Origin and evolution of plateau waves

Experimental observations and a theoretical model

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Laboratory observations made in cats with fluid-percussion head injuries have suggested that plateau waves or Lundberg "A-waves" are not independent of systemic circulatory events. Four distinct phases in the evolution of the plateau wave have been identified, and each related to a circulatory change in a causal manner. The first phase is the premonitory drift phase where intracranial pressure (ICP) gradually increases prior to the plateau proper. This phase is caused by a slow gradual decline in systemic arterial blood pressure (SABP) which increases ICP by autoregulatory vasodilation and reduces cerebral perfusion pressure (CPP) to a range of 70 to 80 mm Hg. The second phase is the plateau phase initiated at a CPP of about 70 to 80 mm Hg, and is characterized by a rapid increase in ICP as CPP falls further to 40 to 50 mm Hg. The plateau lasts as long as the CPP remains stable and above ischemic levels. The third phase is the ischemic response, characterized by CPP being returned toward normal by increases in SABP in response to very low CPP's. The fourth phase is the resolution, characterized by a rapid decline in the ICP to baseline levels with stabilization of the SABP and CPP, and is best explained by autoregulatory vasoconstriction.

Plateau waves appear to occur as the result of intact or mostly intact autoregulation responding to changes in CPP. The series of events that follow are best explained by what is known of normal autoregulation; the various properties of plateau waves are viewed and explained as the expected and logical consequences of an unstable CPP acting upon a generally intact cerebrovascular bed in the face of elevated ICP and decreased compliance.

KEY WORDS • plateau waves • intracranial pressure • autoregulation • cerebral perfusion pressure • head injury

In 1960, Lundberg3 published his observations regarding the behavior of the ventricular fluid pressure in patients with intracranial hypertension from varying etiologies. Among other observations was his description of the "A-wave" or the "plateau wave." This intracranial pressure (ICP) phenomenon is characterized by spontaneous and acute elevations in ICP rapidly rising above moderately elevated baseline levels (usually 15 to 25 mm Hg). These elevations of ICP may reach 50 to 100 mm Hg and last any time from 2 or 3 minutes to as long as 20 or 30 minutes. They usually abort in a manner as sudden and spontaneous as they began. During the ICP plateau wave, patients have been known to complain of additional headache, drowsiness, disorientation, vomiting, and diplopia, but overall these pressure phenomena have been well tolerated.

Lundberg concluded that these spontaneous A-waves reflected vasodilatation with subsequent increases in cerebral blood volume (CBV). It was recognized that vascular phenomena were the only mechanisms that might reasonably explain events that came on so quickly and aborted so suddenly, yet altered the clinical status of the patient to such a minor degree. In general, plateau waves have been considered to represent cerebral vasodilation due to an unstable "cerebrovascular control system."13,33 Human studies have shown them to be associated with increased CBV,6 which tended to be greatest just before termination of the wave,53 and these observations have been confirmed in animals.31

While CBV has been shown to be increased during the plateau, cerebral blood flow (CBF) has generally been found to be slightly reduced.3,6,7,29 Matsuda, et al.,38 confirmed this mild reduction in CBF in four of five patients; their fifth patient had blood flow measurements only slightly higher than baseline. However, plateau waves have always been described in association
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with marked reductions in cerebral perfusion pressure (CPP); this is in contrast to small reductions reported in CBF. This suggests that plateau waves occur in association with marked reductions in cerebral vascular resistance (CVR) consistent with generally intact autoregulation. One would expect CBV to increase under these circumstances, and, indeed, angiography has directly demonstrated that arterial vasodilatation occurs during the plateau wave.

Although Lundberg and later observers have stated that plateau waves generally occur independently of systemic circulatory changes, they have presented little in the way of simultaneous recordings of ICP and systemic arterial blood pressure (SABP) to confirm this statement. Other publications presenting simultaneous recordings of both pressures have shown, although they have not often recognized, that at least under some circumstances the systemic pressure is not independent of plateau wave phenomena. We present here observations suggesting that systemic circulatory events are associated with plateau waves in a causal manner, and that the known physiology of intact autoregulation, its behavior under pathological circumstances, and altered compliance of the intracranial space are sufficient to explain most plateau wave phenomena.

Materials and Methods

Mongrel cats, each weighing 2.5 to 4 kg, were anesthetized with intravenous methohexital sodium (1 mg/kg), intubated endotracheally, and placed on a Harvard ventilator* receiving 70% nitrous oxide and 30% oxygen. Intra-arterial and intravenous catheters were placed through the right groin and connected to strain gauge transducers. The animal was then placed in a stereotaxic head holder, and a fluid-perfusion injury device was fitted according to techniques described previously. Additionally, a subdural ICP monitor was placed, as were biparietal electroencephalographic (EEG) screws which were referenced to the frontal midline. Throughout this period, muscle relaxation was maintained by pancuronium bromide administered in approximately 0.4-mg intravenous doses, and anesthesia was supplemented by 2% xylocaine injected locally at the sites of surgical preparation. Rectal temperature was measured with a thermocouple probe.

