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Chapter 5

# Principles of intracranial pressure monitoring and treatment

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**Abstract**

Intracranial pressure (ICP) is governed by volumes of intracranial blood, cerebrospinal fluid, and brain tissue. Expansion of any of these volumes will trigger compensatory changes in the other compartments, resulting in initially limited change in ICP. Due to the rigid skull, once compensatory mechanisms are exhausted, ICP rises very rapidly. Intracranial hypertension is associated with unfavorable outcome in brain-injured patients. This chapter discusses the pathophysiology of raised ICP, as well as typical waveforms, monitoring techniques, and clinical management. The dynamics of ICP are more important than the absolute value at any given time point, but mean ICP exceeding 20–25 mmHg is usually treated aggressively. Algorithms based on data from patients with traumatic brain injury are applied also in other conditions. However, an understanding of the underlying pathophysiology allows adaptation of therapies to other pathologies. Typically, a three-staged approach is used, starting with restoration of systemic physiology, sedation, and analgesia. If these measures are insufficient, surgical options, such as drainage of cerebrospinal fluid or evacuation of mass lesions, are considered. In the absence of surgical options, stage 2 treatments are initiated, consisting of either mannitol or hypertonic saline. If these measures are insufficient, stage 3 therapies include hypothermia, metabolic suppression, or craniectomy.

## NEUROPATHOLOGY AND PATHOPHYSIOLOGY OF INTRACRANIAL HYPERTENSION:

### Essential principles and semiquantitative relationships

In most organs, perfusion pressure equals the difference between inlet (arterial) and outlet (venous) pressures. Intracranial outlet pressure differs in this respect from central venous pressure or cerebral venous sinus pressure, as the brain is surrounded by a rigid skull. Intracranial venous pressure is coupled to intracranial pressure (ICP). Therefore, cerebral perfusion pressure (CPP) is defined as follows (Miller et al., 1972):

$$\text{Mean CPP} = \text{mean arterial pressure} - \text{mean ICP}$$

One might expect that a rise in ICP would impede blood flow and cause ischemia. However, this is not the case, assuming autoregulation of cerebral blood flow (CBF) works correctly.

ICP is a complex modality derived from volumetric changes of intracranial blood, cerebrospinal fluid (CSF), brain parenchyma plus, in pathologic states, space-occupying lesions. Classically, the Monro–Kellie doctrine states that the sum of all intracranial volumes must remain constant. This is probably not 100% accurate, as the volume of the dural sac in the lumbar channel may expand slightly against internal vertebral venous plexuses.

ICP has dynamic (changing in time) and static (which may also change over time, but at a much slower rate) components. Both fast and slow changes in ICP are

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associated with a change of volume of arterial and venous blood, CSF, and brain tissue (edema formation) or other volume/space-occupying lesions (e.g., hematomas, tumors, or abscesses). It is important to distinguish between different components of ICP, as optimal clinical strategies to combat intracranial hypertension depend on which component is elevated. For example, arterial blood volume may raise ICP to very high levels in a matter of minutes and these elevations are known as plateau waves, which are secondary to massive, intrinsic arterial dilatation. Rapid, short-term hyperventilation usually reduces ICP in such cases. The CSF-circulatory component may elevate ICP in a scenario of acute hydrocephalus. In such cases, extraventricular drainage is particularly helpful. Venous outflow obstruction may also elevate ICP, and proper head positioning or investigation of possible venous thrombosis may be crucial. Finally, if ICP is elevated due to brain edema or a space-occupying lesion, osmotherapy or surgical intervention (including decompressive craniectomy) may be especially beneficial.

Dynamic components of ICP are mainly derived from the circulation of cerebral blood and CSF (the mathematic operator in the formula below should not be represented by a simple sum, therefore the generic symbol # is used):

$$\mathrm{ICP} = \mathrm{ICP}_{\mathrm{vascular}} \# \mathrm{ICP}_{\mathrm{CSF}}$$

The vascular component is difficult to express quantitatively. It is probably derived from the pulsation of the cerebral blood volume (CBV) detected and averaged by nonlinear mechanisms of regulation of cerebral blood and CSF volumes. More generally, multiple variables such as the arterial pressure, state of autoregulation, and cerebral venous outflow all contribute to the vascular component.

The CSF-circulatory component may be expressed using Davson's equation (Davson et al., 1970):

$$\mathrm{ICP}_{\mathrm{CSF}} = (\text{resistance to CSF outflow}) * (\text{CSF formation}) + (\text{pressure in sagittal sinus})$$

Any factor which, under physiologic (e.g., compression of jugular veins) or pathologic conditions (e.g., brain swelling, space-occupying lesion, or obstruction of CSF absorption) disturbs CSF circulation, may provoke an increase in ICP according to this formula.

## Cerebral autoregulation and pressure-volume compensation

Autoregulation concerns the relationship between CPP and cerebrovascular resistance. It is difficult to express quantitatively; therefore, only a pictorial representation is offered. Normally, resistive small arteries and arterioles dilate when CPP decreases. This helps to stabilize CBF within a wide range of CPP. This range is limited by maximal dilatation in the lower range of CPP and maximal vasoconstriction in the upper range (Lassen, 1964). These critical levels of CPP are respectively termed the lower and upper range of autoregulation. Thus, the relationship between CBF and CPP is nonlinear (Fig. 5.1). As CPP represents the pressure gradient

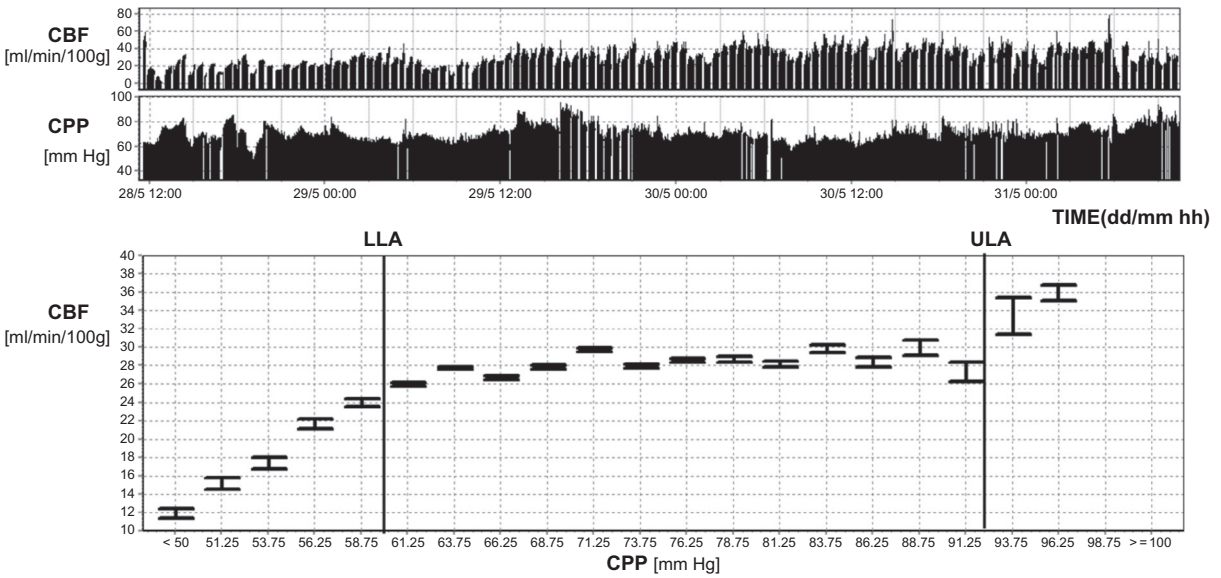


**Fig. 5.1.** Lassen's autoregulation curve illustrating the nonlinear relationship between cerebral blood flow (CBF) and cerebral perfusion pressure (CPP). CBF (using thermodilution probe; gaps in monitoring are related to periodic self-calibration cycles of the CBF monitor) and CPP (mean arterial blood pressure minus mean intracranial pressure) were monitored continuously over 3.5 days in a patient after severe traumatic brain injury. Values of CBF averaged within 2.5-mmHg intervals of CPP from 50 to 100 mmHg and 2 standard error bars were plotted. LLA, lower limit of autoregulation; ULA, upper limit of autoregulation.

acting along the cerebrovascular bed, it is an important factor in the regulation of CBF. Sufficient CPP is required to maintain stable CBF. The autoregulatory reserve is interpreted as the difference between the current mean CPP and the lower limit of autoregulation. Low CPP (beyond a threshold of 40–60 mmHg) may result in exhaustion of the autoregulatory reserve. However, this lower threshold may vary within broader limits, as much as 40–90 mmHg between individual patients. Policies to therapeutically maintain a high CPP are controversial. If the cerebral vessels are nonreactive, an increase in CPP may result in hyperemia, worsening of vasogenic edema, and a secondary increment in ICP. It is also probable that patient- and time-dependent variations in the level of CPP at which autoregulation functions properly may be considerable. Therefore, the threshold between adequate and inadequate CPP should be assessed individually and frequently, as it may change over time (Steiner et al., 2002).

Secondary to cerebral autoregulation is control of cerebral arterial blood volume. Increases or decreases in cerebrovascular resistance lead to its square-root-proportional rise or fall in blood volume in resistive arterioles; the volume of conductive arteries is thought to be more stable. This, in turn, may produce exponential changes in ICP due to the shape of the intracranial pressure–volume curve (Marmarou et al., 1978). It is a relationship between changes of net intracerebral volume and ICP (Fig. 5.2, left).

There is no consensus about which volume should be represented along the *x*-axis of this model of intracranial compliance. CSF volume can be changed using bolus or constant-rate injection, and can be investigated during diagnostic tests of hydrocephalus patients. When the volume of extra- or subdural balloons is studied experimentally, a linear relationship between volume and mean ICP is observed at low pressures. Above a certain ICP threshold (usually still within the range of normal ICP values), an exponential relationship exists:

$$p = (p_b - p_o) \cdot e^{E\Delta V} + p_o$$

where $p_b$ is baseline pressure and $\Delta V$ is an increase in volume; $E$ is elasticity of the system; and $p_o$ is an elusive reference pressure (some researchers consider it to be zero). This curve may also have an upper deflection point, seen when so-called critical ICP is exceeded (Löfgren et al., 1973). This curve may explain the relationship between the pulse amplitude of ICP and mean ICP. For ICP below the linear-exponential breakpoint on the pressure–volume curve, the pulse amplitude does not depend on ICP. The amplitude increases with ICP within the limits of the exponential portion of the pressure–volume curve. Above a critical pressure, it starts to decrease with further increments in ICP (Fig. 5.2, right).

