J Neurosurg 77:15–19, 1992

Blood pressure and intracranial pressure-volume dynamics in severe head injury: relationship with cerebral blood flow

GERRIT J. BOUMA, M.D., J. PAUL MUIZELAAR, M.D., PH.D., KUNIAKI BANDOH, M.D., AND ANTHONY MARMAROU, PH.D.

Division of Neurosurgery, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia

✓ Increased brain tissue stiffness following severe traumatic brain injury is an important factor in the development of raised intracranial pressure (ICP). However, the mechanisms involved in brain tissue stiffness are not well understood, particularly the effect of changes in systemic blood pressure. Thus, controversy exists as to the optimum management of blood pressure in severe head injury, and diverging treatment strategies have been proposed. In the present study, the effect of induced alterations in blood pressure on ICP and brain stiffness as indicated by the pressure-volume index (PVI) was studied during 58 tests of autoregulation of cerebral blood flow in 47 comatose head-injured patients. In patients with intact autoregulation mechanisms, lowering the blood pressure caused a steep increase in ICP (from 20 ± 3 to 30 ± 2 mm Hg, mean ± standard error of the mean), while raising blood pressure did not change the ICP. When autoregulation was defective, ICP varied directly with blood pressure. Accordingly, with intact autoregulation, a weak positive correlation between PVI and cerebral perfusion pressure was found; however, with defective autoregulation, the PVI was inversely related to cerebral perfusion pressure. The various blood pressure manipulations did not significantly alter the cerebral metabolic rate of oxygen, irrespective of the status of autoregulation.

It is concluded that the changes in ICP can be explained by changes in cerebral blood volume due to cerebral vasoconstriction or dilatation, while the changes in PVI can be largely attributed to alterations in transmural pressure, which may or may not be attenuated by cerebral arteriolar vasoconstriction, depending on the autoregulatory status. The data indicate that a decline in blood pressure should be avoided in head-injured patients, even when baseline blood pressure is high. On the other hand, induced hypertension did not consistently reduce ICP in patients with intact autoregulation and should only be attempted after thorough assessment of the cerebrovascular status and under careful monitoring of its effects.

KEY WORDS • **autoregulation** • **cerebral blood flow** • **cerebral metabolism** • **head injury** • **intracranial pressure** • **pressure-volume index**

It is customary to explain raised intracranial pressure (ICP) after head trauma in terms of volume increases within the intracranial compartment, be it caused by hematoma, cerebrospinal fluid (CSF), tissue water (edema), or cerebral blood volume (CBV). The extent to which such volume changes will translate into changes in pressure depends on the compliance or volume-buffering capacity of the system. Compliance of the craniospinal axis, defined as the change in CSF volume per unit change in pressure, is not constant but increases as pressure rises.[25] The exponential volume-pressure curve can be transformed into a linear equation by plotting it on a semilogarithmic scale; the slope of this line yields an index of compliance which is independent of ICP, and is termed the "pressure-volume index" (PVI).[13] The PVI can be viewed as the theoretical volume (in ml) to be added to the CSF space to obtain a tenfold increase in pressure; the normal value is 25 ml.[25] The PVI is considered to be a reflection of the intracranial vascular compartment, and in particular is thought to be influenced by the compressibility of the cerebrovascular bed.[12] Vascular compressibility in turn can be considered a function of stiffness of the vessel wall and intravascular (transmural) pressure. Thus, factors that influence the cerebrovasculature may affect both the ICP (by changes in vascular volume) and the PVI (by alterations in stiffness of the vessel wall and intravascular pressure). The role of changes in systemic blood pressure or cerebral perfusion pressure (CPP) is of particular interest in this regard, as these greatly influence both cerebrovascular diameter (and thus volume) as well as intravascular pressure, depending on whether cerebral autoregulation is intact.

The effects on ICP of blood pressure alterations have

received much attention and are a subject of ongoing controversy. On one hand, concern has been raised that high blood pressure would aggravate brain edema and further raise ICP, and therefore antihypertensive therapy has been advocated.[14,26] Conversely, it has been suggested that low blood pressure or CPP would trigger cerebral vasodilatation (due to autoregulation) and lead to an increase in ICP;[22] consequently, induced arterial hypertension has been proposed as a possible therapy for otherwise uncontrollable high ICP in selected cases.[16] In line with this concept, a protocol to maintain CPP above a certain threshold has been proposed, if necessary even by pharmacologically raising arterial blood pressure.[24] Clearly, with such therapeutic maneuvers, autoregulation is assumed to be grossly intact.