The animals were then injured at approximately 3.0-atm peak injury levels, and allowed to stabilize in the head holder for the next hour. At the end of this time period, the central injury tube was removed, the dura covered by a small amount of Surgicel and then dental acrylic, the skin closed, and the cat placed in a lateral decubitus position. The subdural ICP monitoring device and the EEG screws were left in place, as were the intravenous and intra-arterial lines, and the surgical wounds were closed around the monitoring devices. The animal was maintained on a respirator, with continuous monitoring of end-tidal CO2, SABP, central venous pressure (CVP), ICP, temperature, EEG, and heart rate. Animals were ventilated and monitored for up to 72 hours. All recorded pressures were referenced to the level of the ear bars while the cat was maintained in the head holder, and later to the sagittal midline while the animal was in the decubitus position. All measurements were recorded on a Beckman R612 polygraph, with heart rate calculated from the electrocardiographic pulse using a Beckman cardiotachometer.

In approximately 20% of the animals, we observed the development of plateau waves beginning approximately 18 to 30 hours after injury. These plateau waves were relatively stereotyped in their behavior, and persisted until the death of the animal.

Results

Plateau waves occurred only in animals with persistent increases in ICP. The ICP level required for the development of plateau waves was 21.5 mm Hg (Table 1). Just prior to the development of the plateau wave, there was a slow and gradual rise in the ICP from 20 mm Hg to between 30 and 35 mm Hg (Figs. 1 to 4 and 8). This typically required 7 to 10 minutes, and ICP rose at the rate of 2 to 3 mm Hg per minute. At the beginning of the ICP rise, mean SABP was typically 110 to 130 mm Hg. The CPP was thus 90 to 110 mm Hg and well into the normal range for the cat. However, over the next 10 minutes, blood pressure gradually drifted down to a mean of 100 mm Hg. The CPP dropped to levels of 60 to 70 mm Hg. The correlation coefficient for the SABP - ICP during the drift phase was -0.89 ± 0.04 (p < 0.001, for ten studies).

Consistently, when the CPP reached 60 to 70 mm Hg, the plateau phase of the wave would begin. The ICP rise would occur over the next minute or two to levels of 60 to 70 mm Hg or more. The blood pressure would change little during this phase of ICP rise, either continuing a very slow decline or stabilizing at a constant level. Because of the lack of blood pressure increase during this phase, the CPP continued to decline as the ICP rose. The CPP often fell to or below 50 mm Hg (Figs. 1 to 4 and 8, Table 1).

When CPP reached 50 mm Hg or less, the blood pressure would often respond with a sharp increase (Figs. 1 and 8, Table 2). Concomitant with this rapidly rising blood pressure, the ICP would show a further rapid rate of increase to a maximum level of 60 to 70 mm Hg or occasionally higher. The ICP increase was characterized by an "in phase" relationship to the blood pressure (that is, the latent period between the rise in SABP and ICP was essentially zero). We termed this

* Ventilator manufactured by Harvard Apparatus, Inc., 150 Dover Road, Millis, Massachusetts.

† Polygraph and cardiotachometer manufactured by Beckman Instruments, Inc., 2500 Harbor Boulevard, Fullerton, California.
ICP peak a “termination spike” (Fig. 1), because it heralded the termination of the plateau by CPP restoration.

However, in all cases where this was observed, the ICP, after reaching this peak, rapidly fell to baseline levels. The peak ICP always occurred 8 to 15 seconds before the peak in the blood pressure. We termed this the “ischemic response phase.” Throughout this phase of the plateau wave, the rise in blood pressure and the rise in ICP balanced each other after restoring CPP’s to 70 to 80 mm Hg.

The ischemic response phase was characterized by either a rapid restoration of CPP (Figs. 1 and 8) similar to a Cushing response, or a more gradual but sustained increase in SABP which also restored CPP to normal (Figs. 2 and 3). Taking both patterns together, the average CPP increased from 48 to 71 mm Hg, a rise of 23 mm Hg which always preceded any further change in the ICP. In those animals in which the Cushing response was vigorous (Table 2), there was an initial further increase in ICP (“termination spike”) of about 24 mm Hg which occurred precisely in phase with the Cushing response, but then peaked and began to fall without concomitant change in the SABP. Figure 2 demonstrates a wave that shows gradual restoration of the CPP by the increasing SABP. There is very little further increase in ICP (0.4 mm Hg for five waves with this pattern, Table 2). However, regardless of whether the increase in SABP was rapid or slow, the average CPP was increased from 48 to 71 mm Hg, with an associated 13-mm Hg rise in the ICP. Thus, the SABP was responsible for a net improvement of 23 mm Hg in the CPP. It is worth noting that the ICP never fell unless the SABP had produced an increase in the CPP.