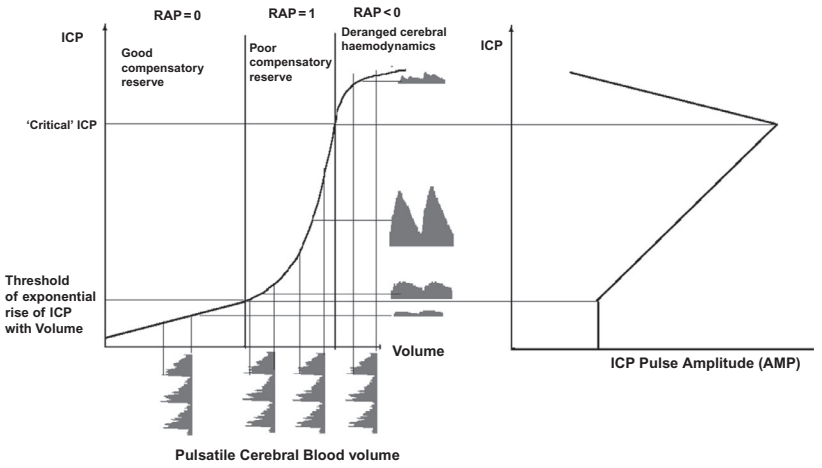


**Fig. 5.2.** Intracranial pressure–volume curve (left) and relationship between mean intracranial pressure (ICP) and amplitude of pulsatile component of ICP waveform (right). The pressure–volume curve has three zones (along the volume axis): first, ICP changes proportionally to changes of intracranial volume (good compensatory reserve). Then ICP increases exponentially with further rise in volume (poor compensatory reserve). Above certain critical ICPs, the pressure–volume curve deflects to the right, probably due to collapse of the cerebral arteriole bed. Accordingly (right panel), pulse amplitude of ICP is not dependent on mean ICP within the range of good compensatory reserve. Then it increases proportionately with increase in mean ICP. Above critical ICP, amplitude decreases when ICP rises further. RAP is the correlation coefficient between changes in pulse amplitude and mean ICP, and is a useful parameter for continuous monitoring of cerebral compensatory reserve.

## CLINICAL PRESENTATION AND NEURODIAGNOSTICS

### Methods of measurement

An intraventricular drain connected to an external pressure transducer is still considered to be the "gold-standard" method (Guillaume and Janny, 1951). ICP is measured as a fluid pressure and can be lowered by CSF drainage. ICP values monitored with an open drain are invalid in most cases. The transducer may be zeroed externally as often as necessary. However, with increasing duration of monitoring, particularly beyond 5 days, the risk of infection starts to increase, with an overall risk estimated to be about 5%. Insertion of the ventricular catheter may be difficult or impossible in cases of advanced brain swelling with compression of the lateral ventricles.

Modern intraparenchymal microtransducers (the most popular types include Camino, Codman, Raumedic, and Pressio-Sophysa) have lower infection rates than ventricular drains. The risk of clinically significant hemorrhage is less than 1% (Koskinen et al., 2013). These monitors have excellent metrologic properties, as revealed during bench tests (i.e., bandwidth and linearity). However, there is a drawback: uniformly distributed ICP can probably only be seen when CSF circulates freely between all its natural fluid pools, equilibrating pressure everywhere according to Pascal's law. With little or no CSF volume left due to brain swelling, the assumption of one uniform value of ICP is questionable. With the most common intraparenchymal probes, measured pressure may be compartmentalized, and not necessarily representative of equally distributed ICP. Moreover, brain tissue microtransducers do not actually directly measure a pressure, but rather a tensor of force (strain) within a tissue. Measurements may be dampened by a direction of this strain that is not necessarily perpendicular to the pressure-sensitive element. In addition, microtransducers can generally not be re-zeroed after insertion, and considerable zero drift may occur during long-term monitoring.

Contemporary epidural sensors are much more reliable than 10 years ago. But the question as to whether epidural pressure can express ICP with confidence and under all circumstances remains unanswered.

Lumbar CSF pressure is seldom measured in neurointensive care, although it could have a role in monitoring of spinal cord perfusion. This form of assessment of craniospinal dynamics is more often used in management of hydrocephalus and idiopathic intracranial hypertension. It is important to emphasize that reliable monitoring over at least a half-hour period, with recording of pressure and pulse amplitude, should be required in making clinical decisions. Instant, manometric assessment by measuring the height of the CSF column (as during a lumbar puncture) may be misleading, since CSF pressure may vary considerably over time (Fig. 5.3).

### Attempts to measure ICP and CPP noninvasively

It would be very helpful to measure ICP and CPP without invasive transducers. A number of techniques are available, but are still in a phase of technical or clinical

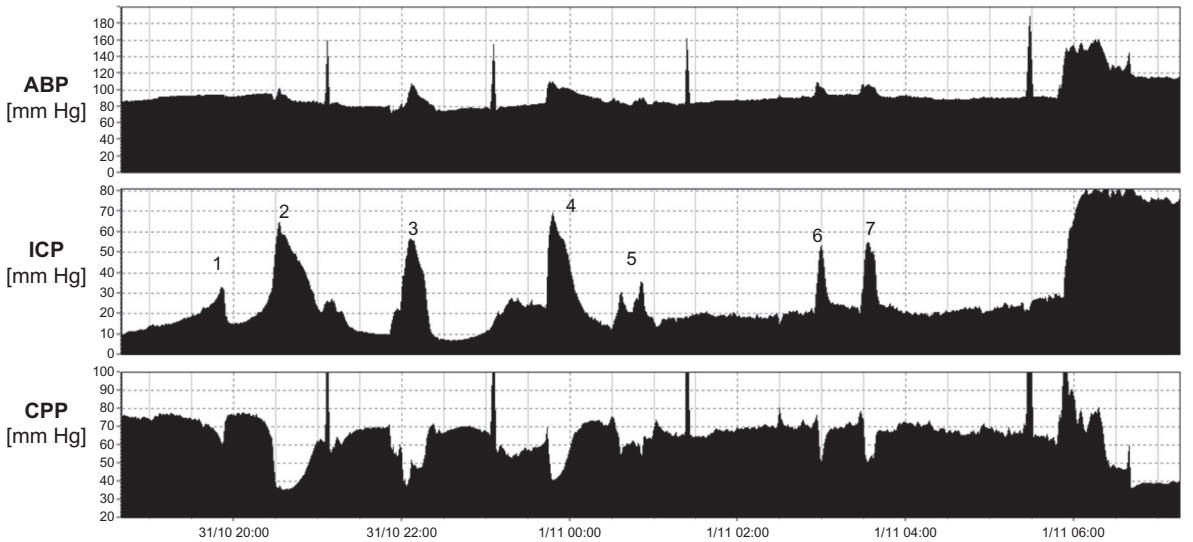


**Fig. 5.3.** "ICP is more than the number." Variations of intracranial pressure (ICP) after head injury. Note that baseline ICP was < 20 mmHg. ICP plateau waves are present with ICP > 60 mmHg. After seven spontaneous plateau waves, the eighth was sustained, with ICP > 70 mmHg and cerebral perfusion pressure (CPP) < 40 mmHg preceding the patient's death. ABP, arterial blood pressure.

evaluation (Robba et al., 2016). Aaslid's description of transcranial Doppler (TCD) sonography in 1982 permitted noninvasive, repeated (or even continuous) monitoring of one index of CBF (Aaslid et al., 1982). TCD measures flow velocity in branches of the circle of Willis, most commonly the middle cerebral artery (MCA). The compliant walls of this large artery can be compared to two physiologic pressure transducers. The pattern of flow within the MCA is modulated by transmural pressure (i.e., CPP), vascular tone affecting arterial compliance, and distal vascular resistance (which is also modulated by CPP). The trouble, as we remain ignorant about the calibration factor, is how stable it is over time, and how we should compensate for unknown nonlinear distortions.

There is a reasonable correlation between the pulsatility index of the MCA velocity and CPP after head injury, but absolute measurements of CPP cannot be done with an accuracy better than 30–35 mmHg. Others have suggested that critical closing pressure derived from flow velocity and arterial pressure waveform approximates ICP (Dewey et al., 1974). This is not accurate, as critical closing pressure is a sum of ICP and arterial wall tension. In a state of intracranial normotension (ICP less than 15 mmHg), wall tension on average amounts to 70–80% of a value of critical closing pressure.

Aaslid et al. (1986) suggested that an index of CPP could be derived from the ratio of the amplitudes of the first harmonics of the arterial blood pressure (ABP) and the TCD MCA multiplied by mean flow velocity. More recently, a method for the noninvasive assessment of CPP has been reported, derived from mean arterial pressure multiplied by the ratio of diastolic to mean flow velocity (Schmidt et al., 2001). This estimator can predict real CPP with an error of less than 10 mmHg for more than 80% of measurements.

A more complex method aimed at the noninvasive assessment of ICP has been introduced and tested by Schmidt et al. (1997). The method is based on the presumed linear transformation between arterial pressure and ICP waveforms. Coefficients of this transformation are derived from a database of real ABP and ICP recordings. A similar linear transformation is built, using the same database, between flow velocity and arterial pressure. Then, the model assumes a linear relationship between arterial pressure and flow velocity and between arterial pressure and ICP. Multiple regression coefficients are calculated. Finally, for each prospective study, ICP is calculated using an ABP to ICP transformation, formed by an ABP to flow velocity transformation and transposed using precalculated regression coefficients.

Comparison of the intraocular and intracranial portions of the ophthalmic artery TCD pulse waveform allows detection when intraocular pressure equilibrates ICP. With external compression of eyeball, such a measurement was demonstrated to be accurate (absolute accuracy ±5 mmHg). A prototype of this promising device is now under test in clinical practice (Ragauskas et al., 2012).

## Typical waves and trends observed in ICP monitoring

It is difficult to establish a universal "normal value" for ICP, as it depends on age, body posture, clinical conditions, and many other factors. In the horizontal position, the normal ICP in a healthy adult subject is estimated to be within the range of 7–15 mmHg. In the vertical body position, it is zero or slightly negative, but not lower than –8 mmHg (based on our own experience in patients suffering from hydrocephalus).

The definition of raised ICP depends on the specific pathology. In hydrocephalus, a pressure above 15 mmHg can be regarded as elevated. Following traumatic brain injury (TBI), anything above 20 mmHg is abnormal, and aggressive treatment usually starts above 25 mmHg. However, recent studies in TBI may justify individualization of elevated ICP, with a proposed definition being the level above which autoregulation of CBF starts to be affected (Lazaridis et al., 2014), which may vary from 15 to 40 mmHg.

It is important to recognize that ICP is "more than a number," and in most cases is time-varying. Averaging for at least 30 minutes is needed to calculate mean ICP. Instant values of ICP read at a once-per-hour interval are not accurate.

The ICP waveform consists of three components, which overlap in the time domain, but can be separated in the frequency domain (Fig. 5.4). The pulse waveform has fundamental and several higher harmonic components. The fundamental component has a frequency equal to the heart rate. The amplitude of this component is very useful for the evaluation of intracranial physiology. The respiratory waveform is related to the frequency of the respiratory rate (8–20 breaths/minute). "Slow waves" are not as precisely defined as in the original Lundberg thesis (Lundberg, 1960). All components that have a spectral representation within the frequency limits of 20 seconds to a 3-minute period can be classified as slow waves. The magnitude of these waves can be calculated as the square root of the power of the signal at the output of the digital filter.