The relationship between blood pressure and PVI has thus far been studied almost exclusively in animals. However, the results of these studies have not been unequivocal,[2,5,9] and the data are compounded by the effects of various anesthetic drugs.[5]

In the present study, we have evaluated the responses of cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRO_2$), ICP, and PVI to induce changes in blood pressure during tests of autoregulation in comatose patients with severe closed head injury. In these patients, anesthetic drugs are usually not administered, while autoregulation may or may not be intact (although for unknown reasons).[3,17] Thus, we were able to examine the above relationships separately in situations of both intact and defective autoregulation, without the disturbing effects of anesthesia. Moreover, these studies may shed some light on the ongoing controversy about optimum blood pressure management in head-injured patients.

Clinical Material and Methods

Patient Population

Forty-seven patients with a Glasgow Coma Scale score of 8 or less after sustaining severe closed head injury were studied during the first days following injury. All patients were ventilated mechanically and paralyzed with pancuronium bromide in order to achieve optimum control of pCO_2 and prevent movement artifacts during the measurements. Details of therapeutic management have been described elsewhere.[1] Patients requiring continuous administration of vasopressor or antihypertensive drugs or barbiturates, as well as patients who received mannitol less than 2 hours prior to the measurements, were not included in this study. All measurements reported here were performed in the Neuroscience Intensive Care Unit of the Medical College of Virginia Hospital and only after written informed consent from the patient's next of kin. The protocol was approved by the Committee on the Conduct of Human Research at the Medical College of Virginia. All procedures involving ^{133}Xe were performed in accordance with the radiation safety regulations of the Office of Environmental Health and Safety of the Virginia Commonwealth University.

Determination of Blood Pressure, ICP, and PVI

In all patients, ICP was measured with an intraventricular catheter connected to a pressure transducer. Arterial blood pressure was continuously monitored from an intra-arterial catheter and digitally displayed as mean arterial blood pressure (MABP), which equals diastolic pressure + $\frac{1}{3}$ pulse pressure. Determinations of PVI were made during each CBF measurement by the intraventricular bolus injection or withdrawal method as described by Marmarou, *et al.*[12,15]

Assessment of CBF, Autoregulation, and $CMRO_2$

Measurement of CBF was performed by the ^{133}Xe intravenous injection technique using a portable apparatus containing 10 external collimators.* Details of the procedures used have been described previously.[17] Autoregulation was tested by a titrated intravenous infusion of phenylephrine in normal saline (80 mg/500 ml) or trimethaphan camsylate (500 mg Arfonad/500 ml of 5% dextrose) to respectively raise or decrease MABP by 25% to 30% over a 20-minute period. These tests were not performed whenever large hemorrhagic contusions, coagulopathies, or other severe systemic complications were present. Blood pressure was lowered only when baseline CBF and MABP were high, and this was effected only when simultaneous monitoring of evoked potentials was available to ensure patient safety. As in earlier studies, autoregulation was defined as intact if the percentage change in CPP divided by the percentage change in cerebrovascular resistance (computed as CPP ÷ CBF) was positive at a level of 2 or less.[17,20] Arterial blood gases were obtained during each CBF measurement. If the pCO_2 had changed by more than 10 mm Hg between two CBF measurements, the study was discarded. Otherwise, small differences in pCO_2 between pre- and postdrug measurements were corrected for by assuming a 3% change in CBF per torr change in pCO_2.[18,21] The arteriovenous oxygen content difference ($AVDO_2$) was determined twice during each CBF measurement by oximetry of simultaneously obtained arterial and jugular venous blood samples, and the $CMRO_2$ was calculated by multiplying CBF by $AVDO_2$.[7,18]

Statistical Analysis

Physiological parameters (CBF, ICP, PVI, and $CMRO_2$) before and after blood pressure manipulations were compared using paired Student's t-test. A p value of less than 0.05 was considered significant.

Results

A total of 58 complete autoregulation studies were performed, 49 using phenylephrine and nine using trimethaphan camsylate. Autoregulation was found to be intact in 40 cases (69%) and defective in 18 (31%). The

* Novo-10a CBF measuring device manufactured by Novo Diagnostic Systems, Bagsvaerd, Denmark.