As the ICP began to fall, the CPP would rise closer to normal levels of 100 to 120 mm Hg. The ICP always declined to less than the level it had attained just prior to the initiation of the plateau phase of the wave. If this blood pressure rise did not occur, the plateau wave was not aborted and ICP continued high until CPP was restored. Therefore, it was our conclusion that this rise in blood pressure occurred as the result of brain-stem ischemia, which then resulted in an adrenergic discharge increasing blood pressure. In essence, a Cushing response occurred and restored the CPP to normal levels and aborted the plateau wave. We have seen no plateau waves in animals where CPP did not drop below 70 to 80 mm Hg.

The demonstration of blood pressure changes occurring in spontaneous fashion in what appeared to be a causal relationship to subsequent plateau wave phenomena suggested that control of the blood pressure might control the plateau waves. This was accomplished by using a very slow infusion of phenylephrine (10 mg/500 ml in 0.9% NaCl) (Fig. 7), not to raise but to prevent the decline in the SABP.

As can be seen from Fig. 7, plateau waves were consistent and frequent in their occurrence up to the point of the phenylephrine infusion. At this point, two or three minor waves occurred, related to declines in the SABP, but once blood pressure stabilized the plateau waves disappeared. With discontinuation of the phenylephrine infusion, the plateau waves reappeared. Their recurrence was gradual and associated with the SABP becoming unstable once again. It is of interest that the blood pressure required several hours to reach the same level of “instability” as before the institution of the phenylephrine infusion. This suggested a possible “therapeutic” effect of elimination of plateau waves and consistent maintenance of normal CPP.

Phenylephrine infusion was begun again several hours later in an attempt to control the occurrence of the A-waves, but the SABP failed to respond to the dose used. The drug had little effect upon blood pressure, and plateau waves continued to occur in relation to cyclic declines in SABP. This suggests that the previous

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<td><strong>Pressure relationships at each phase of the plateau derived from a single wave from each of 10 cats</strong>*</td>
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*All pressures are in mm Hg. SABP = systemic arterial blood pressure; ICP = intracranial pressure; CPP = cerebral perfusion pressure; SEM = standard error of the mean.
†Values at end of phase become values for beginning of subsequent phase.
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Fig. 1. Relatively short plateau waves demonstrating each phase in relation to other cardiovascular events. Note the drifting of the blood pressure, the response of the intracranial pressure (ICP), and the marked reduction in cerebral perfusion pressure (CPP). In this case the CPP is rapidly restored and there is a "termination spike" in the ICP due to the passive stretch of the vasculature (ICP and systemic arterial blood pressure (SABP) in phase) and the active vasoconstriction of autoregulation which terminated the wave. Note that the peak of the plateau during the termination spike occurs a few seconds before the peak in the SABP. The only qualitative difference between Fig. 2 and this wave is the rate of CPP restoration, which probably relates to a more vigorous Cushing response.

success in plateau wave control was related to the blood pressure effects and was probably not due to a direct effect of the drug upon the cerebral vasculature or a neural center, and that plateau waves were prevented by interrupting the drift phase.

Plateau waves are extremely stereotyped in their occurrence. This has led to the definition of four distinct phases in their evolution. These phases we have labeled the drift phase, plateau phase, ischemic response phase, and the resolution phase. The drift phase is a premonitory stage in plateau wave development. Its characteristic is the gradual decline in CPP to levels of about 70 mm Hg (Figs. 2 and 4, Table 1). In our observations,

Fig. 2. Spontaneous plateau wave occurring in a cat approximately 36 hours after injury at 2.85 atm. Note the very gradual decline in systemic arterial blood pressure (SABP) from 150/120 to 125/95 mm Hg occurring over 3 to 4 minutes; there is a corresponding slow increase in the intracranial pressure (ICP, drift phase) probably due to vasodilation occurring in response to the marked drop in cerebral perfusion pressure (CPP). As the CPP reaches about 80 to 90 mm Hg, the rate of rise of the ICP accelerates and plateaus at 65 to 70 mm Hg; the CPP remains fairly constant throughout; as long as the CPP remains fairly low and constant, the ICP remains at a plateau level. As the CPP is restored (ischemic response phase), the plateau wave aborts (resolution phase). The electroencephalogram changes only subtly in response to the lowered CPP. Central venous pressure and end-tidal CO₂ remain constant.