In time domain, ICP pulse waveform usually presents three peaks: P1, P2, and P3 (Cardoso et al., 1983). The earliest peak, P1, called the percussion peak, is probably related to the immediate distension of arterial walls when arterial pressure pulse waveform reaches its systolic maximum. The two delayed peaks, P2 and P3, are probably related to an arterial blood volume increase, and

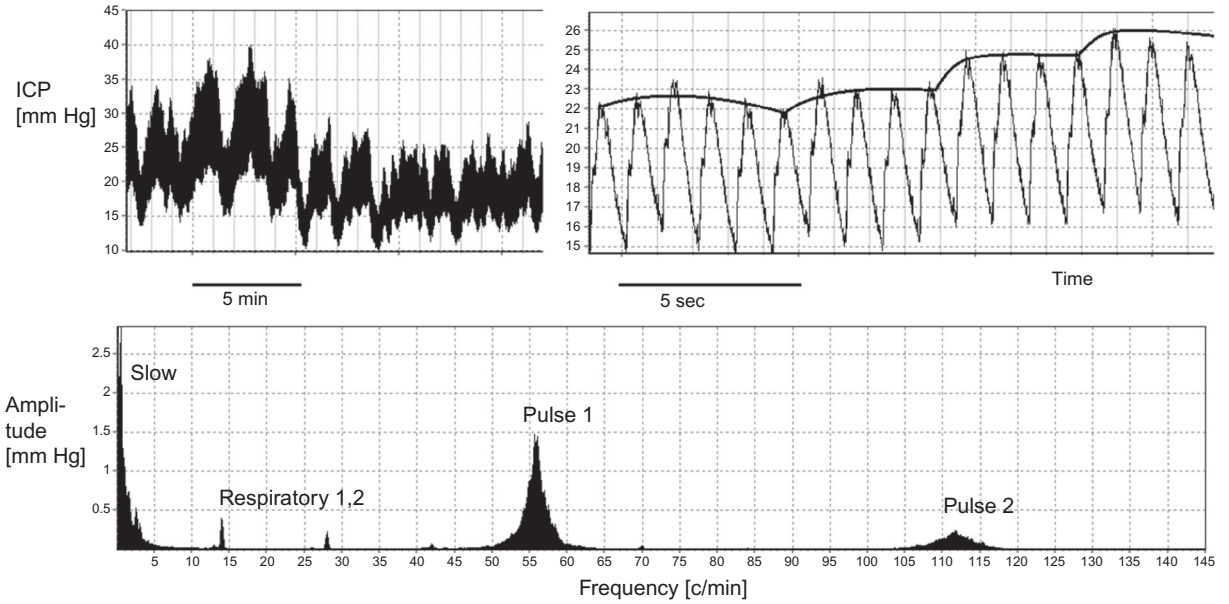


**Fig. 5.4.** Components of intracranial pressure (ICP) observed in the time domain (top) and frequency domain (bottom). Left upper panel illustrates slow vasogenic waves (0.005–0.05 Hz) associated with continuous vasomotor activity, controlling cerebrovascular resistance, cerebral blood flow, and cerebral blood volume. Right upper panel shows pulse waveform of ICP and slower wave. All these components are well separated in the frequency domain: the power spectrum of ICP signal shows slow, respiratory, and pulse waves (fundamentals and higher harmonics).

transport from conductive large cerebral arteries to resistive arterioles, influenced also by intracranial compliance, as described by the pressure–volume curve. Some investigators associate peak P3 with the dicrotic notch and second peak of ABP, which in turn may be attributable to closure of the aortic valve (Fig. 5.5).

There is much more information contained in the ICP waveform than only a time-averaged mean value. Computer-supported displays, with multiscale averaging, show a complexity of different ICP waveform components. When monitored continuously in the acute state (e.g., TBI, poor-grade subarachnoid hemorrhage (SAH), intracerebral hemorrhage), ICP waveforms may show specific fluctuations. They may have the character of repetitive waves or irregular transients. Already mentioned, "slow waves" (also referred to as "B waves," according to the Lundberg nomenclature) have a repetitive character. In the frequency domain, they fall into the bandwidth of 0.005–0.05 Hz. They are coherent with fluctuation of arterial blood volume assessed with near-infrared spectroscopy (NIRS) (Fig. 5.6). Sometimes they are synchronized with fluctuations of ABP. They are thought to be related to cerebral vasocycling, secondary to multiple mechanisms of CBF control, working together and sometimes synchronizing at these specific frequencies. Within faster spectra (around 0.1 Hz for a 10-second period), regular B waves may have a character of Mayer waves, initiated by fluctuations of arterial pressure brought about by oscillations in baroreceptor and chemoreceptor control systems. These waves produce autoregulatory-induced changes in CBV and are phase-shifted compared to responses seen in ICP. Both Mayer waves and classic B waves are important. In clinical practice, they may be used for monitoring a state of cerebral autoregulation (see below).

Lundberg A waves or plateau waves usually have a dramatic appearance. They produce increases of ICP up to 100 mmHg, lasting from minutes to hours, associated with an increase in ICP, loss of autoregulation, and reduction in CPP, CBF, and brain tissue oxygen tension ($P_{bti}O_2$) (Dias et al., 2014) (Fig. 5.7). A waves may be observed as one-off transients or occur in a cyclic manner (e.g., once every hour or every few hours). The mechanism of plateau waves has been explained elegantly by Rosner and Becker (1984) as a "vasodilatatory cascade." This vasodilatory cascade involves a "vicious cycle" or "positive-feedback loop" that is initiated by cerebral vasodilatation, which increases CBV and ICP, and decreases CPP, which in turn produces further cerebral vasodilation, eventually resulting in a crisis. This occurs especially when autoregulation is working and the pressure–volume curve is steep. A "vasoconstriction cascade" works under the same principle, but in the opposite direction, leading to termination of plateau waves. Although they usually terminate spontaneously after a few minutes, every plateau wave constitutes a potential ischemic insult. Plateau waves are relatively common, occurring in approximately 40% of TBI patients, and their appearance is not categorically

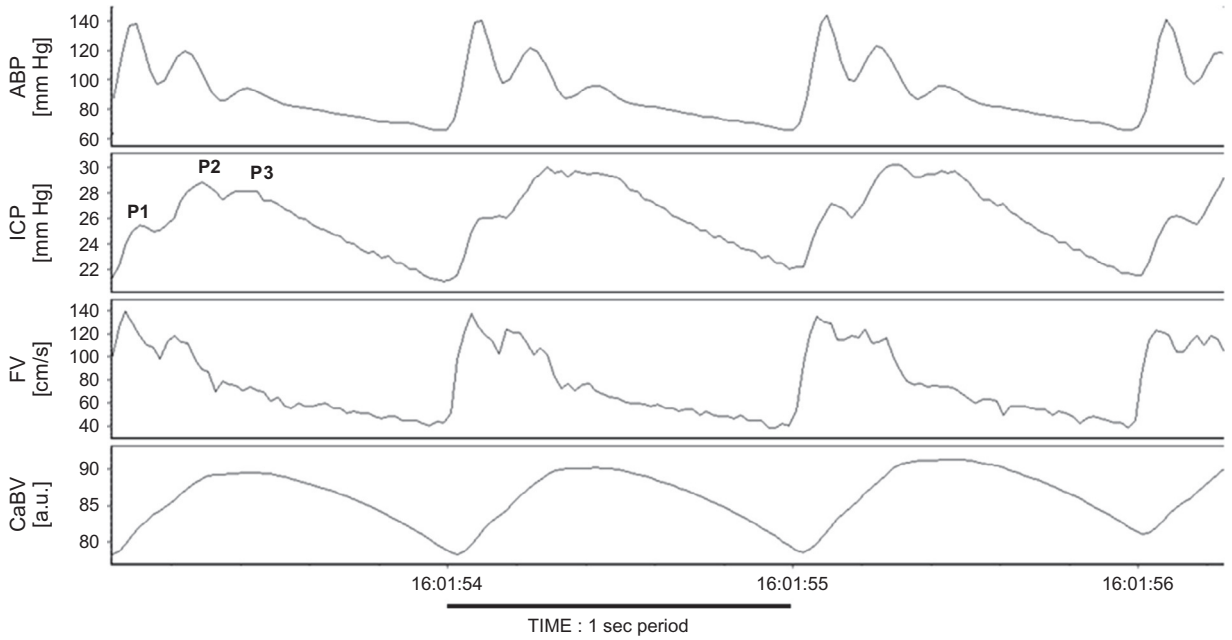


**Fig. 5.5.** P1, P2, and P3 are peaks of the intracranial pulse waveform. P1 is undoubtedly associated with systole of arterial blood pressure waveform. Flow velocity (FV) and cerebral arterial blood volume (CaBV) show recorded parameters of blood FV and CaBV using middle cerebral artery transcranial Doppler tracing. Peaks P2 and P3 are usually associated with peaks seen on CaBV – they are related to blood volume rise and its transmission through the linear pressure–volume curve (Fig. 5.2). ABP, arterial blood pressure; ICP, intracranial pressure.

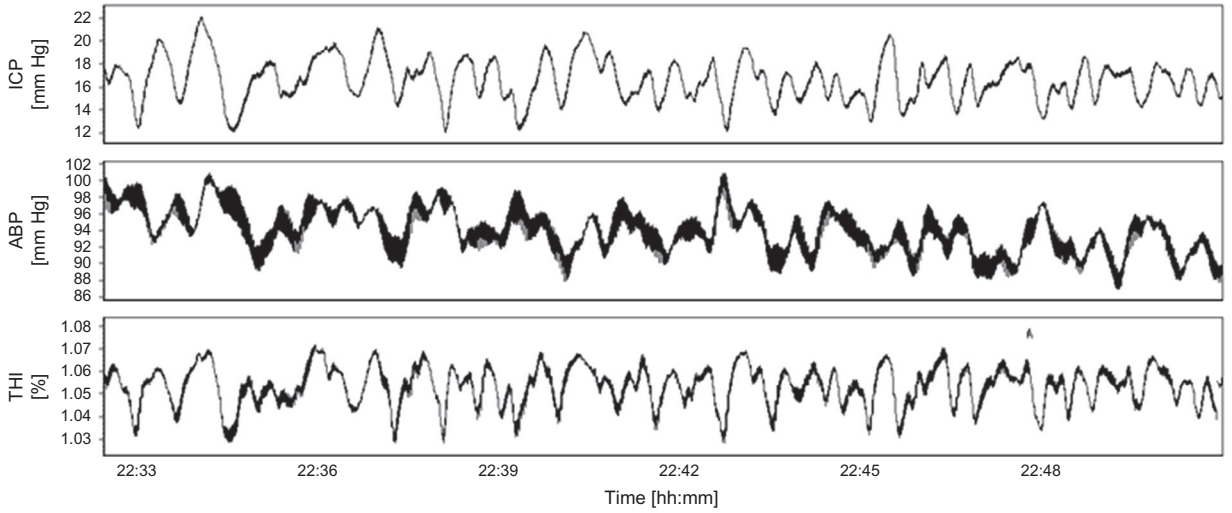


**Fig. 5.6.** Slow vasogenic waves of intracranial pressure (ICP) seem to be ideally synchronized with slow fluctuations of the total hemoglobin index (THI), recorded using near-infrared spectroscopy, which may be treated as surrogate index of changing (fluctuating) cerebral blood volume. ABP, arterial blood pressure.

associated with poor outcomes. However, longer duration of plateau waves, especially when exceeding 30 minutes, has been correlated with worse outcomes (Castellani et al., 2009). At the bedside, any intervention that induces cerebral vasoconstriction, such as transient hyperventilation or a bolus of hypertonic saline, may be sufficient to terminate longer plateau waves.

