Pressure-volume index as a function of cerebral perfusion pressure

Part 1: The effects of cerebral perfusion pressure changes and anesthesia

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The pressure-volume index (PVI) was measured as a function of cerebral perfusion pressure (CPP) in 12 adult cats. Anesthesia was induced with methohexital in six animals and with pentobarbital in six animals; all were maintained on an N2O:O2 (70%:30%) mixture. The CPP was either increased in 10-torr increments using norepinephrine or decreased by a combination of adenosine triphosphate and hemorrhage in subgroups. Three estimations of PVI were made at each level of CPP. The PaCO2, body temperature, and hematocrit were controlled at normal levels throughout. In both groups there was a linear relationship between PVI and CPP with increasing CPP being reflected by a rise in PVI. This relationship was more marked in the methohexital group: PVI = 0.37 ml + 0.0005 mm Hg CPP in the pentobarbital group, and PVI = 0.14 ml + 0.0019 mm Hg CPP in the methohexital group. These results indicate that the PVI is not independent of CPP but is a function of CPP and is profoundly influenced by anesthesia.

KEY WORDS: pressure-volume index, cerebral perfusion pressure, anesthesia, intracranial pressure, cerebral blood flow, autoregulation

Many authors have attempted to quantify the stiffness of the neuraxis in terms of the pressure change in response to a volume load, generating an exponential pressure-volume curve. Compliance, defined as the change in cerebrospinal fluid (CSF) volume per unit change in CSF pressure, is not constant but varies as a function of CSF pressure; thus, compliance is highest at low CSF pressures and decreases as CSF pressure increases. The pressure-volume curve can be transformed to a linear equation when the logarithm of the pressure is plotted against the volume change, the slope of this line being the pressure-volume index (PVI). This is the calculated volume (in milliliters) required to raise the CSF pressure by a factor of 10.

The PVI can also be calculated from the CSF pressure response to the addition of a bolus of known volume. Because of the instantaneous rise in CSF pressure after a bolus injection, it is thought that the PVI is largely a reflection of the vascular component of the intracranial compartment. Within the vascular compartment, cerebral blood flow (CBF) remains relatively constant despite changes in cerebral perfusion pressure (CPP) over the 60- to 170-mm Hg range. Autoregulation of CBF is accomplished by changes in the cerebrovascular resistance (CVR) achieved by alterations in the caliber of the vessels. A consequence of constant flow and changing vessel size is a change in the cerebral blood volume (CBV); however, CBV is influenced by other factors, including PaCO2, blood viscosity, and many anesthetic agents.

The PVI for a normal neuraxis has been thought to be relatively constant; differences in PVI between individuals of the same species and between species have been attributed to differences in intracranial volume, particularly to changes in the size of the intracranial venous pool. While we agree that the vascular compartment is the main determinant of the PVI, factors that influence this compartment will be reflected by changes in the PVI. This present study was undertaken to test the hypotheses that the PVI is not a constant, but will vary with changes in CPP and will also be influenced by the type of anesthetic agent employed.
Materials and Methods

Twelve adult cats of either sex, each weighing 2.5 to 4.5 kg, were used in this study. Anesthesia was induced in six animals with intravenous methohexital (10 mg/kg) and in the other six with intravenous pentobarbital (30 mg/kg). All animals were then paralyzed with pancuronium bromide (0.2 mg/kg), intubated endotracheally, and ventilated with a 70% N₂O/30% O₂ mixture.* Additional pancuronium was administered during each experiment as required. Under added local anesthesia (lidocaine 2%), polyethylene catheters were placed in the abdominal aorta and inferior vena cava, and connected to strain gauge transducers for pressure monitoring.t The animals were held in a stereotaxic frame, and intracranial pressure (ICP) was measured by No. 22 needles placed in each lateral ventricle. All transducers were zeroed to the level of the ear bars. The end-tidal CO₂ was monitored continuously; and adjusted to maintain a PaCO₂ of 30 mm Hg by frequent blood gas analysis.§ The core temperature was monitored with an esophageal probe and an infrared heat lamp was used to keep the temperature between 38.5° and 39°C. An infusion of 8.4% sodium bicarbonate was used to keep pH constant within the normal range.