TABLE 1

*Physiological parameters in head-injured patients before and after blood pressure manipulations**

Parameter	Trimethaphan Group		Phenylephrine Group	
	Before	After	Before	After
autoregulation intact				
MABP	120 ± 13	91 ± 10	93 ± 11	119 ± 11
ICP	20 ± 3	30 ± 2†	20 ± 6	20 ± 8
PVI	22 ± 5	22 ± 6	19 ± 6	21 ± 7
CBF	38 ± 6	35 ± 4	35 ± 10	37 ± 11
$CMRO_2$	1.01 ± 0.29	0.99 ± 0.41	1.71 ± 0.62	1.60 ± 0.52
autoregulation defective				
MABP	112 ± 19	90 ± 17	99 ± 12	126 ± 9
ICP	16 ± 5	11 ± 7†	16 ± 7	20 ± 9†
PVI	21 ± 9	24 ± 2‡	22 ± 5	18 ± 4‡
CBF	79 ± 38	37 ± 10	34 ± 6	50 ± 14
$CMRO_2$	2.07 ± 0.29	1.86 ± 0.49	1.32 ± 0.39	1.50 ± 0.65

* Values are means ± standard deviations, measured before and after administration of blood pressure regulatory agents. MABP = mean arterial blood pressure (mm Hg); ICP = intracranial pressure (mm Hg); PVI = pressure-volume index (ml); CBF = cerebral blood flow (ml/100 gm/min); $CMRO_2$ = cerebral metabolic rate of oxygen (ml/100 gm/min^{-1}). Autoregulation was intact in 40 patients and defective in 18 patients. Statistical significance: † $p < 0.01$, paired t-test; ‡ $p < 0.05$.

results of all measured parameters before and after drug administration, itemized for both the direction of the blood pressure change as well as the status of autoregulation, are shown in Table 1. Changes in blood pressure and CBF were as expected according to our definition of autoregulation, but the alterations in blood pressure did not cause a statistically significant change in $CMRO_2$.

When autoregulation was intact, increased blood pressure did not change ICP significantly, but lowering blood pressure resulted in a steep and significant increase in ICP ($p < 0.01$). By contrast, with defective autoregulation, ICP varied directly with MABP ($p < 0.01$). With preserved autoregulation, the PVI tended to be higher when CPP was increased ($p < 0.05$), although the average change was small (Table 1); however, when autoregulation was defective, the PVI became inversely related to CPP ($p < 0.01$). Figure 1 shows the relationship between ICP and MABP for each case, and demonstrates that the positive correlation between ICP and blood pressure with impaired autoregulation appeared to be fairly consistent in most patients. With intact autoregulation, however, this relationship was more variant and unpredictable in individual cases, especially at higher levels of ICP (> 20 mm Hg).

The individual changes in CPP and associated changes in PVI are shown in the same manner in Fig. 2. As with ICP, the correlations were most consistent with defective autoregulation whereas, with intact autoregulation, the positive correlation between CPP and PVI was marked only at the higher (more normal) levels of PVI, and CPP changes had little effect on low PVI (reduced compliance).

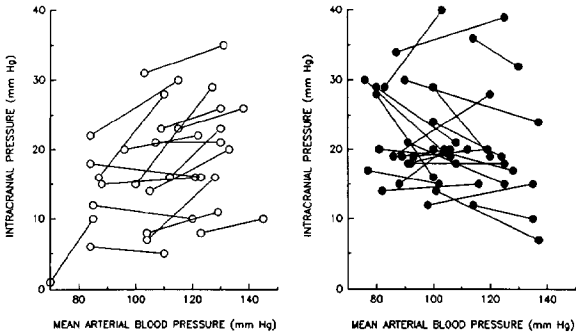

FIG. 1. Graphs showing the relationship between changes in mean arterial blood pressure and intracranial pressure in head-injured patients with defective *(left)* and intact *(right)* autoregulation.

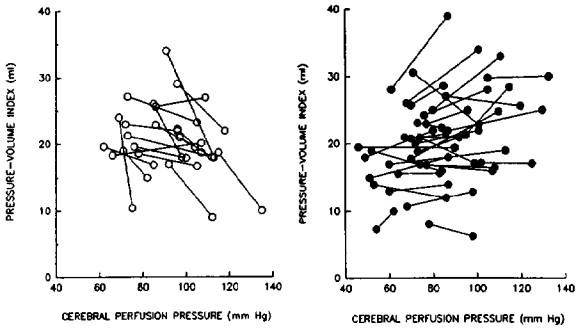

FIG. 2. Graphs showing changes of pressure-volume index in response to altered cerebral perfusion pressure in head-injured patients with defective *(left)* and intact *(right)* autoregulation.