| TABLE 2 |
|-------------------|--------------|-------------|----------------|-----------|
| Pressure changes during each plateau wave phase* |
| Group | SABP | ICP | CPP | SABP | ICP | CPP | SABP | ICP | CPP |
| all waves (10 cats) | -15.3 ± 5.0 | 11.3 ± 2.7 | -27.9 ± 5.0 | 34.7 ± 14.8 | 12.1 ± 7.4 | 23.3 ± 8.6 | -8.4 ± 6.8 | -51.6 ± 11.8 | 43.6 ± 12.5 |
| waves with marked termination spike: rapid SABP increase (5 cats) | 56.0 ± 11.5 | 23.8 ± 4.3 | 31.6 ± 9.4 | 0.4 ± 0.9 | 1.2 ± 3.1 | 13.0 ± 1.6 | 36.6 ± 2.6 |
| waves with minimal termination spike: slow SABP change (5 cats) | 13.4 ± 1.2 | 0.4 ± 0.9 | 1.6 ± 1.6 | 1.2 ± 3.1 | 36.6 ± 2.6 |

* All pressures are in mm Hg. SABP = systemic arterial blood pressure; ICP = intracranial pressure; CPP = cerebral perfusion pressure.
the CPP reduction has been initiated by a gradually declining SABP. The fall in systemic pressure occurs slowly, and often the degree of fall appears negligible. But the correlation between the decline in SABP and ICP is virtually perfect and inverse (−0.89 ± 0.04). The inverse correlation suggests an "active" vasodilatation rather than a "passive" response.

When CPP reaches 70 mm Hg, there occurs a very rapid increase in ICP to "plateau" levels. If the SABP is able to stabilize the CPP above ischemic levels, the plateau wave continues. The plateau itself is often irregular and marked by oscillations in the plateau ICP (Fig. 3) which relate to SABP irregularity.

If the SABP continues to fall, the CPP reaches ischemic levels and blood pressure will be elevated by a brain stem-mediated adrenergic discharge: a Cushing response (Figs. 1 and 8, Table 2). The rise in ICP during this ischemic response is precisely in phase with the SABP change (that is, the latent period is zero). Within 5 to 15 seconds, the secondary ICP increase becomes blunted and reverses itself. The SABP continues to remain high for several seconds or even continues to increase after the peak in ICP. Restoration of CPP occurs, but may be transiently slowed due to the passive ICP response. We have termed this phase the "ischemic response phase," and the transient passive ICP response a "termination spike" (Figs. 1 and 8).

Note that as CPP is restored, the SABP and ICP again become inversely related. Restoration of CPP is now mostly a function of falling ICP, although the SABP increase has initiated these events. This is the resolution phase of the plateau wave. The CPP remains elevated at normal levels and ICP drops to its baseline level—lower than at the beginning of the plateau phase and reflecting the higher CPP.

The termination spike is a function of the rate of SABP increase. In those animals where CPP is restored slowly, the termination spike is absent or greatly diminished in amplitude (Figs. 2 to 5, Table 2). Where SABP increases gradually, restoration of CPP is more consistent and steadier than when a termination spike occurs. However, when CPP reaches 60 to 70 mm Hg, the plateau suddenly aborts.

The variations on this sequence of events tend to be quantitative rather than qualitative. The plateau wave may be prevented or aborted at any stage by either induced or spontaneous restoration of CPP. There ap-

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Fig. 3. Recordings in another fluid-percussion-injured cat demonstrating plateau waves qualitatively similar to previous examples. Again, note the slow decline in systemic arterial blood pressure (SABP). Note the absence of the termination spike, as was true in Fig. 2, which was due to the relatively slow and gradual restitution of SABP and cerebral perfusion pressure. Note the presence of subtle precursor waves which relate to varying SABP during the drift phase.

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Fig. 4. This wave is similar to Fig. 3, but the irregularities during the drift phase are more prominent and related to variation in the rate of decline in systemic arterial blood pressure (SABP) during this phase. If the SABP is unstable during the plateau phase, it will also be marked by variation and instability. No termination spike is seen with this gradual SABP increase and restoration of cerebral perfusion pressure.
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pear to be minor differences from animal to animal with regard to precise thresholds for each phase, although the data in Tables 1 and 2 are remarkably constant.

While the SABP drop recorded in the majority of our cats appeared to be spontaneous, Fig. 5 is an example of a pressure wave brought about by a slight decline in SABP due to pancuronium bromide administration. Presumably, hypotonia induced by the drug transiently decreased cardiac return, cardiac output, and then SABP. With restitution of the SABP, and an appropriate latent period, the wave aborts. Note the slow rise in SABP and the absence of the termination spike.

The length of time the ICP is at plateau levels is a function of the time CPP remains low. If it is restored quickly (Figs. 1, 4, and 8), then the plateau is short-lived; if CPP restoration takes longer, the plateau lasts a concomitantly longer period of time (Figs. 2 and 3). If CPP is restored at a rapid rate, a termination spike occurs; if it returns gradually, the spike is small or absent.