Each animal’s hematocrit was maintained at its baseline level by infusion of packed cells or 0.9% saline, as required.

Cerebral perfusion pressure was reduced in six animals by a combination of withdrawing blood into an arterial reservoir and infusion of adenosine triphosphate (ATP). A fresh ATP solution containing 5 mg/ml in 0.9% NaCl was infused at rates of 0.2 to 2.0 mg/min. The CPP was increased in the other six animals by a continuous infusion of norepinephrine bitartrate (160 μg/ml) in 0.9% NaCl at rates of 3.0 to 15.0 μg/min. The exact infusion rates were adjusted to achieve the desired level of CPP, which was changed in increments of 10 mm Hg. These experimental subgroups are shown in Table 1.

The PVI was calculated by the rapid bolus injection technique. A 0.1-ml bolus of 0.9% NaCl was injected over a period of 1 second into one lateral ventricle, and the peak ICP was recorded from the other lateral ventricle. The PVI was then calculated from the relationship:

$$\text{PVI (ml)} = \frac{V}{\log \frac{P_p}{P_o}}$$

(1)

where V = volume of fluid injected, P_p = peak ICP after injection, and P_o = ICP before injection.

Three PVI estimations were made in all animals at baseline CPP levels. The CPP was then reduced or increased in increments of 10 mm Hg, and three PVI measurements were made when a steady state had been achieved at each level of CPP. After each PVI measure-

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* Small-animal ventilator, Model 665, manufactured by Harvard Apparatus, South Natick, Massachusetts.
† Gould-Stratham P 23 ID pressure transducer manufactured by Gould Inc., Medical Products Division, Oxnard, California.
‡ End-tidal CO₂ monitor, Model 200, manufactured by Instrument Laboratory, Inc., Lexington, Massachusetts.
§ Model 165/2 pH/blood gas analyzer manufactured by Corning Medical, Medfield, Massachusetts.

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TABLE 1
Number of animals in each experimental subgroup

<table>
<thead>
<tr>
<th>Cerebral Perfusion Pressure</th>
<th>Methohexital</th>
<th>Pentobarbital</th>
</tr>
</thead>
<tbody>
<tr>
<td>increased</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>decreased</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

TABLE 2
Group variables before bolus injection*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Methohexital</th>
<th>Pentobarbital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean &amp; SD</td>
<td>No. of Tests</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>113 ± 40</td>
<td>102</td>
</tr>
<tr>
<td>ICP₀ (mm Hg)</td>
<td>5.9 ± 4.3</td>
<td>102</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>29.7 ± 1.1</td>
<td>41</td>
</tr>
<tr>
<td>hematocrit (%)</td>
<td>34.3 ± 6</td>
<td>15</td>
</tr>
<tr>
<td>PVI (ml)</td>
<td>0.35 ± 0.10</td>
<td>102</td>
</tr>
</tbody>
</table>

* Abbreviations: CPP = cerebral perfusion pressure; ICP₀ = baseline intracranial pressure before estimation of pressure-volume index (PVI); SD = standard deviation.

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TABLE 3
Correlation between PVI and CPP in pentobarbital- and methohexital-anesthetized cats*

