Effect on the Cushing response of different rates of expansion of a supratentorial mass

ABDUL HAMID ZIDAN, M.D., AND JOHN P. GIRVIN, M.D.

Departments of Physiology and Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada

The effects on the three components (respiration, blood pressure, and heart rate) of the Cushing response (CR) were studied in cats by the continuous expansion of a supratentorial balloon. The rate of expansion was varied over the range of 0.006 to 0.6 ml/min, during which systemic arterial pressure, heart rate, respiratory rate, and blood gases were monitored. For the different rates the time the CR took to develop, and the balloon volume required for that development were measured. The final volume ("critical volume") for eliciting the CR was more or less constant over the full range of rates of infusion (balloon expansion), a fact that supports the Monro-Kellie doctrine. This constancy of critical volume (CCV) gives rise to a highly statistically significant relationship between the rate of infusion and the latency to the production of the CR, and it is described by a power curve. Thus the development of cerebral dysfunction under these experimental conditions is independent of the rate of expansion and only dependent upon this critical volume. Exceptions to this concept of a critical volume, at the extreme of rates of expansion of lesions in patients, are predicted.

KEY WORDS: intracranial pressure • cerebrospinal fluid • Cushing response • space-occupying lesion • brain edema • Monroe-Kellie doctrine

Many reports appeared before those of Cushing with respect to the cardiovascular and respiratory responses to raised intracranial pressure (ICP), including those of Hill and Kocher. However, it was really Cushing who rejuvenated an interest, particularly in the English literature, in the responses that occur both clinically and experimentally in response to raised ICP. These responses, which consist of respiratory irregularities of various types, arterial hypertension, and bradycardia, form the characteristic triad that has become known as the Cushing response (CR). Many attempts have been made to explain the possible mechanisms, and/or to localize the receptive area that is responsible for the CR. It has been recognized that the classical clinical triad has not been a uniform accompaniment of raised ICP in the human patient. Nevertheless, the triad is seen in some cases and, when seen, is usually of undoubted importance.

Because of the importance of the relationship between the rate and size of an expanding intracranial mass, the present experiments were undertaken. The purpose of the study was to examine the following relationships: 1) the rate of expansion of an...
epidural supratentorial balloon and the differences in latencies of appearance of the various components of the CR; 2) the rate of expansion of the balloon and the latency of appearance of the CR; and 3) the rate of balloon expansion and the final volume required to elicit the CR at different infusion rates.

Materials and Methods

Experiments were performed on 22 cats, unselected with respect to age or sex, and weighing, on average, 3.2 kg. They were anesthetized by intraperitoneal sodium pentobarbital (25 to 30 mg/kg), with maintenance by the intravenous injection of a 1:10 solution. The anesthetic level was as light as possible; that is, corneal reflexes were active and abortive withdrawal reflexes of the extremities to pinch were present although poorly retained.

Tracheostomy was performed in all animals and breathing was spontaneous throughout. The respiration was continuously monitored by a thermistor probe placed into the side of the tracheostomy tube. Systemic arterial pressure was monitored from an aortic catheter introduced via the right femoral artery. Another polyethylene catheter, inserted through the contralateral (left) femoral artery into the thoracic aorta, was used for the periodic collection of arterial blood samples for the analysis of pH, pO2, and pCO2 values.

A small collapsible latex balloon was placed extradurally through a small right parasagittal trephine craniootomy. The skull defect was then sealed by methyl methacrylate (acrylic) around the polyethylene catheter to which the balloon was attached. This polyethylene catheter was connected to a constant infusion pump.* At the beginning of any given experiment the saline-filled balloon was collapsed, the air having been previously expelled.

