were also not encouraging. Other investigators considered different approaches to treat this complication that involved manipulating the blood rheology and intraarterial pressure.

Thus, in cerebral arteries without autoregulation, increasing cerebral perfusion pressure or reducing viscosity could increase cerebral blood flow. This concept became the basis of hypertension, hypervolemia, and hemodilution, better known as "Triple-H" therapy. A neurosurgeon who had a significant interest in such an approach was Thor Sundt, Jr., from Mayo Clinic (who operated on former President Ronald Reagan in 1989). Some of his ideas may have come from experimental work in stroke, such as in Sundt's work *Experimental Cerebral Infarction treating it with Hemodiluting, Hemoconcentrating, and Dehydrating Agents* [3]. However, in 1973, Dr. Sundt described using pressors and fluids to increase cerebral blood flow and augment cardiac output in patients with cerebral aneurysm rupture and vasospasm [4]. He noted the following:

> The development of the infarct could be modified, favorably or unfavorably, by the intravenous administration of agents which influence blood viscosity, aggregation of formed blood elements, or intravascular oncotic pressure. Intravenous injection of a combination of concentrated serum albumin and low-molecular-weight dextran before the occlusion and of concentrated urea after the occlusion resulted in a significantly smaller mean infarct volume when compared to that in untreated cats [4].

The therapeutic effects of dextran were attributed to the reversal of cell aggregation and the reduction of blood viscosity, both of which improved flow within the microvasculature. There were two principal mechanisms for the changes in flow. The first was a rapid and profound increase in plasma volume and an associated drop in hematocrit. A valuable therapeutic agent in the treatment of impeded flow within the microvasculature has been low-molecular-weight dextran. Reports indicated that this agent improves flow within the microvasculature by expanding

*Correspondence: wijde@mayo.edu
Neurocritical Care Services, Saint Marys Hospital, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

the plasma volume with body water and by disaggregation of erythrocyte masses. Both these responses increase the fluidity of blood. Other approaches were with isoproterenol, which increases the heart rate, reinforces myocardial contractility, and increases cardiac output. It also dilates peripheral arterioles, decreases the arterial pressure, and decreases the venous reservoir, with a marked increase in venous return to the heart.

In 1973, Sundt et al. reported the initial experience with intravenously administered isoproterenol and lidocaine hydrochloride in 14 patients with severe spasm from subarachnoid hemorrhage. All patients were actively deteriorating from progressive spasm without other major complications; 12 of 14 improved, and 2 died [4].

Later, in 1982, Sundt et al. wrote the following:

We believe that the following guidelines are sound for the management of vasospasm: 1) early recognition and institution of treatment as soon as a minor deficit is identified; 2) maintenance of a normal blood volume with whole blood or packed cells until a hematocrit of 40% to 45% is achieved; 3) maintenance of fluid restriction with a maximum limit of 1000 ml/ 24 hours; and 4) if all the above are ineffective, infusion of isoproterenol and lidocaine hydrochloride in an effort to increase not only the cardiac output but also the mean arterial perfusion pressure (the cardiac rate must be maintained under 100 beats/min) [5].

Neurosurgeons Kosnik and Hunt were the first to describe the use of postoperative hypertension, but in fact, they used a combination of volume augmentation and hypertension. No experimental study had previously investigated the possible effects of this intervention, and experience came directly from clinical observations [6]. Their article assumed that increasing the cerebral perfusion pressure would be the most effective way to overcome the significant diffuse cerebral vasospasm in these patients. The authors described seven patients with an aneurysmal subarachnoid hemorrhage; some had postoperative neurologic signs, and others had a neurologic decline while the aneurysm was unsecured. Some of these patients did well until the fourth or fifth postoperative day and then became markedly "obtunded with only semi-purposeful movements in response to pain [6]."