<table>
<thead>
<tr>
<th>Cat No.</th>
<th>Linear Regression Equations</th>
<th>No. of Tests</th>
<th>R Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pentobarbital group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>PVI = 0.49 - 0.0014 CPP</td>
<td>25</td>
<td>0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>PVI = 0.32 + 0.0008 CPP</td>
<td>12</td>
<td>0.26</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>PVI = 0.53 - 0.0006 CPP</td>
<td>20</td>
<td>0.17</td>
<td>NS</td>
</tr>
<tr>
<td>4</td>
<td>PVI = 0.36 - 0.0010 CPP</td>
<td>25</td>
<td>0.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td>PVI = 0.32 + 0.0007 CPP</td>
<td>18</td>
<td>0.68</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>6</td>
<td>PVI = 0.35 + 0.0010 CPP</td>
<td>20</td>
<td>0.28</td>
<td>NS</td>
</tr>
<tr>
<td>overall</td>
<td>PVI = 0.37 + 0.0005 CPP</td>
<td>120</td>
<td>0.20</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

| methohexital group |                          |              |         |         |
| 7       | PVI = 0.07 + 0.0025 CPP     | 15           | 0.53    | <0.05   |
| 8       | PVI = -0.32 + 0.0050 CPP    | 11           | 0.80    | <0.005  |
| 9       | PVI = -0.09 + 0.0037 CPP    | 13           | 0.58    | <0.05   |
| 10      | PVI = 0.13 + 0.0018 CPP     | 27           | 0.58    | <0.005  |
| 11      | PVI = 0.19 + 0.0017 CPP     | 26           | 0.72    | <0.001  |
| 12      | PVI = -0.28 + 0.0050 CPP    | 10           | 0.76    | <0.01   |
| overall | PVI = 0.14 + 0.0019 CPP     | 102          | 0.71    | <0.001  |

* Abbreviations: PVI = pressure-volume index (in ml); CPP = cerebral perfusion pressure (in mm Hg); NS = not significant.
Effects of CPP and anesthesia on pressure-volume index

Fig. 1. Biventricular recording of intracranial pressure (ICP) showing that the instillation of 0.1 cc normal saline into a lateral ventricle caused a rise in ICP bilaterally. The pressure-volume index (PVI) is calculated by the formula $PVI = 0.1 / \log (\frac{P_\text{p}}{P_\text{o}})$, see text. $P_\text{p}$ = peak ICP after injection; $P_\text{o}$ = ICP before injection, see text. In all of these recordings the pressure is taken from the top of the wide line; both systemic arterial blood pressure (SABP) and ICP are given as mean pressures.

ment, the ICP was allowed to return to baseline before the next PVI estimation. Any PVI calculations made during periods of CPP instability were excluded. The $\text{PaO}_2$, $\text{PaCO}_2$, pH, and hematocrit were measured at each CPP interval to ensure constancy and were adjusted as necessary before continuing.

At the end of the experiments all the animals were killed by an overdose of potassium chloride. In three of the animals, all from the pentobarbital group, a series of PVI estimations were made after death (that is, at a CPP of zero).

Results

A total of 222 PVI estimations were made, 102 in the methohexital group and 120 in the pentobarbital group. A typical response to the bolus injection is shown in Fig. 1. The recorded measurements of initial ICP before bolus injection, CPP, $\text{PaCO}_2$, and hematocrit as well as the calculated PVI are given in Table 2.

There was no significant difference in the baseline ICP levels in the two groups. The ICP had a tendency to increase slightly as CPP was reduced, but this change was not significant in either of the two groups. The difference between the mean $\text{PaCO}_2$ levels in the two groups was less than 1 mm Hg and, although this was significant ($p = 0.05$), it was not considered to have had any bearing on the results. The animals in the pentobarbital group had a lower hematocrit than did those in the methohexital group ($p < 0.001$). However, when the variation in hematocrit was examined for individual animals in both groups, the baseline values were found to vary by less than ± 3%.

In both groups, the PVI varied with changes in CPP. The linear regression equations are given in Table 3. In the pentobarbital group (Fig. 2), two animals (Cats 1 and 4) showed a slight but significant decrease in the PVI as CPP increased, while one animal (Cat 5) showed a slight but significant increase in PVI as CPP was increased. In the other three animals, there was no significant correlation between PVI and CPP. When the results for all six animals were taken together, there was a slight increase in PVI with increased CPP which attained significance ($p = 0.05$), but there was a wide scatter of results. In contrast, the animals in the methohexital group showed a significant positive correlation between PVI and CPP, both as a group and as individual animals (Fig. 3).