Changes in other parameters parallel CPP changes. The EEG may lose amplitude and become slower during a plateau wave to greater and lesser degrees (Figs. 1 to 4, and 8) or it may not change at all, depending upon the level of CPP. Heart rate changes are usually minor and reflect the degree of SABP response. Either reflex bradycardia to the SABP increase or tachycardia as a direct reflection of the sympathoadrenal discharge may occur (Figs. 3 and 8). End-tidal CO₂ changes are not required for plateau wave abolition or occurrence. Changes in CVP reflect only the expected effects of a sympathoadrenal discharge and are transient.

Discussion

Our experimental observations suggest that the drift phase of the plateau begins when the CPP is about 100 mm Hg, while the plateau phase is initiated when CPP begins to drop below 70 to 80 mm Hg. This sudden increase in ICP does not relate to a worsening of compliance (see below), but to a rapid increase in CBV. This increase has its origins in what we now know to be normal vascular physiology.

Between 80 and 100 mm Hg, the amount of vasodilation occurring in the pial vasculature is low. Kontos et al. 20,21 demonstrated that the change in diameter of pial vessels from a control pressure of 130 mm Hg to that measured at 80 mm Hg is about 10%. While CPP reductions in the range of 130 to 80 mm Hg are capable of inducing CBV increases due to arterial dilatation, the actual CBV increase will be small over this range (Fig. 5). Therefore, given a decreasing CPP, CBV will increase slowly; the ICP increase will also be minor and slow and appear only to be drifting higher in this CPP range.

From 80 to 40 mm Hg the increase in diameter is an additional 25% to 70% over that occurring between 130 and 80 mm Hg — the level at which dilatation averaged about 10%. Below CPP levels of 80 mm Hg, the vascular bed dilates rapidly at about a 1.8%/mm Hg drop in SABP (for 40-μ class arterioles) to 0.6%/mm Hg (for 200-μ class arterioles). The average rate for the corresponding vessels when pressure is above 80 mm Hg is 0.1%/mm Hg and 0.2%/mm Hg, respectively. Below a CPP of 80 mm Hg, the 40-μ vessels dilate 20 times faster and the 200-μ vessels three times faster than the rate when CPP is above this level. Intermediate sized arterioles dilate at intermediate rates. 21

Therefore, the vascular bed dilates at an exponential rate to decrements in CPP, and the rapid increase begins as CPP falls below 80 mm Hg. We have a situation where CBV change in the arterial phase will occur very rapidly when CPP begins to drop below the 70 to 80 mm Hg range, but increases by only small increments as CPP falls through the range of 130 to 80 mm Hg (Fig. 5).

To the extent that decreased compliance of the brain represents a turgid vasculature, we might expect the compliance to "improve" during a plateau wave since the vasculature is under greatly reduced pressure. In fact, this does happen, as reported by Avezaat and van Eijndhoven, 1 and has also been observed by Miller (JD Miller, personal communication, 1982).

Figures 1 to 4 are recordings of the ICP and SABP,
and hand-plotted traces of the CPP. The drift phase is clearly shown, and ends with a sudden increase in the ICP to plateau levels. This increase occurs in the CPP range where one expects the cerebral vasculature to dilate markedly to only small decrements in CPP. In essence, the plateau wave or A-wave represents a large and rapid increase in CBV due to relatively minor additional decrements in CPP; the plateau wave is the logical consequence of intact autoregulation interacting with an unstable CPP when intracranial compliance has been reduced by edema, mass lesion, or hydrocephalus. If the CPP should remain constant at low levels, but still above pressures resulting in cerebral ischemia, then the ICP will remain elevated at plateau levels.

Thus, the drift phase represents a slow rate of vasodilation and blood volume increase. The transition to the plateau phase occurs as the perfusion pressure declines into the range where the vasculature normally dilates at a much faster rate. These rates of vasodilation will be reflected in varying rates of ICP increase: initially slow but then very rapid. Note that the rate of SABP decline does not necessarily increase (Figs. 1 to 4); it may even appear to stabilize (Figs. 5 and 8). It is the rate of vascular dilatation that changes, and this translates to large exponential changes in CBV (Fig. 6).

Blood flow is slightly reduced at low CPP's when autoregulation is normal, since the slope of the flow versus CPP curve is not zero in what is usually considered the autoregulatory range. Additionally, in the damaged or traumatized brain, CBF may decline faster than normal as CPP falls. Therefore, in the range of CPP's where we have observed plateau waves, CBF can actually be expected to be slightly low. This was clinically proven by Matsuda, et al., in five patients, and Cooper and Hulme made identical observations. Thus, during a plateau wave, the CPP is low, CBV is high, and CBF is slightly reduced. Because the CPP is at the lower limits of normal, the situation is inherently unstable, and the ICP and CBV cannot be expected to remain steady at these extreme values for very long.