Low and stable ICP, with low waveform amplitude can be observed in TBI just after admission. More frequently, we see elevated and stable ICP (>20 mmHg). Many ICP waves and transients are related to changes in arterial pressure. If changes in ABP are deep and very fast, ICP usually changes in the same direction (Fig. 5.8A). If changes in ABP are slower, the direction

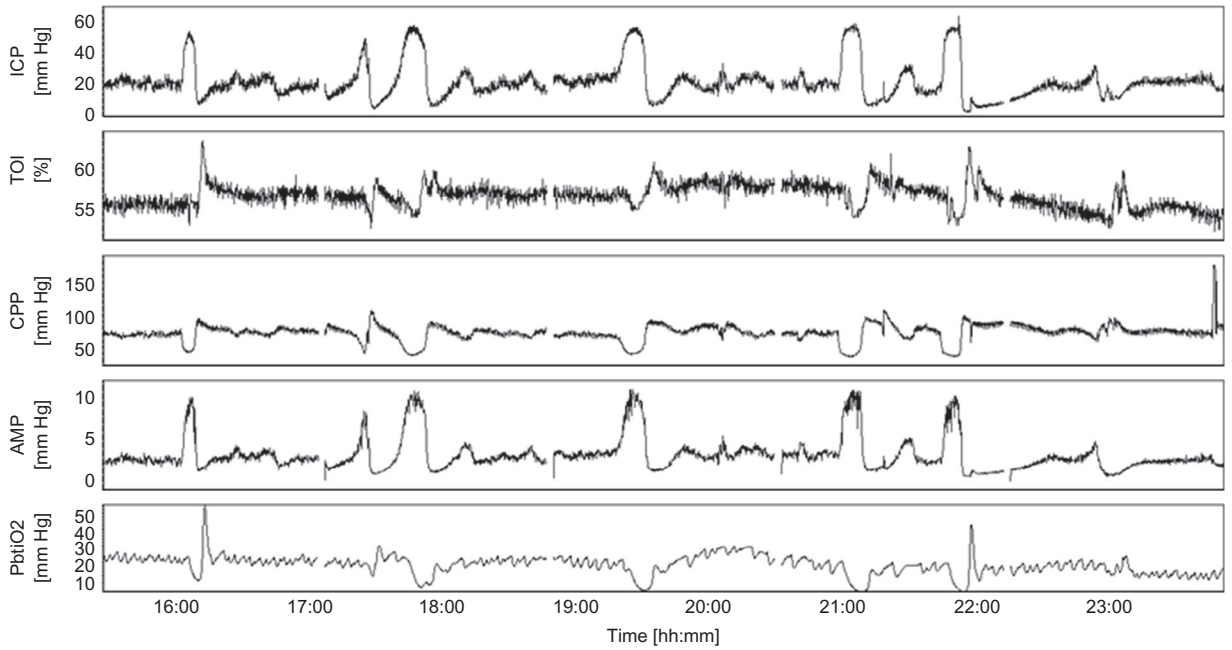


**Fig. 5.7.** Plateau waves of intracranial pressure (ICP) in multimodal monitoring (brain tissue oxygenation ($P_{bti}O_2$), near-infrared spectroscopy-derived tissue oxygenation index (TOI), cerebral perfusion pressure (CPP), and pulse amplitude of ICP tracing (AMP)). During each plateau wave, CPP, $P_{bti}O_2$, and TOI decrease. Cerebral blood flow (not monitored in this segment) also decreases and amplitude increases. Specific periods of hyperemia can be seen in $P_{bti}O_2$ and TOI after each plateau wave.

of changes in ICP depends on cerebrovascular reactivity. With reactive vessels, ICP changes in the opposite direction to changes in ABP. With nonreactive vessels the change is in the same direction (Fig. 5.8B). Elevations of ICP can be also seen during hyperemia. In this case, changes in ICP are in the same direction as changes in CBF or $P_{bti}O_2$, due to an increase in CBV (Fig. 5.8C). Episodes of refractory intracranial hypertension are sometimes accompanied by the characteristic upper breakpoint in the relationship between ICP pulse amplitude and mean ICP level (Fig. 5.8D).

## Cerebrovascular pressure reactivity and autoregulation

A useful ICP-derived modality is the pressure–reactivity index (PRx), which incorporates the philosophy of assessing cerebrovascular reactions by observing the response of ICP to slow spontaneous changes in ABP (Czosnyka et al., 1997). When the cerebrovascular bed is reactive, any change in ABP produces an inverse change in CBV and hence ICP. When reactivity is disturbed, changes in ABP are passively transmitted to ICP. Using computational methods, PRx is determined by calculating the correlation coefficient between 30 consecutive, 10-second time-averaged data points of ICP and ABP. A positive PRx signifies a positive gradient of the regression line between the slow components of ABP and ICP, which we hypothesize to be associated with passive behavior of a nonreactive vascular bed. A negative value of PRx reflects a normally reactive vascular bed, as ABP waves provoke inversely correlated waves in ICP.

PRx is strongly dependent on CPP. It increases with decreasing CPP, when the lower limit of cerebral autoregulation is breached (Brady et al., 2008). In clinical practice (TBI patients), PRx correlates well with indices of autoregulation based on TCD ultrasonography. It has been positively verified against the static rate of autoregulation with positron emission tomography-mapped CBF (Steiner et al., 2003). It can also be used to illustrate changes in cerebrovascular reactivity during phenomena containing a strong vascular component (e.g., loss of reactivity during plateau waves of ICP (Fig. 5.9A) or during refractory intracranial hypertension (Fig. 5.9B).

Averaged PRx is, besides age, Glasgow Coma Scale, and mean ICP, an independent predictor of outcome after TBI. A critical value of PRx, associated with increased mortality, is approximately +0.25. The prognostic implications of average value from +0.25 to 0 are uncertain, while an average $PRx < 0$ is associated with favorable outcome (Sorrentino et al., 2012).

## Optimal CPP and critical ICP

PRx plotted against CPP often shows a U-shaped curve (Steiner et al., 2003). The minimum of this curve theoretically indicates the midpoint between the lower and

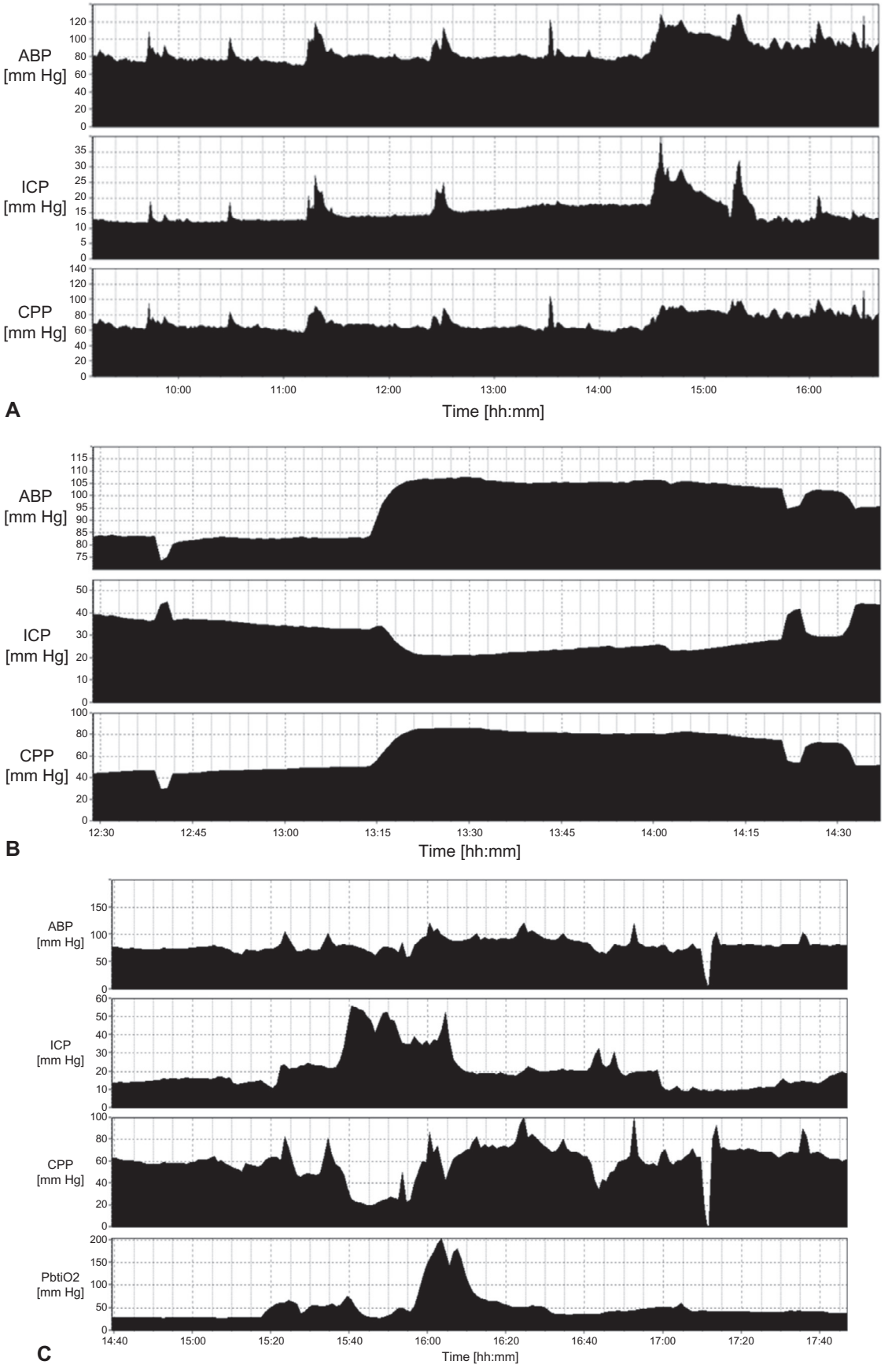
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**Fig. 5.8—Cont'd**

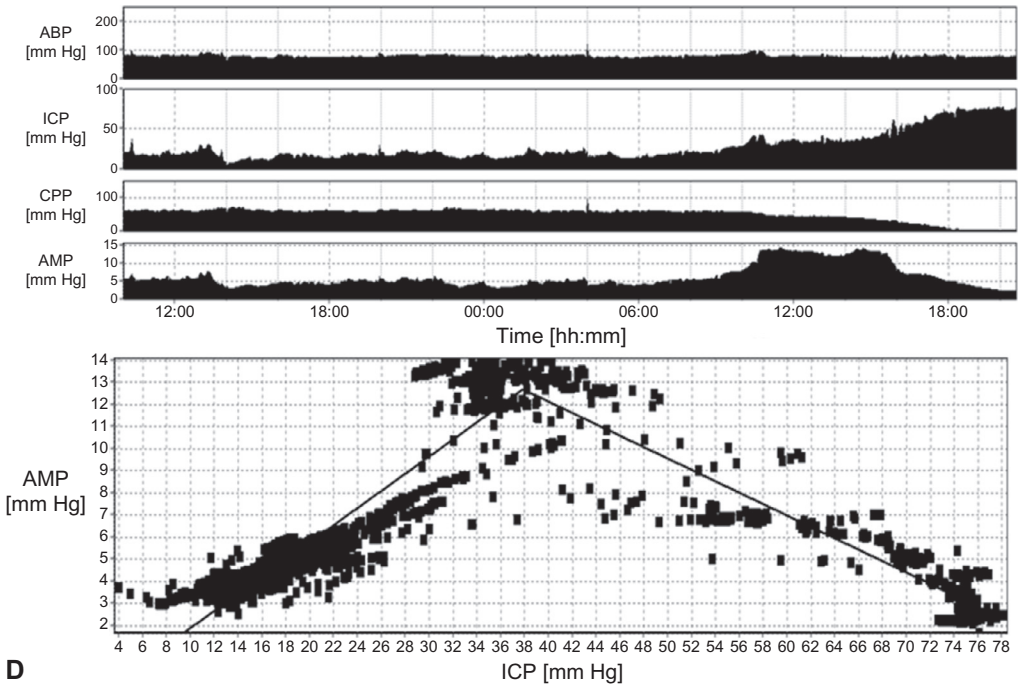


**Fig. 5.8—Cont'd** Typical intracranial pressure (ICP) patterns, seen in continuous monitoring. (**A**) ICP-arterial blood pressure (ABP) fast waves. Fast changes in ABP (faster than 0.1 mmHg/second, experimental data; Barzó et al., 1993) are always transmitted to ICP, regardless of the state of cerebral autoregulation. (**B**) ICP-ABP responses during slower transients in ABP. Association may be positive (disturbed autoregulation) or negative (functional autoregulation). In this case autoregulation was intact. (**C**) Hyperemic waves. Increases in ICP secondary to increase in cerebral blood flow. $P_{bti}O_2$ also increases with CBF and after the wave- reacting with temporary deep hyperaemia. (**D**) Refractory rise in ICP, related to uncontrollable increase in brain swelling, increasing ICP > 50 mmHg. Note the behavior of ICP pulse amplitude and an amplitude (AMP)–pressure line, presenting upper breakpoint associated with "critical ICP" at 36 mmHg. CPP, cerebral perfusion pressure.