The response of PVI to CPP was examined in the animals in each group that had been rendered hypertensive and in those that had been rendered hypotensive (Fig. 4). Again, the same relationships were demonstrated: there was a significant positive correlation between PVI and CPP in the methohexital animals, but a much less pronounced effect in the hypertensive and the hypotensive pentobarbital animals, with nearly a horizontal slope.

The PVI measurements in the dead animals are given in Table 4. In these animals, because the ICP rise following a bolus injection of 0.1 ml was so small, the PVI was calculated using a bolus of 0.2 to 0.3 ml. In one animal (Cat 1) the preinjection ICP levels were negative, so it was not possible to calculate the PVI by the usual formula (Equation 1). In the other two ani-
TABLE 4

<table>
<thead>
<tr>
<th>Cat No.</th>
<th>Postmortem Study</th>
<th>Best Live Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PVI (ml)</td>
<td>CPP (mm Hg)</td>
</tr>
<tr>
<td>4</td>
<td>0.93</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.68</td>
<td>0</td>
</tr>
</tbody>
</table>

*Abbreviations: PVI = pressure-volume index; CPP = cerebral perfusion pressure.

FIG. 3. Regression lines of pressure-volume index (PVI) as a function of cerebral perfusion pressure (CPP) in animals under light N₂-O₂ anesthesia who had undergone anesthesia induction with methohexital (10 mg/kg). The overall group equation is given and plotted here (broken line); for equations for each animal see Table 3. All of the animals in this group showed strongly positive slopes with very clear direct variation of the PVI with CPP. Compare these results with those shown in Fig. 2. The overall slope of the PVI versus the CPP line was nearly four times that of the slope for those animals under deep barbiturate anesthesia. Similarly, there is relatively little variation between animals, and all slopes are positive under this anesthetic regime.

Table 3 contains all the animals (Cats 4 and 5) the PVI results after death were significantly higher than the PVI results seen during the experiment; in both animals, the PVI after death was more than 50% higher than the best PVI estimation during the experiment.

Discussion

Previous publications on the influence of changes in systemic arterial blood pressure (SABP) on brain "stiffness" have produced conflicting results. Avezaat, et al.,

using dogs anesthetized with sodium thiopentothal (30 mg/kg), studied the volume-pressure response during continuous inflation of a supratentorial extradural balloon. They found that when the ICP was below 55 mm Hg, compliance values were similar at SABP levels of 89, 135, and 175 mm Hg. When ICP was increased above 55 mm Hg, compliance varied with changes in SABP, being highest in the hypotensive state. They attributed this change in compliance at ICP levels greater than 55 mm Hg to a breakdown in autoregulation with a passive relationship developing between SABP and CBF. Leech and Miller,

found a similar result in adult baboons anesthetized with sodium thiopentothal; at low levels of ICP, changes in CPP did not significantly alter the volume-pressure response. When ICP was increased by balloon inflation, autoregulation was progressively impaired and the volume-pressure response increased in a linear fashion with increasing CPP (that is, compliance decreased as CPP increased).

The response of the PVI to changes in SABP in the cat have been studied by Takagi, et al., and the conclusions of this group were that the PVI did not change across the 85- to 145-mm Hg CPP range in autoregulating animals, but when autoregulation was impaired, PVI varied with SABP in a linear fashion.

The studies cited above have all suggested that brain "stiffness" (whether it is measured by volume-pressure response, compliance, or PVI) is not influenced by changes in CPP in autoregulating animals, but when autoregulation is impaired brain "stiffness" increases as CPP is increased. Although we did not measure the CBF in these animals, autoregulation has been shown to be intact in this preparation, and the PVI was found to be very much affected by CPP variation within the range of autoregulation. Previous workers have missed this relationship because they studied too narrow a range of SABP, did not specifically study CPP, and used pentobarbital anesthesia which profoundly influences the relationship.