The epidural balloon was expanded by saline infusion at different rates over the range of 0.006 to 0.6 ml/min in the following steps, 0.006, 0.008, 0.0096, 0.017, 0.024, 0.042, 0.06, 0.096, 0.15, 0.17, 0.24, 0.42, and 0.6 ml/min. The different rates of infusion were used in random order. Because of the well known problem of deterioration in the experimental preparation as a result of repeatedly raising ICP, no experiment was carried beyond 8 hours, nor in any given experiment were more than four “runs” (expansion of balloon) undertaken. Therefore, for example, when the very slow rates of expansion, which might take more than 6 hours, were used only a single “run” was undertaken in that particular animal; that is to say, expansion until the appearance of the CR. After deflation of the balloon the animal was allowed to return to “normal.” Normality was judged by three sets of criteria: 1) clinical (pupillary size and reaction, corneal reflexes, withdrawal reflexes); 2) physiological (respiratory rate and rhythm, blood pressure, heart rate); and 3) blood gas analyses (pCO2, pO2, pH). In the case of failure to return to normal, the animal was rejected from further experimentation.

Although there has been a tendency to broaden the definition of the CR, in that many refer to only the cardiovascular components, for the present study the fully developed triad has been considered the *sine qua non* of the response. Thus each rate of infusion was maintained until all the elements of the CR were evident, with the time of onset of each component recorded. The endpoint of the respiratory change was taken as a loss of the normal respiratory rate and/or a slowing of respiratory rate to half the control value. The endpoint of the vasopressor response was considered to have been reached when the mean arterial pressure was sustained at an increase of at least 10 mm Hg. The endpoint of the third component of the response, bradycardia, which was infrequently present at the time of the vasopressor response, was taken as a reduction of 10% of the control value. In addition to the specific components of the CR, pupillary size and reaction and the state of the corneal and withdrawal reflexes were tested throughout the periods of saline infusion.

At the time that these experiments were performed, ICP was not monitored for the following reasons: 1) in order to minimize cranial surgery we did not wish to perform a separate trephine for such monitoring; 2) monitoring from our particular balloon (due

Effect on Cushing response of mass expansion rate

TABLE 1

<table>
<thead>
<tr>
<th>Pump Rate (ml/min)</th>
<th>No. of Runs</th>
<th>Cushing Response Latency (min)</th>
<th>Respiration Latency (min)</th>
<th>Heart Rate Latency (min)</th>
<th>Blood Pressure Latency (min)</th>
<th>Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.006</td>
<td>3</td>
<td>381.0 ± 1.0</td>
<td>320.0 ± 20.0</td>
<td>364.9 ± 4.88</td>
<td>360.0 ± 20.0</td>
<td>2.3 ± 0.006</td>
</tr>
<tr>
<td>0.008</td>
<td>4</td>
<td>242.5 ± 3.9</td>
<td>210.0 ± 13.7</td>
<td>242.5 ± 23.9</td>
<td>235.5 ± 20.8</td>
<td>1.8 ± 0.09</td>
</tr>
<tr>
<td>0.0096</td>
<td>3</td>
<td>156.3 ± 24.7</td>
<td>140.0 ± 30.8</td>
<td>138.7 ± 31.9</td>
<td>154.0 ± 22.6</td>
<td>1.5 ± 0.22</td>
</tr>
<tr>
<td>0.017</td>
<td>5</td>
<td>105.8 ± 9.28</td>
<td>99.5 ± 8.75</td>
<td>102.9 ± 9.0</td>
<td>102.4 ± 9.3</td>
<td>1.8 ± 0.16</td>
</tr>
<tr>
<td>0.024</td>
<td>4</td>
<td>84.3 ± 14.6</td>
<td>74.0 ± 13.8</td>
<td>82.3 ± 14.7</td>
<td>78.4 ± 14.1</td>
<td>2.0 ± 0.23</td>
</tr>
<tr>
<td>0.042</td>
<td>6</td>
<td>30.4 ± 2.73</td>
<td>28.7 ± 2.54</td>
<td>29.3 ± 2.49</td>
<td>30.0 ± 2.79</td>
<td>1.3 ± 0.11</td>
</tr>
<tr>
<td>0.06</td>
<td>4</td>
<td>26.3 ± 1.51</td>
<td>23.0 ± 1.91</td>
<td>26.1 ± 1.60</td>
<td>25.2 ± 2.04</td>
<td>1.6 ± 0.09</td>
</tr>
<tr>
<td>0.096</td>
<td>4</td>
<td>16.3 ± 1.83</td>
<td>13.5 ± 1.26</td>
<td>14.0 ± 0.82</td>
<td>15.8 ± 2.25</td>
<td>1.6 ± 0.17</td>
</tr>
<tr>
<td>0.15</td>
<td>6</td>
<td>13.6 ± 2.90</td>
<td>9.5 ± 1.91</td>
<td>13.6 ± 2.90</td>
<td>12.6 ± 2.45</td>
<td>2.2 ± 0.16</td>
</tr>
<tr>
<td>0.17</td>
<td>4</td>
<td>11.1 ± 1.54</td>
<td>10.1 ± 1.47</td>
<td>11.1 ± 1.84</td>
<td>10.3 ± 1.58</td>
<td>2.2 ± 0.17</td>
</tr>
<tr>
<td>0.24</td>
<td>5</td>
<td>8.7 ± 0.36</td>
<td>6.6 ± 1.51</td>
<td>8.4 ± 1.18</td>
<td>8.0 ± 0.83</td>
<td>2.1 ± 0.20</td>
</tr>
<tr>
<td>0.42</td>
<td>4</td>
<td>5.3 ± 0.97</td>
<td>3.7 ± 1.05</td>
<td>5.3 ± 0.97</td>
<td>4.9 ± 1.03</td>
<td>2.3 ± 0.22</td>
</tr>
<tr>
<td>0.6</td>
<td>4</td>
<td>3.2 ± 0.62</td>
<td>2.1 ± 0.26</td>
<td>3.0 ± 0.74</td>
<td>2.7 ± 0.34</td>
<td>1.9 ± 0.20</td>
</tr>
</tbody>
</table>