upper breakpoint of the autoregulatory curve (Fig. 5.1). PRx increases below the lower limit of autoregulation (ischemia) and above the upper limit (hyperemia). This optimal CPP can be clinically estimated in real time by plotting and analyzing PRx–CPP curves in sequential 4-hour time windows (Fig. 5.10A). It has been demonstrated in retrospective studies that a greater discrepancy between the actual and optimal CPP is associated with worse outcomes in TBI patients (Steiner et al., 2002; Aries et al., 2012). This potentially useful methodology attempts to refine and individualize CPP-oriented therapy. Both too low (ischemia) and too high CPP (hyperemia and secondary increase in ICP) are detrimental. In one study, ischemia was associated with increased mortality, while hyperemia was associated with an increased rate of severe disability (Aries et al., 2012). Hence, it has been suggested that CPP should be optimized to maintain cerebral perfusion in the globally most favorable state. However, this concept still awaits multicenter prospective study. Retrospective analysis shows that optimal CPP may vary individually (from 60 to 100 mmHg) and may differ dramatically from guideline-fixed thresholds. Moreover, optimal CPP may vary over the course of postinjury intensive care. This same concept is probably valid in patients after poor-grade SAH (Bijlenga et al., 2010).

Several related methods have been suggested to detect and monitor optimal CPP with 1-minute averaged ICP and ABP values to calculate a so-called "long-PRx" (Santos et al., 2011) and using varying time windows for tracing an optimal CPP using the long-PRx versus CPP U-shaped curve (Depreitere et al., 2014).

PRx and the optimal CPP U-shape curve are only valid if pressure–volume compensatory reserve is normal or low. In patients with increased reserve (e.g., following decompressive craniectomy), detection is problematic. In such cases, instead of using PRx, the PAx index may be helpful (correlation between pulse amplitude of ICP and mean ABP: Radolovich et al., 2011). In addition, NIRS-based indices of cerebrovascular reactivity (see further remarks) have some potential value (Brady et al., 2008).

Per analogy to the U-shaped PRx–CPP curve, the relationship between PRx and ICP can be observed. Usually, PRx monotonically increases with rising ICP. The value

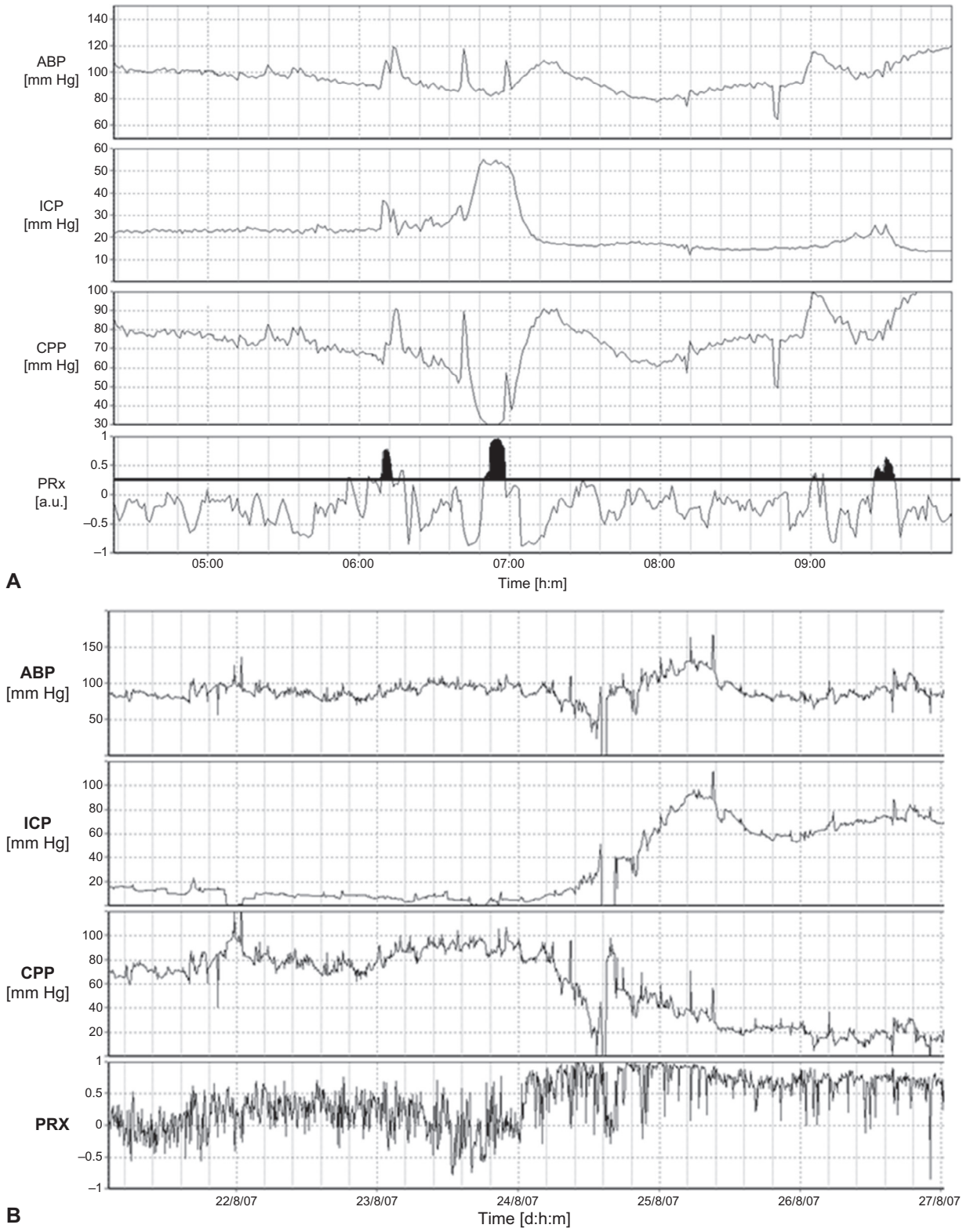


**Fig. 5.9.** Variability in pressure–reactivity index (PRx). (**A**) During plateau wave, PRx increased to nearly +1. (**B**) During refractory intracranial hypertension, PRx increased above 0.3, 12 hours before ICP increased above 20 mmHg, initiating a positive-feedback loop leading to final transtentorial herniation. ABP, arterial blood pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure.

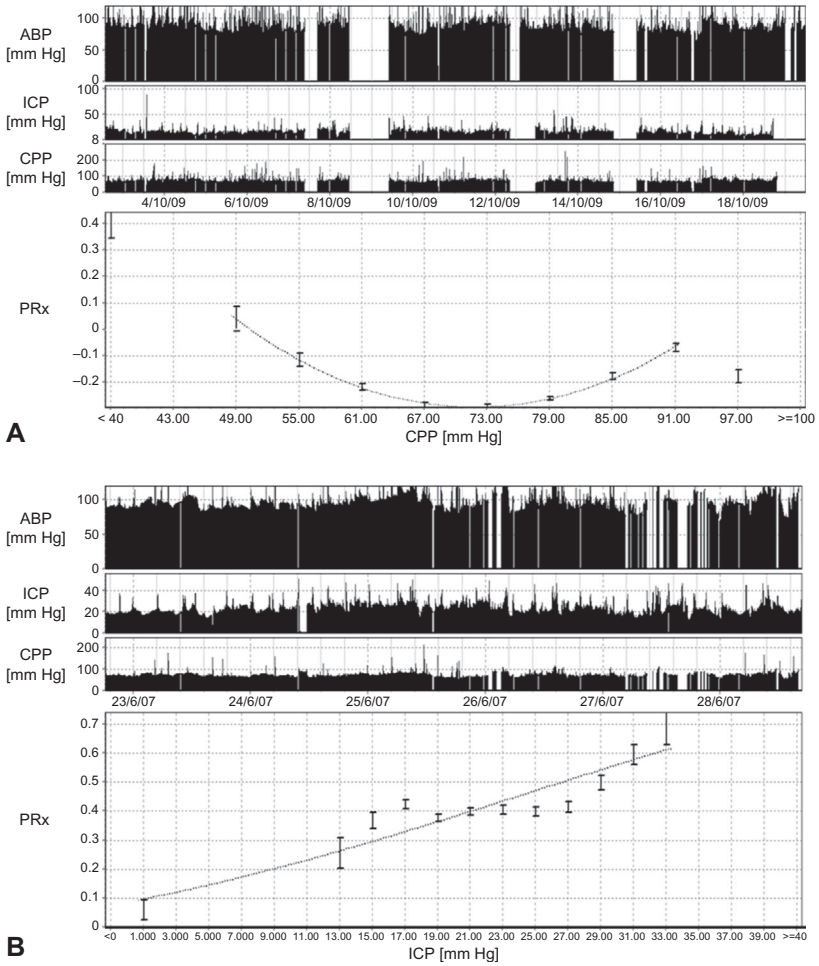


**Fig. 5.10.** It is not true that "one shoe number suits everyone." Therapeutic targets for cerebral perfusion pressure (CPP) and intracranial pressure (ICP) can be assessed individually. (**A**) Pressure–reactivity index (PRx) plotted against CPP, often usually a U-shaped curve. Minimum of this curve indicates midpoint between lower limit of autoregulation and upper limit of autoregulation (compare with Fig. 5.1). This is a hypothetic "optimal" value of CPP, which may substantially vary from patient to patient. (**B**) PRx plotted against ICP usually shows monotonically rising level. Value of ICP for which PRx increases above 0.3 is postulated as therapeutic threshold for elevated ICP. ABP, arterial blood pressure.

of ICP above which vascular reactivity is disturbed ($PRx > 0.25$) has been postulated as the individual critical ICP level (Fig. 5.10B). In a group of more than 300 patients after TBI, the critical threshold of ICP varied from 15 to 40 mmHg (mean 24 mmHg) (Lazaridis et al., 2014). Time with ICP greater than this individual critical ICP correlated with worse outcome, stronger than mean ICP, or fixed-threshold time integral of ICP.