Kosnik and Hunt treated with patients with colloid replacement and Plasmanate followed by norepinephrine. They selected norepinephrine because of its powerful peripheral vasoconstriction and its inotropic-stimulating effects on cardiac muscle. The investigators developed a regimen that they described as "enough norepinephrine to elevate the blood pressure 40 to 60 points systolic or to produce unmistakable clinical improvement." In addition,

they administered plasma followed by whole-blood transfusion. After blood-volume expansion and a rise of the central venous pressure, they weaned the patients to lower doses of norepinephrine. After the neurologic deficit improved, they maintained blood pressure several more days and then gradually allowed it to drift down to pretreatment levels [6] (Fig. 1).

Equally important, they noted that a reduced blood volume could have been present in some of these patients because there was a rapid response with volume augmentation. Additionally, in one patient with adequate systolic blood pressures in the 140-mm Hg range, further blood pressure augmentation was successful, suggesting an unknown ceiling of blood pressure goals. The authors also emphasized the importance of timing of augmentation: "The most serious hazard seems to be the institution of treatment too late, after the cerebrovascular system is so damaged that increasing perfusion pressure only increases brain swelling."

The authors recognized the potential hazards of increasing perfusion that could potentially result in brain edema. There was a concern that fluid overload in patients with congestive heart failure could further complicate management.

Literature reviews usually mention two other important articles concurrently. One group described intravascular volume expansion in four additional patients; their approach was similar, i.e., keeping the patient hypervolemic and additionally using vasopressors or discontinuing antihypertensive medication [7]. In 1982, another group led by Kassel published their surefooted experience in 58 patients who deteriorated neurologically from angiographically confirmed cerebral vasospasm. In this study, a high proportion (81%) of their patients responded favorably to therapy, and failure in the remainder was related to delay in initiating therapy or development of complications, particularly pulmonary edema from overhydration. Congestive heart failure was not observed in their patients [8]. These articles tackled the key issues: timing and target of blood pressure augmentation. Kassel's study was unique because it introduced for the first time Swan-Ganz catheterization to monitor intravascular volume, an approach later universally used in hemodynamic augmentation of patient with subarachnoid hemorrhage complicated by vasospasm.

Complications of aggressive monitoring also became apparent. One study [9] found catheter-related sepsis in 13% but much lower congestive heart failure (2%), incidence of subclavian vein thrombosis (1%), and pneumothorax (1%).

One other important question emerged. Could prophylactic Triple-H therapy instituted before symptom onset be more effective? This was further studied in a series of 47 consecutive patients with ruptured intracranial

Postoperative hypertension in the management of patients with intracranial arterial aneurysms

EDWARD J. KOSNIK, M.D., AND WILLIAM E. HUNT, M.D.

Department of Surgery, Division of Neurological Surgery, Ohio State University College of Medicine, Columbus, Ohio

✔ Elevation of systemic arterial pressure in seven patients with intracranial arterial aneurysms has been shown to be effective in alleviating ischemic symptoms attributed to cerebral vasospasm. Autoregulation is at least partially lost in patients with cerebral hemodynamic crisis. Blood volume expansion was used to augment vasopressors in maintenance of systemic hypertension. The management of these cases is discussed. Caution in the use of this technique is advised, since the regimen is not without risk.

KEY WORDS · cerebral vasospasm · hypertension, therapeutic · hypervolemia, therapeutic · intracranial arterial aneurysm · cerebral hemodynamic crisis · cerebral ischemia

ALL neurosurgeons are familiar with the problem of arterial spasm, cerebral ischemia, and infarction after intracranial aneurysm repair. Much work has been done with regard to the nature of vascular response, its etiology and physiology.[1-4,10,11,14-16,24,29,30] Numerous medications have been tried locally and systemically with equivocal results, especially in the clinical situation.[7,8,13,17,20,23,27] The neurological deficit is clearly due to tissue ischemia or infarction, whether secondary to cerebral vasospasm, embolization, or thrombosis. Over the past few years we have treated symptoms of ischemia by means of induced arterial hypertension in several carefully selected cases.