In all animals, when CPP was changed, there was a transient change in ICP in the same direction, but ICP always returned close to its previous level within a few seconds despite the persisting change in CPP: ICP levels remained low throughout the experiments. All animals had normal (uninjured) brains, and measurements of PVI were started at normal levels of CPP. While autoregulation may have been inoperative above or below its limits at the extremes of CPP change, CPP was raised or reduced slowly in 10-mm Hg increments from normal levels, and in no animal was a combination of hypertension and hypotension used.

Our results demonstrate a different relationship between brain stiffness and CPP changes to those studies previously mentioned. In the pentobarbital and methohexital groups, the PVI increased as CPP was increased, this effect being much more striking in the methohexital animals. Traditionally this indicates that the brain is becoming less stiff as CPP increases. To explain this apparent contradiction, one must examine the effects of anesthesia and CPP changes on cerebral hemodynamics.

When attempting to interpret changes in PVI in relation to changes in cerebral hemodynamics, it is important to examine what, in fact, is being measured by the PVI. Using a bolus technique, as in this study, most authors agree that the vascular intracranial
Effects of CPP and anesthesia on pressure-volume index

Fig. 4. Scattergrams of the individual pressure-volume index (PVI) results obtained as a function of cerebral perfusion pressure (CPP), showing the same basic findings as previously described, with very little variation of PVI with CPP in animals under deep barbiturate anesthesia and a very strong positive correlation between PVI and CPP when anesthesia was very light. The open circles and lower line represent those animals where anesthesia had been induced using methohexital (10 mg/kg) and light anesthesia was maintained with N₂O:O₂. The filled circles and the upper line represent those animals where these values had been obtained in cats anesthetized with sodium pentobarbital and N₂O:O₂. Each PVI plotted represents the mean of three determinations. Left: Results obtained when CPP was reduced using a combination of hemorrhage into a heparinized reservoir and infusion of adenosine triphosphate. Thus, the blood pressure was only reduced and not brought from one low level to an upper level. Right: Results obtained when CPP was raised from baseline blood pressure levels using an infusion of norepinephrine. The blood pressure was taken from the normal baseline levels to upper levels to avoid confounding results by raising and lowering blood pressure in the same animal.

component is the most important determinant of the pressure response to the volume load. The immediate rise and then steady decay in ICP cannot be explained by alterations in CSF dynamics, but only by a vascular response. Because of the relative stiffness and high wall tension of the arterial tree, it is believed that the venous capacitance vessels provide the bulk of the vascular response. Shapiro, et al., 39 have cited differences in the size of the intracranial venous pool as the main reason for different PVI responses between individuals of the same species and between different species.

Although it was demonstrated that the PVI rises as CPP increases, indicating a better tolerance to a volume load at higher CPP levels, the reason for this effect is still unclear. Although vasoconstriction on the arterial side in response to CPP increase is well documented, 11,20 there is little information on the response of the venous capacitance vessels. It is not known whether the venous pool increases, decreases, or remains unchanged as CPP changes, or whether there is a shift in the ratio of arterial:venous blood volume. Within the neuraxis, the spinal compartment is thought to contribute 30% of the total PVI; 25,27 again, it is not known whether this is a constant contribution or whether the influence of the spinal component changes in relation to changes in CPP.

Despite these uncertainties, it has been demonstrated in both cats and dogs by Schrader, et al., 36 that intracranial tolerance to a volume load is directly dependent on SABP levels. Using continuous expansion of a supratentorial balloon in both dogs and cats to the point of respiratory arrest, they established that the volume tolerated by these animals increased as SABP increased. The magnitude of volume tolerance at an SABP of 190 mm Hg was 87% higher than at an SABP of 60 mm Hg.