*Data are given in means ± 1 standard error.
†Final volumes required to produce the Cushing response.

Results

Table 1 is a composite of the analyzed results. It relates the latency (mean ± SE) of development of the various components of the CR to the rate of expansion of the extradural balloon. It serves to emphasize a number of points. 1) The data clearly show the expected inverse relationship that exists between the rates of infusion and the latencies of the responses. 2) By comparing the latencies of response of the various components of the Cushing triad, it can be seen that the most sensitive component is, as one would expect, respiratory abnormality. That is to say with the expansion of the balloon the respiratory abnormality always appeared before the cardiovascular abnormalities. 3) The results also show on the basis of the same comparisons, that the heart rate was nearly always the most insensitive gauge to raised ICP. Thus, the latency to the development of the bradycardia was always longer than that of the development of the respiratory abnormality or the vasopressor response. This is most striking at the rates of the expansion of 0.008, 0.15, 0.17, and 0.42 ml/min. Indeed, at these latencies those of the whole triad were exactly the same as those of the heart rate response. Therefore, at each of these rates, the heart rate developed sufficiently late that this determined the latency of the whole response. 4) Finally, perhaps the most surprising finding of the study is shown in the right-hand column of Table 1, in which for each of the rates of expansion the final volumes of the balloon required for the production of the response was tabulated. It can be seen that in fact there is no systematic predictable relationship between the different infusion rates and this volume.

*Gould Brush Recorder manufactured by Gould Instruments, Inc., Systems Division, 3631 Perkins Avenue, Cleveland, Ohio.
†Hewlett-Packard calculator, model 9810A, and calculator/plotter, model 9862A, manufactured by Hewlett-Packard, 1601 California Avenue, Palo Alto, California.
A. H. Zidan and J. P. Girvin

Relationship of Infusion Rate and Components of CR

Plotting the three components of the response latencies (Fig. 1), reveals the expected finding that there is no striking difference in the three responses at the various infusion rates that might explain differences in parts of the curve. Rather, there is reasonable concordance between these latencies with the previously noted observations (Table 1) that respiration was always altered before the cardiovascular parameters. This dissociation between the respiratory alteration on the one hand and the cardiovascular alterations on the other was most noticeable at the slower infusion rates.

The Student t-test for independent samples shows that only the dissociation between the latencies of respiration and heart rate reaches statistical significance ($p < 0.05$) for the 0.006 ml/min expansion rate.