If CPP remains stable and no other intervention is carried out (such as cerebrospinal fluid (CSF) drainage or hyperventilation), the plateau will continue. If CPP falls further, the ICP will soon be maximal and then passively follow blood pressure variations as the CPP will be in a range where the vasculature is normally passive (less than 50 mm Hg).

The alternative is cerebral ischemia, stimulating a Cushing response (Figs. 1 and 8, Tables 1 and 2) which will rapidly restore the CPP toward normal. The cerebral vasculature will respond with vasoconstriction and CBV will decrease: ICP will fall. A variation on this theme is a slower, more gradual rise in SABP with restoration of CPP and concomitant vasoconstriction, reduction in CBV, and a drop in the ICP (Figs. 2 to 5). With either scenario, the cerebral vasculature will constrict in a manner that will be similar but opposite to the sequence occurring during developing hypotension. The greatest part of vasoconstriction will occur before a CPP of 70 to 80 torr is reached. Above this level, additional increments in CPP may lead to further, but only slight, reductions in ICP. The absolute ICP change will depend upon the baseline level of ICP and intracranial compliance, but the greatest ICP change (drop) will have occurred as CPP rises to about 80 torr. Above this, further ICP decrements will be relatively slight as CPP increases, and nil with CPP's much above 100 torr.

As the SABP rises, the CPP is restored and vasoconstriction occurs, leading to the precipitous drop from high ICP characteristic of the termination of the A-wave. There is a variation that will occur during this sequence of events dependent upon the rate of rise of the blood pressure and the normal lag between change in CPP and vessel diameter response, that is, the normal latency between pressure change and autoregulation.

When CPP changes in either direction, intact autoregulation demands an inverse diameter change in the vessels exposed to these pressure changes. However, this diameter response lags behind the pressure change by 5

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**Fig. 6.** The physiological basis for these phenomena is the logarithmic rate of vasodilation occurring in response to reductions in cerebral perfusion pressure (CPP). The increases that may occur in cerebral blood volume (CBV) in the different arterial beds are shown here. Intermediate-sized arterioles dilate at intermediate rates. Note that below a CPP of about 40 mm Hg, the vessels will no longer dilate but collapse passively. Passive collapse of the vasculature is normal below these limits and does not necessarily imply lost autoregulation. ICP = intracranial pressure. (Reproduced with permission from Rosner MJ, Becker DP: The etiology of plateau waves: A theoretical model with experimental validation, in Ishii S, Nagai H, Brock M (eds): Intracranial Pressure V. Berlin/ Heidelberg/New York: Springer-Verlag (In press).)
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to 15 seconds or more. 20-22,26 This is of no consequence when the rate of blood pressure change is slow; under the circumstance of a slowly changing SABP and CPP, the ability of the vessel to change diameter will remain virtually in phase with the pressure change and resultant ICP changes will be essentially in phase with, but inversely related to, CPP changes.
When the blood pressure drops quickly or, as in the case of a Cushing response, rises rapidly, the effects and their time course on the ICP are quite different. It has been pointed out that a true autoregulatory response in the ICP, with reflected in the ICP, will correlate negatively with the pressure change. In the face of rapid pressure changes before autoregulation becomes effective, vessel diameters will vary directly and affect ICP directly. There will be no latent period between the SABP and ICP change, and the change will be in the same direction as the perfusion change.
Both of these differences have their basis in mechanical stretching (or passive collapse) of the vessels involved. Careful examination of the figures in the study by Kontos, et al., 21 will reveal that, with rapid falls in pressure due to vagal stimulation, an immediate decrease in vessel diameter occurred. Of course, this passive decrease in diameter was followed by the expected increase as vascular smooth muscle relaxed. Similar results were obtained by Weiss, et al., 68 when sodium nitroprusside was used to rapidly decrease SABP. There was an initial drop in ICP (passive vascular collapse) followed by an increase as autoregulatory vasodilation occurred. Magnaes, 35,36 demonstrated this effect on ICP (latency of 10 seconds and inverse change) when studying the effects of rapid positionally induced CPP changes. He even induced plateau waves in patients by this “iatrogenic” and positional reduction in CPP.
The converse situation occurs with rapid increases in CPP. There will be mechanical stretching of the vasculature with a subsequent increase in CBV. The volume increase is transient and will soon reverse as the smooth muscle in the vasculature is able to contract and produce the appropriate change. This has been well described by many investigators. 2,8,31,57,66,69
Therefore, the important concept is that every vessel will react both passively and, when undamaged, actively. The passive response is characterized by zero latency and direct correlation with blood pressure change. Active responses will be out of phase with blood pressure change by about 5 to 15 seconds or longer and will vary inversely with blood pressure.
Transient peaks in ICP are typically seen in association with very rapid changes in SABP and CPP, as seen in plateau waves aborted by an ischemia-induced Cushing response. As described above, the Cushing response induced by cerebral ischemia incurred at low CPP’s is composed of a rapid SABP increase that raises the CPP and aborts the plateau wave. However, because of the lag in autoregulatory vasoconstriction, the ICP rises further above the plateau level due to mechanical distention of the vasculature. We have termed this a “termination spike” (Figs. 1 and 8), and believe that this mechanism underlies the observation of Risberg, et al., 33 that CBV tends to be maximal just prior to termination of the plateau.
This peak can be seen in the records of many publications as a short sharp spike in the ICP occurring just before the wave aborts. Its presence indicates a rapid restoration of CPP, and its absence indicates a slower gradual restoration of the CPP (Table 2). Lorenz 29 has demonstrated the association of a Cushing response with plateau waves, but the resolution of his recordings inhibited a more precise description of their role, as we present here. However, in many of his illustrations, the relation of the Cushing response to a “termination spike” in the ICP is clear, and his observations and recordings are consistent with our own.
There is another situation in which a further rise in ICP is associated with the restoration of CPP, and that is when the CPP is very low. The cerebrovasculature is normally passive in response to CPP changes below 40 to 60 mm Hg; decrements in CPP result in passive collapse of the vasculature with reduction in CBV. With increments in CPP, the inverse will be true. In essence, when the CPP drops below the point of minimal CVR, the CBV will tend to vary directly with CPP. 11 Above this level, the CBV will tend to be inversely related to CPP. Therefore, if the CPP is significantly below the limits of autoregulation, there will be a rise in the ICP as CPP is restored, and this will continue until CPP reaches levels where vasoconstriction can result in reductions in CBV.
This latter concept is strongly supported by the work of Langfitt, et al. 27 These investigators used epidural balloons as mass lesions and found that once the ICP was elevated to high levels, small (0.2 cc) volume increments could induce pressure waves which were worsened by subsequent hypertension (Cushing response). Their figures demonstrated that this worsening occurred when the CPP was substantially less than 40 to 50 mm Hg, a finding consistent with the well established passive response of the “normal” vessel at low CPP levels. 15 Interestingly, Langfitt, et al., 27 showed examples of such pressure waves being aborted by the Cushing response occurring with additional volume loading, and this termination of the wave occurred when the CPP had been restored to ranges where autoregulation became effective (see their Fig. 6).
Langfitt, et al., 27 were quite correct in stating that the “vasopressor response is the principal mechanism whereby cerebral blood flow is maintained in the face of rising intracranial pressure . . . .” However, we believe the “vasopressor response” also to be the primary mechanism for termination of plateau waves, since restoration of the CPP to levels of 80 mm Hg or more will induce autoregulatory vasoconstriction. The concept of “vasoparalysis” 25-28,66-68 nicely explains many aspects of