We propose that the PVI remained relatively constant in the pentobarbital model because of the effects of this drug on the cerebral metabolic rate of oxygen (CMRO₂) and CVR. Normally, vasodilatation would be expected as CPP is reduced, and vasodilatation would increase CBF. If CVR is held relatively constant, and at a profoundly (50% to 100%) increased level by pentobarbital anesthesia, then reducing CPP will have little effect on vessel reactivity, and consequently there will be little change in CBF. We believe that this is reflected by the minimal change in PVI in response to changes in CPP, and this could also account for similar results in previous studies. 23,42

With methohexital, a different response is seen. Our results have established a linear relationship between PVI and CPP. Similar results have previously been reported by Schettini and Walsh. 37 in hypotensive dogs receiving 20 mg/kg methohexital, they found that brain elastance (inversely related to PVI) increased with decreasing SABP while the CBF remained constant. As hypotension continued, CBF started to fall, indicating the lower limit of autoregulation, and below this point...
elastance began to fall, although it did not return to the baseline levels established at normal CPP.

The findings suggest that in a more normal physiological brain preparation, as exhibited by the methohexital group, CBV is highest at low CPP, and falls when CPP is increased. The rise in ICP caused by a bolus injection of fluid will be less when CBV is low (at high CPP) and maximal when CBV is maximal (at low CPP). Thus, the PVI will be highest at high CPP and will fall in relation to falling CPP. The PVI was not systematically examined at CPP of less than 50 mm Hg, but we suspect that, as autoregulation becomes ineffective below this level, CBF would diminish and develop a passive relationship with CPP, and CBV would also fall. It would be expected that the PVI would therefore tend to rise again. Our PVI results in cats post mortem, with CPP at zero, were consistent with this hypothesis. Similarly, at very high levels of CPP, above the upper limits of autoregulation, CBF would increase, CBV would rise, and PVI would fall.

In this study, other factors known to influence cerebrovascular hemodynamics were kept to a minimum. The hematocrit was kept as constant as possible, as this will influence CBF. In chronic anemias, it has been shown that CVR is reduced and CBF is increased from 30% to 47% above normal. Conversely, observations in polycythemia have demonstrated increases in CVR and a 50% reduction in CBF when blood viscosity was three times normal. The relationship between blood viscosity and hematocrit is semilogarithmic, with an increased in hematocrit from 30% to 60% causing an increase in blood viscosity of over 100%. The hematocrit of individual animals in this present study was kept within ± 3% of baseline in order to avoid these confounding effects.

Alterations in PaCO₂ have a profound effect on CBF. Waltz demonstrated in normal cat cortex that CBF varied as an exponential function of PaCO₂ over a 20- to 80-mm Hg range. A similar change was found in CBF in the monkey by Reivich. Other reports have confirmed this relationship at normal levels of blood pressure, but have suggested CBF to be less sensitive to PaCO₂ changes during hypotension. Although there was a small difference in PaCO₂ levels between the two groups in our study (less than 1 mm Hg), it was not considered to be important.

When studying the effects of changes in CPP on intracranial hemodynamics, it is important that the agents used to produce these changes in CPP do not have any direct effect on the cerebral vessels. Adenosine triphosphate was used to reduce CPP, and norepinephrine to increase CPP because of these inherent qualities. Previous work with systemically administered adenosine and ATP have demonstrated that they have little direct influence on cerebrovascular reactivity. Buyanski and Rapela found minimum reactivity of canine cerebrovascular smooth muscle to intracarotid infusions of adenosine. Berne, also demonstrated that intra-arterially administered adenosine in the dog and cat produced little or no change in CBF or in pial arteriole diameter when given in amounts that reduced arterial blood pressure. Kontos, et al. used an intravenous ATP infusion in the cat, and concluded that the compound had no direct effect on cerebrovascular smooth muscle, but exerted its effects by causing peripheral vasodilatation.

With regard to norepinephrine, Olesen found that intracarotid infusions, in doses of 2 to 10 μg/min, produced no significant changes in CBF in man, and Kontos, et al. found that vasoconstriction of the pial vessels following intravenous norepinephrine in the cat was due to the increase in SABP, and not to any direct cerebrovascular response.