Discussion

Arterial Blood Pressure and ICP

When autoregulation is intact, cerebral vessels respond to a change in CPP by either vasconstriction or vasodilatation, resulting in altered vascular resistance so that CBF remains more or less constant. This also leads to changes in cerebrovascular volume and transmural pressure which in turn affect the ICP and the volume-pressure relationship.[19] Accordingly, it has been proposed that, depending on the status of the autoregulation mechanisms, induced changes in CPP or arterial blood pressure may be used to manipulate CBV in order to treat raised ICP after head injury.[16,23] Indeed, the present data show that, with intact autoregulation, reduced blood pressure sharply increases ICP due to vasodilatation and the subsequent increased CBV. Raised blood pressure, however, did not lead to the expected decrease in ICP. This may be explained by the fact that autoregulatory vasoconstriction is much smaller (maximum approximately 8% to 10% of baseline diameter) than autoregulatory vasodilatation (up to 65% of baseline diameter),[8] with consequently much larger changes in CBV with hypotension than with hypertension (Fig. 3). Moreover, autoregulatory vasoconstriction predominantly takes place in the larger

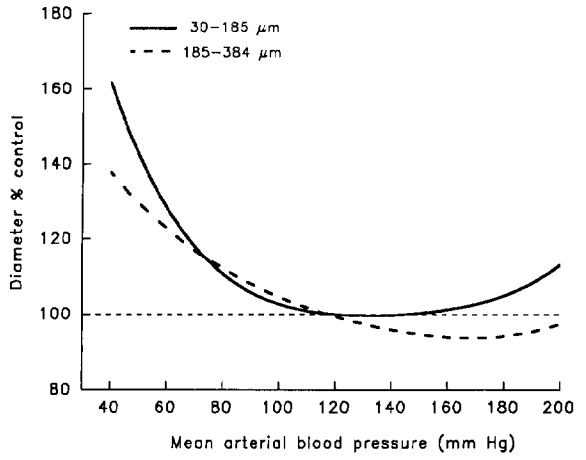

FIG. 3. Graph showing relationship between mean arterial blood pressure and diameter of cerebral surface arteries (> 185 μm, *dashed curve*) and arterioles (< 185 μm, *solid curve*). (Adapted from Kontos HA, Wei EP, Navari RM, et al: Responses of cerebral arteries and arterioles to acute hypotension and hypertension. **Am J Physiol 234**:H371–H383, 1978, with permission.)

arterioles (> 200 μm diameter), while the bulk of CBV is probably contained in the smaller vessels, because of their larger number. With intracranial hypertension, factors other than CBV (such as edema or mass lesions) may also contribute to raised ICP and may be responsible for the inconsistency in the results obtained at higher levels of ICP (Fig. 1). Thus, given the unpredictability of the effect of induced arterial hypertension on high ICP, even with intact autoregulation, we would not recommend this as a routine treatment to control ICP. Although effective in some cases, we consider that this method remains a "last resort" when all other treatments have failed, and should only be performed with careful monitoring of CBF and ICP.[16]

Cerebral Perfusion Pressure and PVI

Changes in intravascular pressure and CBV will affect not only ICP, but also the mechanical properties of the brain and the volume-buffering capacity of the intracranial space. The PVI is a measure of brain compliance and is considered to be a reflection of the vascular component of the intracranial contents.[12] Consequently, the relationship between CPP and PVI has been the subject of investigation by several authors;[2,9,27] in studies using pentobarbital-anesthetized animals, most reported that PVI or brain compliance did not change with CPP alterations within the limits of autoregulation. Outside the autoregulatory range, changes in PVI became inversely related to CPP. Contrary to these reports, Gray and Rosner[5,6] found a significant positive correlation between PVI and CPP within the limits of autoregulation. They postulated that the changes in PVI were due to the fact that, with intact autoregulation, CBV increases when CPP decreases and *vice versa*. However, this correlation was hardly present in animals anesthetized with pentobarbital; presumably because of its own vasoconstricting effect, this drug blunted the vascular responses to CPP changes and obscured the relationship between PVI and CPP.[5]

In the present study in patients without anesthesia, there was a weak positive correlation between PVI and CPP with intact autoregulation, which seems to be in agreement with Gray and Rosner's observations.[5,6] However, the fact that the induced changes in PVI were relatively small suggests that the effect is in part counteracted by increased intravascular pressure, the latter reducing the compressibility of the vascular bed. The increase in transmural pressure may partially be offset by a thickening of the vessel wall due to vasoconstriction, but the degree of this effect probably differs from patient to patient, which may account for the variability of the results in Fig. 2 *right*. Moreover, the positive correlation between the PVI and the CPP was absent at lower levels of PVI, suggesting a nonvascular contributory cause for the reduced compliance in these cases.