## Pressure–volume compensatory reserve

Theoretically, compensatory reserve can be studied through the relationship between ICP and changes in volume of the intracranial space, known as the pressure–volume curve. The index RAP (correlation coefficient ($R$) between amplitude ($A$) and mean ICP ($P$)) can be derived by calculating the linear correlation between consecutive, time-averaged data points of amplitude and ICP (usually 30 averages are used) acquired over a reasonably long period to average respiratory and pulse waves (usually 10-second periods) (Czosnyka et al., 1994).

An RAP coefficient close to 0 indicates a lack of synchronization between changes in amplitude and average ICP. This denotes favorable pressure–volume compensatory reserve at low ICP (Fig. 5.2), where a change in intracranial volume produces little change of ICP. When RAP rises to +1, amplitude varies directly with ICP, indicating that the working point of the intracranial space shifts towards the right to the steep part of the pressure–volume curve, where compensatory reserve is low. Therefore, any further rise in volume may produce a rapid increase in ICP. Following TBI and subsequent brain swelling, RAP is usually close to +1. With any further increase in ICP, amplitude decreases and RAP values

fall below zero. This occurs when the cerebral autoregulatory capacity is exhausted and the pressure–volume curve bends sharply to the right as the capacity of cerebral arterioles to dilate further in response to a CPP decrement has reached its limit, and the arterioles tend to collapse passively (Fig. 5.2). This indicates terminal cerebrovascular derangement with a decrease in pulse pressure transmission from the arterial bed to the intracranial compartment. Monitoring of RAP in time after head injury may be helpful in understanding phenomena related to increase or decrease of brain edema, or when ICP level reaches the critical threshold for the integrity of CBF (Fig. 5.11).

## Other methods of ICP analysis

There are numerous controversies about how to best utilize and characterize the ICP signal. Even how to perform time averaging, is a source of disagreement. With its various waves and transients, ICP is "more than a number"; information about changes over time contains potentially useful clinical information. Averaging over the whole monitoring period gives us a single number, which is associated with outcome after TBI. The "dose of ICP" above a certain predefined threshold (Vik et al., 2008) produces a number with apparently stronger outcome association. Cumulative time above an individual threshold of critical ICP, above which pressure reactivity of cerebral vessels is impaired has been advocated as an even stronger outcome predictor (Lazaridis et al., 2014).

Another high priority in brain monitoring would be to develop a technique that helps predict decompensation or herniation. Rises of ICP can be anticipated within a 10–30-minute time horizon using sophisticated data analysis methods and machine-learning algorithms (Güiza et al., 2013).

Brain compliance monitoring (Piper et al., 1993), integrated into the so-called Spiegelberg monitor, was an interesting concept. It was based on direct measurement of the rise of ICP to repetitive expansion of a balloon placed in the intracranial space. Initial results were promising, but wider use was hampered by the invasive nature of the method.

Analysis of the pulse waveform of ICP, known as the high-frequency centroid, was based on evaluation of the power spectrum of a single-pulse ICP waveform and calculation of its power-weighted average frequency within the range of 5–15 Hz. The high-frequency centroid was demonstrated to decrease with increasing ICP. The centroid increases in the state of refractory intracranial hypertension where the blood flow regulation mechanism fails (Robertson et al., 1989).

Pulse transmission between arterial pressure and mean ICP has been investigated by various groups

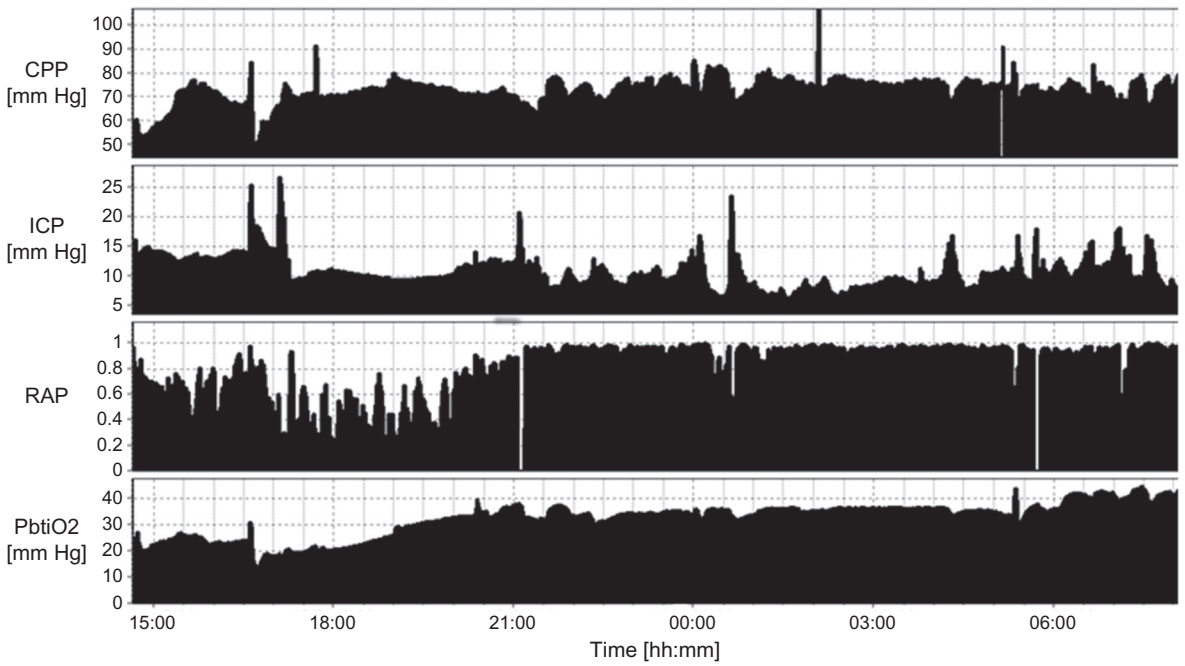


**Fig. 5.11.** Continuous monitoring of cerebrospinal compensatory reserve. Patient with traumatic brain injury monitored over first day after head injury. Compensatory reserve was good during initial period (RAP around 0.4) with gradual depletion of the reserve (RAP close to +1) later, due to brain swelling. Note that this is not automatically associated with a rise in mean intracranial pressure (ICP). CPP, cerebral perfusion pressure; RAP, correlation coefficient ($R$) between amplitude ($A$) and mean intracranial pressure ($P$).

(Piper et al., 1990). The utility of this approach depends upon assumptions about the linearity of the transmission model. Such assumptions are probably unrealistic, particularly in pathologic circumstances.

Morphologic analysis of pulse ICP waveform, with a sophisticated method of detection of peaks P1, P2, P3, and delineation of different curvatures and proportions between peaks and valleys (Hu et al., 2010), was proposed to detect ischemic brain insults, prediction of intracranial hypertensive episodes, and state of vascular wall tension.

Recently, the power of slow waves of ICP was reported to be predictive of outcome in patients suffering from intracranial hypertension following TBI. A low proportion of slow waves in the overall ICP dynamics was associated with a fatal outcome (Balestreri et al., 2005), highlighting a possible link of these events with cerebral autoregulation. Also, the complexity of long-term monitored ICP signals after TBI showed promising clinical correlation (Lu et al., 2012). Multiscale entropy measured as a global index was decreased in patients with worse outcome.

No matter how sophisticated new variables or outcome-predicting models become, perhaps the most useful tool at the bedside is a computerized display that presents the trends of multiple parameters over time. This gives an opportunity to react to a crisis situation, understand cerebral dynamics in multiple dimensions, and predict an optimal strategy for individual patients' care.

## Consequences of raised ICP observed with multimodal brain monitoring

### Cerebral oxygenation

Jugular venous bulb oxygen saturation ($S_jO_2$) may be monitored, preferably continuously, with an indwelling catheter. Single measurements of $S_jO_2$ are of little value given the many fluctuations during the day. The cerebral arteriovenous oxygen content difference should normally be 5–7 mL/dL. Values below 4 mL/dL may indicate cerebral hyperemia, whereas values above 9 mL/dL suggest global cerebral ischemia.

Transcutaneous, transcranial NIRS is a completely noninvasive method of assessing cerebral oxygenation. NIRS is a promising technique, but the scope for technologic refinement is still very large. While contamination of extracranial blood has been largely eliminated with spatial resolved spectroscopy (Lam et al., 1997), the unknown sample volume still poses problems. Moreover, fractioning between arterial, capillary, and venous blood sampling remains unknown. The cerebral oxygenation index is not always well correlated with $S_jO_2$. However, changes in NIRS-derived tissue oxygenation index, and slow waves of blood pressure or CPP have great potential to monitor cerebrovascular reactivity or cerebral autoregulation. Moreover, these data are useful to evaluate optimal CPP or optimal ABP in pediatric patients (Brady et al., 2009), neonates (da Costa et al., 2015), and adults (Zweifel et al., 2010).

Oxygen content of cerebral tissue is reactive to high ICP. However, $P_{bti}O_2$ may be provoked by other factors, such as hyperventilation, low ABP, microvascular problems, and mitochondrial dysfunction. Therefore, the specificity of the method is low. Moreover, the measurement covers only a limited area of the brain. Changes in cerebral oxygenation reactive to changes in ICP can be observed in multimodal monitoring of the injured brain (Fig. 5.7).

### Cerebral biochemistry/microdialysis

Limitations specific for brain oxygenation parenchymal probes can also be raised in the case of microdialysis. Measurement is extremely local and invasive, and the sampling rate is low (classically one per hour, although prototypes of fast microdialysis machines are now available). Measurement of the lactate/pyruvate ratio is an accepted marker of brain ischemia, with a proven correlation with outcome and cerebrovascular pressure reactivity (Timofeev et al., 2011). However, a high lactate/pyruvate ratio may also occur in the absence of ischemia, referred to as metabolic distress. Glutamate is an excitatory neurotransmitter that may rise in the extracellular space because of excessive release from neurons or impaired cellular uptake. Glycerol is a marker of membrane degradation. Each of these markers may have a patient-specific interaction with raised ICP.

### Cerebral blood flow

CBF can be monitored clinically using TCD (more global but nonquantitative) or a thermal diffusion method (quantitative but regional). Increments in ICP that lead to reductions in CPP below the lower limit of autoregulation produce a decrease in CBF. Both modalities are extremely useful for direct monitoring of cerebral autoregulation.

### Cerebral electric activity

The compressed electroencephalogram (EEG) is helpful in deciding whether cerebral metabolic depressants may be indicated in the treatment of intracranial hypertension. Such therapy will be less helpful if EEG activity is already markedly suppressed. During seizures, ICP is often transiently elevated due to increase in CBV (Vespa et al., 2007). Changes in ICP during cortical spreading depolarization are less specific, and either an increase or decrease in ICP may be observed (Rogatsky et al., 2003).

## HOSPITAL COURSE AND MANAGEMENT

### Treatment of raised intracranial pressure

Due to the many interactions between intracranial pathophysiology and extracranial variables, intensive care treatment of raised ICP is complex. Guidelines that classify the current evidence and make recommendations for a systematic approach are only available for TBI (Bratton et al., 2007a) and to a lesser extent for stroke (Broderick et al., 1999; Adams et al., 2003). However, depending on the dominant mechanism leading to intracranial hypertension, these algorithms may be adapted to suit the needs of patients with other forms of brain injury. Management algorithms usually intensify treatment in a stepwise fashion based on the results of neuromonitoring (Table 5.1). As clinical signs, particularly in unconscious patients on a ventilator, are not reliable, ICP should be monitored when intracranial hypertension is expected or when active treatment is started in unconscious patients. For TBI patients, there are guidelines for when monitoring of ICP is appropriate (Bratton et al., 2007b). For all other patients, the decision to insert monitors must be based on the computed tomography (CT) scan and the clinical presentation.