The cardiovascular effects of both pentobarbital and methohexital have been well documented. Priano, et al. noted a fall in cardiac output (CO) of 30%, a fall in core body temperature of 1.4°C, and a rise in total peripheral resistance of 68%, 2 hours after administering 30 mg/kg pentobarbital to normal dogs. Forsyth and Hoffbrand, using the same dose of pentobarbital in adult monkeys documented falls in mean SABP of 30%, in the total peripheral resistance of 21%, and in CO of 14%, but a rise in CVR of 52% and a concomitant reduction in CBF of 54%. Cerebral hemodynamics studied by Lafferty, et al. using 40 mg/kg pentobarbital in dogs, have shown a similar fall in CBF and rise in CVR, and these changes persisted for over 5 hours after anesthesia induction.

Methohexital has also been shown to cause changes in cardiovascular hemodynamics. In human studies with this barbiturate in a dose of 10 mg/kg, Allen, et al. found that SABP fell by 15%, CO rose by 15%, and total peripheral resistance fell by 25%; reversal of these effects was rapid. Prys-Roberts, et al. found a similar picture in humans using methohexital infusion (60 to 120 μg/kg/min), noting falls in SABP of 33%, in CO of 25%, and in total peripheral resistance of 13%. In a recent comparative study of thiopental and methohexital in dogs, Boarini, et al. found similar reductions in CO, CBF, and CMRO₂ with both drugs, but a fall in CVR and peripheral vascular resistance with methohexital compared to a rise in CVR and peripheral vascular resistance with thiopental. One hour after cessation of barbiturate administration, all of these parameters were returning close to preanesthetic levels in the methohexital animals, but in the thiopental group CBF, CMRO₂, and CO were still markedly depressed while CVR and peripheral vascular resistance were 80% and 137% above baseline levels, respectively. Rapid recovery from methohexital anesthesia was noted by Hudson, et al. in a group of nine patients. They estimated the elimination half-time of methohexital to be 3.9 hours compared with 11.6 hours for thiopental.

In our series of experiments, the time from induction of anesthesia to the first measurements was more than 1 hour in all animals. At this time, most of the cardiovascular changes induced by methohexital would be returning close to baseline levels and having minimal

W. J. Gray and M. J. Rosner

J. Neurosurg. / Volume 67 / September, 1987
Effects of CPP and anesthesia on pressure-volume index

effect, while pentobarbital would continue to exert a considerable effect for the duration of the experiment.

We did look at PVI responses in three animals in which CPP was zero. All these animals were from the pentobarbital group. In one animal we were unable to calculate PVI. In the other two, PVI was significantly higher than the best PVI calculated during the experiment. We are unable to explain this finding, but it may be a reflection of the very low blood volume in these dead brains resulting in, on paper, an extremely “good” PVI response.

Although it is not possible to draw comparisons directly with the human brain, especially one that has been injured, it is hypothesized that isolated measurements of PVI or elastance have little meaning if the effects of CPP are not considered. If a PVI measurement at low CPP is compared with a second PVI some hours later at a high CPP value, the results may suggest an improvement in “stiffness” when this may not be totally true. At very low CPP, especially when autoregulation is impaired (a not uncommon situation in multiply-injured patients), the PVI response may give an inaccurate indication of the patient’s progress.

Conclusions

1. The PVI varied directly with CPP when studied within the autoregulatory range. All studies (laboratory and clinical) must take the CPP factor into account when making conclusions or recommendations based upon PVI.

2. The relationship of PVI to CPP is profoundly depressed by pentobarbital anesthesia, and is clearly present when the short-acting barbiturate, methohexitol, is utilized. With methohexitol anesthesia, PVI is almost four times more dependent on CPP changes than with pentobarbital anesthesia. This implies that CPP variation may be even more important in the clinical situation where no anesthesia may be in use.

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References


J. Neurosurg. / Volume 67 / September, 1987 375


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