The inverse correlation that we found between CPP and PVI with defective autoregulation is in agreement with earlier data. In these cases, higher transmural pressure across the vessel wall is not offset by arteriolar vasoconstriction, but instead is transmitted to the distal parts of the cerebral microcirculation, leading to forced vascular expansion with decreased compressibility of the venous part of the cerebrovascular bed, thus "stiffening" the brain. Conversely, reduced CPP causes vessel collapse and lower transmural pressure, which makes the brain more "slack."

Blood Pressure Management in Head-Injured Patients

Based on the present data, a few comments on blood pressure management in severe head injury can be made. Two effects of blood pressure manipulations should be distinguished in this regard: namely, the effects on cerebral perfusion on one hand and on ICP and compliance on the other, both of which are dependent on the status of the autoregulation system, as alluded to above.

Thus, when autoregulation is defective, lowering blood pressure will decrease CBF and may even incur the risk of provoking cerebral ischemia, especially when baseline CBF is low, as is often the case in the first 12 hours after injury;[4,11] in contrast, elevating blood pressure will increase CBF. In evaluating the resulting changes in CBF, it is important to determine whether these are also reflected by changes in cerebral metabolism as measured by the $CMRO_2$. For instance, if low CBF is increased by induced hypertension but $CMRO_2$ is left unchanged (because $AVDO_2$ decreased), the higher flow would be considered "luxury perfusion" and is not likely to be beneficial.

The present study suggests that a decline in blood pressure is always detrimental; with impaired autoregulation it may invoke the risk of cerebral ischemia, while with intact autoregulation it may lead to danger-

ous increases in ICP and brain stiffness due to compensatory vasodilatation. However, artificially raising blood pressure, if necessary to maintain CPP, would only seem prudent when autoregulation is known to be intact. In such cases, induced hypertension has little effect on ICP and may even improve the PVI somewhat; thus, it may be regarded as safe. It should be borne in mind that, with very high blood pressure, autoregulation breakthrough may be caused,[8] with a subsequent increase in CBV (Fig. 3) and almost certainly enhanced edema formation. Moreover, the threshold for breakthrough may have shifted to lower levels of blood pressure after severe head injury.[10] With defective autoregulation, increased blood pressure caused a significant deterioration in the biomechanical status of the brain, while the increased CBF in most of these cases was not accompanied by an increase in $CMRO_2$, and could thus be considered "luxury perfusion." However, it should be emphasized that, when CBF is below ischemic levels at baseline, induced hypertension may be beneficial and may lead to improved $CMRO_2$, irrespective of autoregulation.[4] Obviously, optimum management of blood pressure after severe brain injury requires both extensive monitoring of the factors involved and an in-depth understanding of the mechanisms at work.