Relationship between Rate of Infusion and CR

Figure 2 is a graphical representation, as plotted by the Hewlett-Packard calculator/plotter, relating the latencies of all of the experimental data to the various rates of expansion of the balloon. The relationship is obviously not linear and indeed also, by analysis, shows no correlation that fits to parabolic or exponential curves. However, there is a remarkably good fit with the power curve. When the data are averaged in groups at each individual infusion rate, the correlation is even greater, as demonstrated in Fig. 3. In this case the curve is described by the expression $y = 1.92x^{-0.83}$ and the correlation coefficient is 0.988. This very high correlation coefficient of course indicates a very highly significant correlation of the relationship between the latency of response and the rate of balloon expansion being described by the power function.

As a means of examining the relationship further, the data were plotted graphically on semilog paper (Fig. 4) and one can see that, at least by eye, the curve would seem to be made up roughly of three exponential components. Although this interpretation is open to question, yet, from this curve and the consideration of the power curve seen in Fig. 3, there are without doubt at least two distinct phases of the curve. One phase involves rates below 0.01 ml/min while the other involves those over 0.04 ml/min. However, there seems to be an intermediate phase, which may or may
not have some type of biological significance. The initial phase at the slower rates of expansion involves latencies from about 150 minutes through 380 minutes, or a range over nearly 4 hours. This is in striking comparison for the range of infusion rates in the second phase, which vary from 0.04 to 0.6 ml/min, a range of fifteenfold, over which there is only a 27-minute difference in latencies.

Relationship between Rate of Infusion and Final Balloon Volume Required to Elicit CR

As seen in Table 1 there is a relatively restricted range of the final volume obtained at the endpoint for the development of the CR. The range of final volumes varied from 1.3 ml at the infusion rate of 0.042 ml/min to 2.3 ml at 0.006 ml/min. Although this

FIG. 4. Semilog plot of the same data as plotted linearly in Fig. 3. Each vertical bar represents two standard errors of the mean.
Fig. 5. Histographic representation of the final volumes required to produce the Cushing response (CR) according to the chronological sequence in which they were carried out on any given experimental day. First bar represents the mean final volume required to bring about the production of the CR during all "runs" carried out first on the experimental days over the course of the study, irrespective of the rate of expansion. Second bar represents the mean final volume required to achieve the endpoint (CR) in all animals with but one previous "run" (rate of expansion). Likewise, third and fourth bars represent the mean of all those animals in which, chronologically, third and fourth balloon expansions were carried out. Each bar represents two standard errors of the mean. \( n \) = the number of experiments represented by each group. The differences between the first and the third and fourth groups are statistically significant.

represents a difference of 43% with respect to the final extradural mass, it represents a very small change (3.5%) in the total intracranial volume (27 to 30 ml). With the intracranial volume of 27 to 30 ml in the cat, then, the average final volume required to produce the CR (for instance, 1.9 ml), irrespective of infusion rate, represents about 6% to 7% of the intracranial space.

As noted previously there is no systematic predictable difference in the final volume required for the production of the CR with variation in the rate of expansion of the balloon, even though admittedly there are statistically significant differences between some of the means. Of perhaps more importance is the lack of any differences (\( p = 0.4 \)) when the average final volumes of the two phases of the power curve are compared.

Because of the concern about deterioration of the preparation with the passage of time during a given experiment, a further analysis was carried out relating not the rate of infusion with the final volume, but rather the final volume as a function of the sequence of trials of expansion of the balloon over all the experimental days. This analysis appears in Fig. 5. Each data point was derived by considering the final volumes and the chronological sequences, within the individual experiments collectively, at which those volumes were obtained. Irrespective of what the rate of infusion was, it can be seen from this graph that over the course of the experimental day, on average, there was a smaller volume required to elicit the CR.

Statistical analyses of pairs of data points by the Student t-test disclose only significance (\( p < 0.005 \)) between the first runs on the one hand and the third and fourth runs on the other hand.

Miscellaneous Observations

Blood gas and pH analyses disclosed only minor variations during the infusions before
Effect on Cushing response of mass expansion rate

the onset of the CR. Analysis at the height of the full CR disclosed the predicted hypercar- bia, acidemia, and hypoxia. Ipsilateral pupillary dilation occurred with the earliest changes in the components of the CR. This was then followed by contralateral dilation, loss of withdrawal reflexes, and, finally, loss of the corneal reflexes.