#### Treatment thresholds

Based on data from TBI patients showing worse outcome in patients with ICP above 20–25 mmHg, current guidelines recommend treating ICP if it exceeds 22 mmHg (Brain Trauma Foundation, 2016; Bratton et al., 2007c). Such a fixed threshold has been recently challenged, with many clinicians and researchers believing that ICP thresholds should instead be individualized (Lazaridis et al., 2014). Moreover, ICP therapy has side-effects and needs to be selectively targeted if it is not to be counterproductive.

#### First level of treatment intensity: prevention of intracranial hypertension

This section lists simple general medical and nursing care preventive measures and interventions that should be used in all patients who are either at risk of developing intracranial hypertension or are documented to have raised ICP. A summary of relevant factors that may increase ICP is shown in Table 5.2.

The position of the patient's head should minimize any obstruction of cerebral venous drainage. It is standard practice to raise the head of the bed to improve venous drainage from the brain. Direct measurement of global CBF and CPP suggests that elevation to 30° is safe, but CPP needs to be monitored carefully in individual patients. It is recommended to zero blood pressure transducers to the ear, which roughly corresponds to the foramen of Monro, rather than to the heart level. Relevant obstruction to venous outflow can also be caused by lateral head tilt, tight cervical collars, bands used for fixation of endotracheal tubes, thrombosis of the internal jugular vein, or inappropriately high levels of positive end-expiratory pressure (PEEP).

Maintaining adequate CPP is critical, and ICP treatment must consider CPP, as the two parameters are often closely linked. Low CPP will lead to ischemia, which may increase cytotoxic edema and, in turn, ICP. Moderately low CPP may also increase ICP due to cerebrovascular autoregulation. In patients with intact autoregulation, decreases in CPP will lead to vasodilatation, which may lead to an

*Table 5.1*

**Generic treatment algorithm for raised intracranial pressure (ICP)**

**First level of treatment intensity: correct factors that may increase ICP**

- Head-up positioning (maximum 30°)
- Maintain cerebral perfusion pressure 50–70 mmHg
- $Pa_{O_2} > 8$ kPa (60 mmHg), preferably > 10 (75 mmHg) or even 12 kPa (90 mmHg)
- Keep $Pa_{CO_2}$ normal (4.5–5.0 kPa; 34–38 mmHg)
- Sedation (propofol, fentanyl, neuromuscular blockers where required)
- Temperature: normothermia (36–37.5°C)

If ICP >20 mmHg, perform computed tomography scan and check for surgical treatment options (new or increasing space-occupying lesions that require surgical treatment or drainage of cerebrospinal fluid).

If there are no surgical options go to second level.

**Second level of treatment intensity: increased intensity of medical treatment**

- Mannitol 20% (e.g., 2 mL/kg up to three doses; caution if osmolality > or 320 mosmol/L)
- Hypertonic saline (e.g., 5% NaCl 2 ml/kg (do not repeat if Na >155 mmol/L)
- Consider reducing $Pa_{CO_2}$ (3.5–4.5 kPa; 30–34 mmHg) and establishing ischemia monitoring ($P_{bti}O_2$ or $S_jO_2$)
- Consider electroencephalogram and anticonvulsants if indicated
- Consider lowering body temperature to 35°C

If ICP > 20–25 mmHg despite these measures, go to third level.

**Third level of treatment intensity: therapies with controversial impact on outcome**

- Consider deeper hypothermia (target 33–34°C)
- Consider barbiturate coma (maintain cerebral perfusion pressure)
- Consider craniectomy

adapted from Patel HC, Menon DK, Tebbs S, Hawker R, Hutchinson PJ, Kirkpatrick PJ (2002). Specialist neurocritical care and outcome from head injury. Intensive Care Med 28 (5): 547–553. Epub 2002 Feb 14. PubMed PMID: 12029400.

*Table 5.2*

**Potential problems exacerbating raised intracranial pressure**

| |
|---|
| Technical problems |
| • Incorrect calibration of intracranial pressure and arterial blood pressure transducers and monitors |
| • Dysfunction/obstruction of external ventricular drainage |
| Obstruction of venous drainage from the head |
| • Inappropriate position of head and neck |
| • Constricting tape/tube fixations around neck |
| • Thrombosis of internal jugular vein |
| Cardiovascular problems |
| • Inadequate cerebral perfusion pressure |
| • Cerebral vasodilating drugs |
| Respiratory problems |
| • Hypercapnia |
| • Hypoxia |
| • Inappropriately high positive end-expiratory pressure |
| • Secretions, bronchospasm, coughing |
| Metabolic problems |
| • Fever |
| • Infusion of hypo-osmotic fluids |
| Intensive care unit management |
| • Insufficient sedation and/or analgesia |
| • Inappropriate muscle activity (e.g., shivering, straining) |
| Seizures |
| Developing or new intracerebral space-occupying lesions |

increase in ICP, particularly in patients with low intracranial compliance. In patients with impaired autoregulation, increases in CPP will be mirrored by increments in ICP. Excessively high CPP will increase vasogenic edema. There is no consensus as to the level of CPP that is appropriate in an individual patient. The current guidelines of the Brain Trauma Foundation recommend a CPP target range of 60–70 mmHg (Brain Trauma Foundation, 2016; Bratton et al., 2007d). Other studies suggest that the best, or optimal CPP level, should be individually set at the pressure where cerebral autoregulation works best (Steiner et al., 2002; Aries et al., 2012). Clinical proof of this concept is still awaiting appropriate prospective trials. Consideration must also be given to the effects of aggressive blood pressure augmentation on hemodynamics and gas exchange.

For pediatric TBI, specific guidelines with age-dependent thresholds are available (Adelson et al., 2003a, b). If CPP is too high and the decision is made to decrease blood pressure (e.g., in patients with hemorrhagic stroke or untreated ruptured subarachnoid aneurysms), it is important to use a drug that has no vasodilating effect on the cerebral vasculature.

Adequate ventilation is critical. There is no role for prophylactic hyperventilation in brain-injured patients, and the arterial partial pressure of $CO_2$ ($Pa_{CO_2}$) should initially be kept in the low normal range (4.5–5.0 kPa; 34–38 mmHg) (Bratton et al., 2007f). Hypoxia must be avoided, as it is one of the most important secondary insults to the injured brain. On the other hand, short-term hypocapnia can be safely used for terminating sudden increases in ICP during plateau waves. Waves longer than 30 minutes (with ICP > 40 mmHg) are detrimental and are clearly associated with poor outcome (Castellani et al., 2009). An arterial partial pressure of oxygen ($Pa_{O_2}$) below 8 kPa (60 mmHg) lowers arterial oxygen content enough to cause vasodilatation, and treatment algorithms for brain-injured patients typically aim for 10 kPa (75 mmHg) or more of $Pa_{O_2}$. There is a certain reluctance to use PEEP > 5 $cmH_2O$ in brain-injured patients, as the associated increase in intrathoracic pressure may impede venous drainage from the brain and raise ICP. However, in many patients with raised ICP, the gradient governing cerebral venous drainage is not the difference between arterial and central venous pressure, but the difference between arterial pressure and ICP. Accordingly, ICP will often not rise if PEEP remains lower than ICP. Nevertheless, this will have to be tested in an individual patient. Management must be adapted to optimize the effects of PEEP on ICP and $Pa_{O_2}$. The effects of supranormal levels of $Pa_{O_2}$ on the brain are controversial; this is an area of active investigation.

Fever not only increases cerebral metabolism and, hence, CBV, but also cerebral edema. Patients should be kept normothermic, by administration of acetaminophen, nonsteroidal anti-inflammatory drugs, provided there are no concerns regarding their effects on platelet function, active cooling, or a combination of these. With active cooling, attempts should be made to avoid shivering, as it may have deleterious effects on brain oxygenation and metabolism. Brain temperature is usually about 0.5°C higher than core temperature, although this may vary from one patient to another.

Severe hyperglycemia should be treated aggressively. There is considerable evidence that cerebral ischemia and infarction are made worse by hyperglycemia, and the use of glucose solutions is contraindicated unless there is significant evidence of benefit in a particular metabolic encephalopathy. Target values for serum glucose are typically in the range of 6–10 mmol/L (Oddo et al., 2008). Lower blood glucose values have been associated with insufficient glucose supply to the injured brain. If glucose-containing solutions are used, they should be administered as a solution with normal osmolality. Because of concerns about worsening cerebral edema by infusing fluids with low osmolarity, many units also avoid Ringer's lactate or similar balanced solutions in brain-injured patients, and instead use normal saline as the preferred maintenance fluid.

Adequate sedation and analgesia are important components of initial management, even in comatose

patients, and are essential to control ICP. Coughing, straining, and "fighting the ventilator" all lead to considerable increases in ICP. Sedation not only alleviates stress, but also suppresses cerebral metabolism, thereby improving the supply–demand balance. Propofol is widely used because of its cerebral vasoconstrictor effect and its relatively short duration of action, but care has to be taken to avoid hypotension, which is likely to occur in hypovolemic patients. Due to the possibility of the "propofol infusion syndrome," propofol is not commonly used for sedation in children. However, the syndrome has also been documented in adults, especially with prolonged usage (Kam and Cardone, 2007). Short-acting benzodiazepines, such as midazolam or lorazepam, may also be used for sedation. More recently, dexmedetomidine has been suggested as a useful sedative drug. However, at present there are insufficient data with regard to sedation of brain-injured patients (Grof and Bledsoe, 2010; Erdman et al., 2014).

Seizures have long been known to increase ICP, and have the potential to induce cerebral ischemia, due to an increment in cerebral electric activity and oxidative metabolism. Up to 25% of patients have been shown to have seizures in the first 7 days after TBI, and it has been estimated that more than 10% have nonconvulsive seizures that may only be detectable with continuous EEG monitoring (Varelas et al., 2013). Seizures must be treated aggressively, but may be difficult to recognize when patients are pharmacologically paralyzed. Some units use continuous EEG monitoring to detect occult seizures. Prophylactic administration of anticonvulsants has been advocated for cortical tumors, head-injured patients with acute subdural hematomas (evacuated and nonevacuated), depressed skull fractures, and penetrating missile injuries. Phenytoin can be administered intravenously, and is widely used, despite lingering concerns about potential long-term neuropsychologic effects. It is unknown whether modern antiepileptic drugs such as levetiracetam would be preferable. Many antibiotics, including carbapenems, fluoroquinolones, and metronidazole, are known to have proconvulsant properties.

Glucocorticoids such as dexamethasone are effective at reducing vasogenic edema around focal, relatively chronic, cerebral lesions. Patients deteriorating with a cerebral tumor or an abscess rapidly improve within as little as 24 hours of administration. However, steroids are harmful and should not be used in the management of raised ICP in patients with TBI (Roberts et al., 2004).