Denny-Brown[5] was the first to describe treatment of cerebral ischemia by increasing arterial blood pressure. Shanbrom and Levy[21] discussed two patients with advanced arteriosclerotic disease of the carotid and basilar systems in whom a critical-level systemic arterial pressure was found necessary to overcome ischemic symptoms. Farhat and Schneider[6] reported four patients with cerebrovascular insufficiency. Two of these patients were treated in the postoperative period, and two were treated for postangiographic complications. These authors raised the systolic pressure 50 to 60 mm Hg with good results. Wise, *et al.*,[28] reported a series of patients with cerebral ischemia in whom raising the systemic arterial blood pressure with vasopressors brought about reversal of neurological deficit. Recently Wernick and Sugar[25] reported a case of postangiographic hemiplegia which was successfully treated with vasopressors.

We have raised the systemic mean arterial pressure in a series of aneurysm patients who were suffering from a postoperative cerebral-flow crisis, with good results in most cases. Some cases with clear-cut clinical response are reported below.
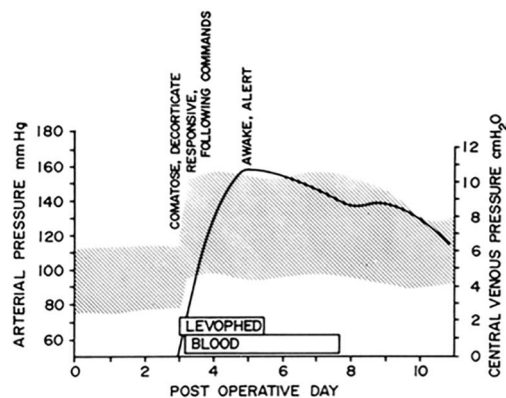
FIG. 1. Postoperative course in Case 1, showing the patient's blood pressure, central venous pressure, and neurological status. Note the improvement occurring with pressure elevation.

Fig. 1 Cover page of article by Kosnik and Hunt [6] and effect of blood pressure augmentation, used with permission from *Journal of Neurosurgery* Publishing Group

aneurysms treated with prophylactic volume expansion for up to 2 weeks after subarachnoid hemorrhage, and no cases of cerebral infarction were found. However, another study revealed no difference in the mean global cerebral blood flow CBF (using 133 xenon clearance) in hypervolemic and normovolemic patients. Symptomatic vasospasm occurred in 20% of patients in each group despite better intravascular volume parameters [10, 11].

Kosnik and Hunt also studied the effect of 5% albumin solution on sodium balance and blood volume after subarachnoid hemorrhage in 47 patients treated with either hypervolemia or normovolemia treatment for a week after aneurysm clipping. The hypervolemia group received significantly more total fluid, sodium, and 5% albumin solution than did the normovolemia group and had higher central venous pressure levels. Supplemental 5% albumin solution prevented sodium and fluid losses but did not have an impact on blood volume [11].

An intervention here to stay?

Current published data on the best approach are unconvincing because consistent measurements of relevant clinical and laboratory variables are lacking, with different methods used in each cohort. Still lacking is a randomized study of hemodynamic augmentation in aneurysmal subarachnoid hemorrhage. Nonetheless, neurointensivists and neurosurgeons have often seen significant improvement of the patient with aggressive fluid management and supplemental blood pressure increase soon after onset of symptoms. When a patient deteriorates, management now has shifted toward early endovascular management. Triple H (hypervolemia, hypertension, and hemodilution) has few advocates. Hypervolemia cannot produce a sustained increase in cerebral blood flow and perfusion, and it can impair brain oxygenation. Furthermore, there is serious risk of volume overload syndrome. Hemodilution, if excessive, can compromise oxygen-carrying capacity with insufficient brain oxygen delivery. But this prior work in the 1960s and its reconstruction of what happened is more than only of historical interest because it did gradually change practice, so when cerebral vasospasm emerged, patients were already normovolemic and comparatively hypertensive, leaving little other options than to change the vasoconstriction with mechanical stretch, intraarterial vasodilators, or systemic high-dose

vasodilators (i.e., Milrinone). Medical history of patient care is conditioned by its changing environment.

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