Discussion

The intracranial cavity, bounded by rigid skull, is of constant volume and its contents are seemingly incompressible.18,20,27,37 The cerebrospinal fluid (CSF) and blood each constitutes approximately 10% of the intracranial volume (with some alterations in blood volume estimation depending upon technique and animal), and the brain substance constitutes 80% in primates28,32 and man.15,26,28 Any significantly expanding mass within the intracranial cavity can only expand if an equal volume of one or more of the normal intracranial components is displaced extracranially. This constitutes the classic Monro-Kellie doctrine. If this thesis is broadened to include the spinal compartment as well, then the doctrine remains acceptable.

The accommodation of the intracranial cavity to an expanding mass may involve a number of mechanisms. These compensatory mechanisms have been the subject of much discussion.1,2,28,34 The general consensus is that at least the initial expansion under normal conditions occurs without the accompaniment of a rising ICP, and presumably it accomplishes this by simple displacement of varying proportions of CSF and/or blood.9,20,29,33,35 Obviously, the ability of the cavity and its contents to accommodate the expanding mass will depend upon the volume of the mass ... also its rate of expansion?

If the Monro-Kellie doctrine is a valid thesis then, within limits, irrespective of the rate of expansion of an intracranial space-occupying lesion, the final volume required to bring about "critical cerebral compression" should be constant. "Critical cerebral compression" may obviously consist of various endpoints depending upon the experimental design. In the present study it has been taken arbitrarily as a development of the CR.

Clinical experience led us to predict, before the present experiments, that the final balloon volume required to produce the CR would be inversely related to the rate of balloon expansion. At the same time, the observations of Nakatani and Ommaya28 in the monkey suggested the converse. Our findings, in fact, disclosed no predictable differences in the final volumes at different rates of expansion. This observation suggests that irrespective of what compensating mechanisms might be involved in accommodating an expanding intracranial mass, there is a relatively constant critical volume of the mass beyond which no further accommodation is possible, that is, there is no further compensation. However, it should be emphasized that this is provisional upon the experimental model and the rates of expansion involved in the present experiments with the endpoint of cerebral dysfunction taken as the production of the CR. Given these limitations, our observations provide strong experimental proof for the validity of the Monro-Kellie doctrine.

From the above one might extrapolate that there would be a probable "critical volume" for various experimental animals with the absolute volume depending upon the species. Whether the relative volume is constant or varies from one species to another is perhaps less certain. There are some observations suggesting the former. For example, according to Sergienko,34 who expanded intracranial balloons in dogs, this value would be somewhere between 4% and 10% of the intracranial volume. He found that when the balloon occupied 4% of the intracranial volume, ICP began to rise, and that at 8% to 10% the animals died. In the monkey, Nakatani and Ommaya28 calculated that when a similar balloon occupied about 5% of the intracranial volume, EEG flattening and the vasopressor response were produced. Thus, our finding that a critical volume of about 6% to 7% was required to produce the CR is consistent with similar observations in the literature.

In the present experiments on the cat, the mean critical volume was 1.9 ml over the range of infusion rates. There is good agreement between this, for example, and the volume of 2.0 ml found by Sullivan, et al.,35 in the same animal species, using the dilated pupil and the isoelectric EEG as endpoints. There is even a more remarkable concordance when their rate of 0.023 ± 0.001 ml/min is compared to our rate of 0.024 ml/min where the values are 2.0 ± 0.2 and 2.0 ± 0.23, respectively.
The smaller critical volumes required when previous expansions have been carried out in the same animal (see Fig. 5) demonstrate an altered intracranial physiology with successive brain compression. Our interpretation is that this provides the basis for the "deterioration" noted under such circumstances by other investigators and could best be explained on the basis that some additional space-occupying factor is present intracranially under these circumstances. Intuitively, it would be expected that this factor would most likely be represented by fluid associated with brain swelling.