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ICP behavior with SABP change. However, it is clear from much of this work that these "passive" responses usually occurred at CPP levels below the lower limits of autoregulation where vessels are normally passive. The term "vasoparalysis" is certainly descriptive, but probably inappropriate for CPP ranges above or below the known limits of autoregulation.

While true disorders of autoregulation exist, it is unreasonable to test its integrity outside its known physiological limits. Similarly, "vasoparalysis" should be reserved for essentially absent vascular responses when tested within the physiological CPP range. Data from experimental head injury show active vascular responses to be frequently altered and attenuated, but not absent. Pálvolgyi has shown in humans with neoplastic lesions that generalized loss of autoregulation was the exception rather than the rule: altered vascular reactivity in the region of a tumor was common, but net autoregulation was still present. Alterations in pO2 and pCO2 also affect the slope of autoregulation, but not its presence.

When perfusion is within the limits of autoregulation, CBV will vary inversely with pressure, and ICP will follow. When intracranial compliance is low, the CPP drops quickly to levels where vasodilatation occurs at accelerating rates and plateau waves may occur. They are aborted when CPP returns to pressure levels where vasoconstriction becomes effective. If the CPP falls below the lower limits of autoregulation where vessels are normally passive, CBV will vary directly with CPP and ICP will follow SABP pari passu. A similar situation should occur if the CPP is above the upper limits of autoregulation where the vasculature is also passive. This latter is probably rare except in cases of hypertensive encephalopathy.

Therefore, the changes in ICP characteristic of plateau waves generally require a low or unstable blood pressure. This was indirectly described by Clubb, et al., when they found that barbiturates and sodium nitroprusside eliminated plateau waves but not plateau pressures; we believe this is secondary to stabilization of the SABP, but at lower CPP levels. Pettorossi, et al., made similar observations when they stated that rapid ICP variations nearly always reflected SABP changes. Stable CPP is associated with the absence of ICP waves (Figs. 7 and 9).