References

1. Alberico AM, Ward JD, Choi SC, et al: Outcome after severe head injury. Relationship to mass lesions, diffuse injury, and ICP course in pediatric and adult patients. **J Neurosurg 67**:648–656, 1987
2. Avezaat CJJ, van Eijndhoven JHM, Wyper DJ: Effects of hypercapnia and arterial hypotension and hypertension on cerebrospinal fluid pulse pressure and intracranial volume-pressure relationships. **J Neurol Neurosurg Psychiatry 43**:222–234, 1980
3. Bouma GJ, Muizelaar JP: Relationship between cardiac output and cerebral blood flow in patients with intact and with impaired autoregulation. **J Neurosurg 73**:368–374, 1990
4. Bouma GJ, Muizelaar JP, Choi SC, et al: Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. **J Neurosurg 75**:685–693, 1991
5. Gray WJ, Rosner MJ: Pressure-volume index as a function of cerebral perfusion pressure. Part 1: The effects of cerebral perfusion pressure changes and anesthesia. **J Neurosurg 67**:369–376, 1987
6. Gray WJ, Rosner MJ: Pressure-volume index as a function of cerebral perfusion pressure. Part 2: The effects of low cerebral perfusion pressure and autoregulation. **J Neurosurg 67**:377–380, 1987
7. Kennedy C, Sokoloff L: An adaptation of the nitrous oxide method to the study of the cerebral circulation in children; normal values for cerebral blood flow and cerebral metabolic rate in childhood. **J Clin Invest 36**: 1130–1137, 1957
8. Kontos HA, Wei EP, Navari RM, et al: Responses of cerebral arteries and arterioles to acute hypotension and hypertension. **Am J Physiol 234**:H371–H383, 1978
9. Leech P, Miller JD: Intracranial pressure-volume relationships during experimental brain compression in primates. 2. Effect of induced changes in systemic arterial pressure and cerebral blood flow. **J Neurol Neurosurg Psychiatry 37**:1099–1104, 1974
10. Lewelt W, Jenkins LW, Miller JD: Autoregulation of cerebral blood flow after experimental fluid percussion injury of the brain. **J Neurosurg 53**:500–511, 1980
11. Marion DW, Darby J, Yonas H: Acute regional cerebral blood flow changes caused by severe head injuries. **J Neurosurg 74**:407–414, 1991
12. Marmarou A, Maset AL, Ward JD, et al: Contribution of CSF and vascular factors to elevation of ICP in severely head-injured patients. **J Neurosurg 66**:883–890, 1987
13. Marmarou A, Shulman K, Rosende RM: A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics. **J Neurosurg 48**:332–344, 1978
14. Marshall WJS, Jackson JLF, Langfitt TW: Brain swelling caused by trauma and arterial hypertension. **Arch Neurol 21**:545–553, 1969
15. Maset AL, Marmarou A, Ward JD, et al: Pressure-volume index in head injury. **J Neurosurg 67**:832–840, 1987
16. Muizelaar JP: Induced arterial hypertension in the treatment of high ICP, in Hoff JT, Betz AL (eds): **Intracranial Pressure VII.** New York: Springer-Verlag, 1989, pp 508–509
17. Muizelaar JP, Lutz HA II, Becker DP: Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. **J Neurosurg 61**: 700–706, 1984
18. Muizelaar JP, Marmarou A, DeSalles AAF, et al: Cerebral blood flow and metabolism in severely head-injured children. Part 1: Relationship with GCS score, outcome, ICP and PVI. **J Neurosurg 71**:63–71, 1989
19. Muizelaar JP, Marmarou A, Wachi A: ICP and PVI with blood pressure alterations and relation with CBF autoregulation, in Hoff JT, Betz AL (eds): **Intracranial Pressure VII.** New York: Springer-Verlag, 1989, pp 825–828
20. Muizelaar JP, Ward JD, Marmarou A, et al: Cerebral blood flow and metabolism in severely head-injured children. Part 2: Autoregulation. **J Neurosurg 71**:72–76, 1989
21. Obrist WD, Langfitt TW, Jaggi JL, et al: Cerebral blood flow and metabolism in comatose patients with acute head injury. Relationship to intracranial hypertension. **J Neurosurg 61**:241–253, 1984
22. Rosner MJ, Becker DP: Origin and evolution of plateau waves. Experimental observations and a theoretical model. **J Neurosurg 60**:312–324, 1984
23. Rosner MJ, Coley IB: Cerebral perfusion pressure, intracranial pressure, and head elevation. **J Neurosurg 65**: 636–641, 1986
24. Rosner MJ, Daughton S: Cerebral perfusion pressure management in head injury. **J Trauma 30**:933–941, 1990
25. Shapiro K, Marmarou A, Shulman K: Characterization of clinical CSF dynamics and neural axis compliance using the pressure-volume index: I. The normal pressure-volume index. **Ann Neurol 7**:508–514, 1980
26. Simard JM, Bellefleur M: Systemic arterial hypertension in head trauma. **Am J Cardiol 63**:32C–35C, 1989
27. Takagi H, Walstra G, Marmarou A, et al: The effect of blood pressure and $PaCO_2$ upon bulk compliance (PVI), in Shulman K, Marmarou A, Miller JD, et al (eds): **Intracranial Pressure IV.** Berlin: Springer-Verlag, 1980, pp 163–166

Manuscript received September 23, 1991.

Address reprint requests to: J. Paul Muizelaar, M.D., Division of Neurosurgery, Medical College of Virginia, MCV Station Box 631, Richmond, Virginia 23298-0631.