Nakatani and Ommaya\textsuperscript{28,29} studied the characteristics of the vasopressor response to inflation of an extradural balloon in monkeys over the ranges of 0.5 to 0.005 ml/min. They found that no vasopressor response could be elicited at expansion rates of less than 0.02 ml/min. Thus, they concluded that this component of the CR was dependent upon the rate of expansion of the extracerebral mass as well as its volume, as opposed to the absolute height of the ICP. Our results have clearly demonstrated the presence of a fully developed CR at slower rates of infusion than those found by Nakatani and Ommaya. Two-thirds of our infusion rates were slower than their critical rate of 0.02 ml/min. Why this discrepancy should occur is not clear. Although the present experiments bear some similarity to those of Nakatani and Ommaya in that an extracerebral balloon was expanded at various rates, the experiments differ in some respects. First, we used cats, as opposed to monkeys. Second, our animals were not artificially ventilated but were allowed to breathe normally so that all three components of the triad could be specifically studied, whereas Nakatani and Ommaya were interested primarily in the vasopressor response. This may, therefore, merely represent a species difference.

Initially the finding of a power curve as the best-fit graphical representation of the relationship between the rate of expansion of the balloon and the latency of the development of the CR was unexpected. Even more puzzling was the finding of the extremely high correlation coefficient. However, upon further analysis it appears that this simply provides further evidence of the importance of the constancy of the critical volume of the balloon required to produce the CR. This interpretation was arrived at by plotting the rates of expansion versus latencies, where the latter are derived by using a fixed constant final volume from the formula:

$$\text{latency} = \frac{\text{final volume (ml)}}{\text{rate of expansion (ml/min)}}$$

For example, with our mean final volume of 1.9 ml, the power curve becomes $y = 1.908x^{-0.999}$ with a correlation coefficient of 1.0000! Therefore, we may conclude that this relationship, initially incomprehensible, does in fact lend additional proof to the importance of the concept of a constant "critical volume" for the production of the CR over the range of expansion rates utilized.

Can any clinical extrapolation be made from these experiments? It is generally recognized that an expanding intracranial mass can be accommodated in the first instance. This early stage of compensation in the evolution of an expanding intracranial mass has been known since the work of Duret\textsuperscript{7} and Kocher\textsuperscript{19} (see also Cushing\textsuperscript{4}). More recent interpretation of this stage of compensation is that principally CSF is expelled from the intracranial cavity with initially little or no rise in ICP. We propose a constant critical volume (CCV) for the production of cerebral dysfunction from an expanding intracranial lesion that is independent of the rate of growth of the lesion. Putting this into clinical perspective, it would be expected that the rate of expansion, per se, would become an important factor at the extremes of growth of lesions. For example, a slowly growing meningioma would almost certainly exceed our proposed CCV (for the human) if it grew slowly enough to be accommodated by permanent displacement of brain substance (viscous accommodation) and, more importantly, by the reduction in brain tissue (such as by atrophy).

At the other end of the scale, the acutely expanding intracranial hematoma represents the most rapidly expanding clinical lesion. If this rate of expansion exceeds the limit of expulsion of CSF/blood from the intracranial cavity, then it would be predicted that the final volume of the hematoma required to produce cerebral dysfunction would be less than the hypothesized CCV.

Therefore, it is proposed, contrary to our initial expectations, that under our experimental methodology the rate of expan-
Effect on Cushing response of mass expansion rate

d ision of an intracerebral mass is not an important variable with respect to its effect on cerebral function, but rather the important factor is the size, or volume, of the mass.

References

18. Kellie G: An account of the appearances observed in the dissection of two of three individuals presumed to have perished in the storm of the 3rd, and whose bodies were discovered in the vicinity of Leith on the morning of the 4th November 1821, with some reflections on the pathology of the brain. Trans Med Chir Soc Edinb 1:84-122 (Part I), pp 123-169 (Part II), 1824
29. Nakatani S, Ommaya AK: Volume pressure curves and pial vascular pressure gradients in

J. Neurosurg. / Volume 49 / July, 1978 69


This study was supported by grants from the Medical Research Council of Canada (MA-3383) and the Richard and Jean Ivey Fund.

This paper was presented in part at the Sixth International Congress of Neurological Surgery, Sao Paulo, Brazil, June, 1977.

Address for Dr. Zidan: Associate Professor of Neurosurgery, Department of Neurosurgery, Faculty of Medicine, Cairo University, Cairo, Egypt.

Address reprint requests to: John P. Girvin, M.D., University Hospital, 339 Windermere Road, London, Ontario, N6G 2K3, Canada.