**Fig. 7.** Simultaneous recording of systemic arterial blood pressure (BP, lower traces) and intracranial pressure (ICP, upper traces) for nearly 33 hours. Phenylephrine (Neoephrine, 10 mg/500 ml in 0.9% NaCl) was infused at a rate sufficient to prevent the decline in blood pressure which preceded each plateau wave, and for the next 4 hours no such waves occurred. The next morning the infusion was begun again, but the rate was inadequate to maintain the blood pressure, and plateau waves continued; however, their frequency and magnitude were reduced.
Experimental observations of plateau waves

The essential point is that the cerebral vasculature responds to changes in CPP. A decrement in CPP within the region of rapid vasodilatation will induce a self-perpetuating cycle of vasodilatation which increases ICP, causing CPP to decline further, which raises the ICP. . . . The process must terminate when vasodilatation is maximal.

Reductions in CPP may be brought about by hypoxia, hypercarbia, hypotension (spontaneous or postural), cerebrospinal fluid (CSF) infusion, venous obstruction and vasodilating drugs, and anesthetic agents. Each has been shown to precipitate plateau waves; we believe that the response of reasonably normal autoregulation to CPP changes induced within a relatively narrow range explains the plateau wave phenomena under each of these situations, and that CPP-induced vasodilatation is the "final common pathway" in creating plateau waves. It follows that restoration of the CPP will induce a similar cascade of vasoconstriction and terminate the wave. The precise manner of CPP increase is unimportant. Hyperventilation, CSF withdrawal in small amounts, arousal, exogenous catecholamines, and mannitol have all been shown to be capable of aborting the waves. We believe that each acts via CPP restoration. This overall theory accounts for the "paradoxical" effect of barbiturates described by Nakatani, et al., if CPP is marginal and lowered further by a barbiturate, ICP may well increase as opposed to declining.

The relative preservation of CBF during the plateau wave is responsible for the relatively minor clinical and electrical changes that usually accompany these waves. However, it should be recognized that these CPP's are at a level where further reductions will lead to frank ischemia. If the Cushing response does not occur, or restoration of CPP is prevented by drugs, hypovolemia, positive end-expiratory pressure, or change in position, then the clinical result may be disastrous.

We believe that the relatively normal CBF during a plateau wave is responsible for the general lack of association between plateau wave occurrence and EEG change which has been described. Our observations suggest EEG changes are related to plateau waves, with depression and slowing of the EEG occurring only at very low CPP's (Figs. 1 to 4, and 8).

All neurosurgeons have observed patients deteriorate incredibly rapidly. This rapidity of deterioration is often not easily explained by progression of edema, clot, or tumor; however, the phenomena of cascading vasodilatation and rapid ICP increases, as described by Weinstein and Langfitt and ourselves, may provide the explanation. Slight changes in SABP due to sedation, hypovolemia, or even sleep may initiate this cascade under certain circumstances, with devastating results.

The normal or even moderately abnormal cerebrovasculature is a dynamic system capable of affecting ICP changes in an exponential manner. Recognition of this interaction indicates greater use of ICP and SABP monitoring in critically ill patients, greater attention to fluid balance and avoidance of hypovolemia, and more careful use of vasodilating and sedating drugs in the intensive care unit (barbiturates, chlorpromazine) and especially in the operating room. The key to the successful management of certain problems of ICP may rest in greater attention to the importance and maintenance of CPP.

Conclusions

1. Plateau waves are the product of an unstable CPP which then acts upon an intact or mostly intact autoregulating cerebrovascular bed. Autoregulatory vasodilatation results in Lundberg A-wave phenomena, and a key to these plateau phenomena is the progressive rate of vasodilatation occurring in response to changes in CPP. All of the characteristics of plateau waves are best explained by what is known of normal autoregulation, and recourse to concepts such as "abnormal vasomotor control systems" is probably unnecessary.

2. While our observations suggest that a gradually declining SABP is the most common etiology for CPP reduction, this mechanism is nonspecific. Any maneu-

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Fig. 8. Another wave with very short drift phase but with intense Cushing response increasing systemic arterial blood pressure (SABP) from about 140 to 200 mm Hg and associated with a 25-mm Hg termination spike in the intracranial pressure (ICP). Note the prolonged elevation of SABP after the ICP has returned to levels lower than baseline.
ver that decreases CPP (such as added CSF volume, hypercarbia, metabolism-induced changes in CVR) is capable of initiating the autoregulatory cascade typical of a plateau wave. Similarly, any maneuver capable of increasing CPP will abort a plateau wave, although a spontaneous increase in SABP appears to occur most commonly.

3. Experiments regarding ICP should be examined in the light of concomitant CPP changes. Drugs, treatments, and manipulations that affect the cardiovascular system in even subtle ways should have their consequences in terms of CPP evaluated carefully and critically.

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