## Second level of treatment intensity

If, despite these measures, ICP exceeds 20 mmHg, more invasive treatments must be considered. If no CT scan has been performed recently, repeat imaging is advisable to exclude conditions that are amenable to surgical interventions. Apart from evacuation of expanding intracranial hematomas or other mass lesions, external ventricular drainage of CSF is a rapid procedure to reduce raised ICP. CSF should generally be removed gradually against a positive pressure of 15–25 $cmH_2O$ to avoid unrestrained drainage. In patients with diffuse brain swelling, the ventricles are small and not always easy to cannulate. Even when cannulation is successful, catheters in very tight ventricles may easily become blocked. CSF drainage is the optimal method of controlling intracranial hypertension in patients with SAH where the predominant cause is often a disturbance of CSF circulation. Biventricular drainage may be required for third ventricular lesions, which occlude both foramina of Munro. In the case of posterior fossa tumors, upward herniation may be precipitated if the supratentorial ventricles are drained too rapidly. In patients with a hemispheric mass lesion causing midline shift and contralateral hydrocephalus, drainage of that ventricle may make the shift worse. In certain patients, particularly those with communicating hydrocephalus, lumbar drainage of CSF may be an option (Munch et al., 2001).

## Hyperosmolar treatment: mannitol and hypertonic saline

On the second level of treatment, hyperosmolar therapy with mannitol or hypertonic saline is usually the first step. Intravenous mannitol is invaluable as a first-aid measure in a patient with brain herniation as a result of raised ICP (Wakai et al., 2013). In practice, mannitol tends to be given as an intermittent bolus (2 mL/kg of a 20% solution over 15–20 minutes) whenever individual patients' ICP rises significantly above the threshold of 20–25 mmHg. Effects of mannitol last for up to 4 hours. Since osmotic diuresis may lead to hypovolemia, it is crucial to avoid volume depletion and latent hypotension, with careful attention to fluid balance. Mannitol has traditionally not been recommended once the plasma osmolality exceeds 320 mosmol/L, although this opinion is not based on high-quality data. Repeated doses of mannitol should generally not be given unless ICP is monitored.

Hypertonic saline solutions ranging from 1.6 to 29.2% have been used. Commonly recommended regimens include 2 mL/kg 5% NaCl, 250 mL of 7.5% NaCl, or 30–60 mL of 23.4% NaCl. The action of hypertonic saline may be augmented if colloids are administered at the same time. A duration of action of approximately 2 hours has been reported (Lazaridis et al., 2013). There is more than one mechanism of action. Hypertonic saline has an osmotic effect, which leads to removal of water

from the interstitial and intracellular compartment in areas with intact blood–brain barrier. In addition, there is an increase in regional CBF, most likely caused by a reduction in size of swollen endothelial cells. Hypertonic saline should generally no longer be used once plasma Na has reached 155 mmol/L. It is preferred that it be given through a central venous line due to its high osmolarity.

### Hyperventilation

Hyperventilation reduces ICP via a reduction of CBV. Unfortunately, hyperventilation also causes a reduction in CBF and, therefore, the main concern when patients are hyperventilated is the possibility of inducing cerebral ischemia. Prophylactic hyperventilation of TBI patients to a $PaCO_2$ of 3.4 kPa (26 mmHg) has been shown to be detrimental to outcome and aggressive hyperventilation to below a $PaCO_2$ of 3.5 kPa is therefore not recommended. There is an ongoing controversy about the risk of moderate hyperventilation ($PaCO_2$ 4.5–3.5 kPa; 34–26 mmHg) to cause ischemia in brain injury. Nevertheless, it is recommended to monitor cerebral oxygenation if moderate hyperventilation is used. Our means of monitoring critical reductions of CBF during hyperventilation are very limited. $S_{jv}O_2$ or $P_{bti}O_2$ monitors are frequently used to avoid overaggressive hyperventilation (Bratton et al., 2007e). There is growing awareness that hyperventilation should be used sparingly, primarily to treat ICP plateau waves and herniation. For TBI patients, the Brain Trauma Foundation guidelines recommend moderate hyperventilation as a short-term measure only, except when other forms of medical ICP treatment have failed (Bratton et al., 2007f).

### Third level of treatment intensity – therapies with controversial impact on outcome

If the second-level measures are inadequate to control ICP, therapy will again be intensified. The three options are hypothermia, barbiturate coma, and craniectomy. All these treatment options have relevant side-effects, and there is no clear evidence that they improve patient outcome.

### Hypothermia

Hypothermia exerts many theoretic beneficial effects on the injured brain and can be used to lower ICP (Polderman, 2004a). In contrast to sedation, which only reduces electric activity, hypothermia also reduces the metabolic demand caused by the processes needed to uphold structural integrity. Typically, temperature is not reduced beyond 33–35°C. Hypothermia can be achieved by surface cooling or with various forms of heat exchangers that are inserted into a large vein, possibly combined with initial rapid infusion of cold fluids. Patients may shiver when cooled, and may require neuromuscular blockade.

The Eurotherm trial recently demonstrated that earlier use of hypothermia (administered as a second-level therapy prior to consideration of osmotic agents) to a target temperature of 32–35°C is harmful, even if it did reduce the need for other third-level therapies (Andrews et al., 2015). As such, hypothermia should not be applied prophylactically, and should only be used as a rescue therapy when other treatments have been ineffective. The safety of maintaining temperature below 35°C has been questioned by these results.

When it is used, the question of how long hypothermia should be maintained has not been answered definitively. One approach is to cool the patient until ICP is consistently less than 20 mmHg and then to increase temperature slightly (e.g. 0.1°C/hour) and observe the response of ICP. Too rapid rewarming may be detrimental to an injured brain. For SAH, a trial to prove the efficacy of intraoperative hypothermia (IHAST) was also negative. Hypothermia has relevant side-effects: a significantly higher rate of pneumonia, electrolyte abnormalities, and thrombocytopenia when compared to normothermic patients (Polderman, 2004b).

### Metabolic suppression – barbiturate coma

Hypnotic agents such as propofol or barbiturates depress cerebral oxidative metabolism and, hence, lower CBF, CBV, and ICP. Barbiturates are commonly used for this purpose. Cerebral electric activity and normal coupling mechanisms between metabolism and flow must be present if barbiturates are to lower ICP. Flow metabolism coupling mechanisms may be assessed by the cerebrovascular response to carbon dioxide, and barbiturates are only effective if some $CO_2$ reactivity is retained. For thiopental, repeated boluses of 250 mg (up to 3–5 grams) are recommended, followed by an infusion of 4–8 mg/kg/h. Pentobarbital is initiated with a loading dose of 10 mg/kg, possibly followed by 5 m/kg/h for 1–3 hours, and then an infusion of 1–5 mg/kg/h. Barbiturate therapy should be targeted to a predefined EEG burst suppression ratio. Unfortunately, all agents that depress cerebral metabolism have adverse effects. For propofol and barbiturates, the most relevant effect is systemic hypotension, which is often exacerbated by hypovolemia. Synergy with even moderate hypothermia may be helpful, provided mean arterial pressure is maintained. After initial reports of the effectiveness of short-acting barbiturates in lowering ICP after head injury, several trials have failed to show any significant improvement in outcome, or reduction in the

number of patients dying with intracranial hypertension (Roberts and Sydenham 2012). Elimination of barbiturates takes several days, and an unconfounded neurologic assessment will not be possible during this time.

### Decompressive craniectomy

Decompressive craniectomy (i.e., removal of a bone flap) has become more popular as a treatment for refractory intracranial hypertension. Although there is a place for decompressive craniotomy following head injury, there is also the potential to do harm. Hemicraniectomy is effective in the treatment of large ischemic strokes in the region of the MCA (Vahedi et al., 2007). In selected patients with raised ICP following aneurysmal SAH, a benefit of craniectomy has also been suggested (Holsgrove et al., 2014). In patients with TBI, the data are unclear, as it has not been possible to show that craniectomies improve outcomes (Cooper et al., 2011; Hutchinson et al., 2016). Due to the insufficient evidence, craniectomy is often only performed when medical treatment, including hypothermia and/or barbiturate coma, has failed.

### Treatment of acute exacerbations of intracranial pressure

Patients who are rapidly deteriorating or are unconscious require immediate resuscitation followed by a diagnostic CT scan. As initial treatment goals before invasive monitoring are established, a systolic blood pressure of more than 90 mmHg and a peripheral arterial oxygen saturation >90% are required. Patients with a Glasgow Coma Scale score ≤8 need to be intubated and ventilated to protect their airway prior to scanning. In this particular circumstance, hyperventilation may be used as a temporizing measure. An intravenous bolus of mannitol 20% (2–5 mL/kg over 15 minutes) may be required if there is evidence of transtentorial herniation, such as unilateral pupillary dilatation. Ventricular dilatation necessitates immediate ventricular drainage, sometimes bilateral if the lesion is midline. Significant space-occupying lesions require surgical intervention. If an intracranial tumor or abscess is identified as the cause of intracranial hypertension, dexamethasone (initial dose 10 mg IV bolus) should be given.

## Is ICP monitoring useful?

The continuous measurement of ICP is an essential modality in most brain monitoring systems. After decades of enthusiastic attempts to introduce new modalities for brain monitoring (e.g., $P_{bti}O_2$, microdialysis, CBF, TCD, $S_jO_2$), it is obvious that ICP measurement is robust, only moderately invasive, and can be realistically conducted in regional hospitals.

Clearly, the treatment of raised ICP has side-effects. It has never been shown conclusively that monitoring ICP and using treatment protocols such as the one discussed above, based on monitoring, improve outcome. Indeed, the recent publication of the BEST TRIP trial (Chesnut et al., 2012) has fueled further controversy regarding the usefulness of monitoring of ICP and its treatment in head-injured patients. To put the results of this important trial into perspective, a consensus statement of 23 clinically active, international opinion leaders in TBI management has been published (Chesnut et al., 2015). It was concluded that the BEST TRIP trial: 1) studied protocols, not ICP-monitoring *per se*; 2) applies only to those protocols and specific study groups and should not be generalized to other treatment approaches or patient groups; 3) strongly calls for further research on ICP interpretation and use; 4) should be applied cautiously to regions with much different treatment milieu; 5) did not investigate the utility of treating monitored ICP in the specific patient group with established intracranial hypertension; 6) should not change the practice of those currently monitoring ICP; and 7) provided a protocol, used in non-monitored study patients, that should be considered when treating without ICP monitoring.

In addition to these statements, we would re-emphasize that "ICP is more than a number," and end-hour instant values of ICP read from the bedside monitor are not an efficient modality to manage intracranial hypertension.

A previously published audit (Patel et al., 2005) showed substantially lower mortality in neurosurgical centers where ICP is usually monitored versus general intensive care units where it is not monitored. However, the availability of ICP monitoring is not the only difference between neurosurgical and general intensive care units that might explain the difference in mortality after head injury.

The ICP waveform contains valuable information about the nature of cerebrospinal pathophysiology. Autoregulation of CBF and compliance of cerebrospinal system are both expressed in ICP. Methods of waveform analysis are useful both to derive this information and to guide the management of patients.

The value of ICP in acute states such as TBI, poor-grade SAH, and intracerebral hematoma depends on a close link between monitoring and therapy. CPP-oriented protocols, osmotherapy, and the Lund protocol cannot be conducted correctly without ICP guidance. A decision about decompressive craniectomy is often supported by the close inspection of the trend of ICP

*Table 5.3*

**Summary of management of raised intracranial pressure (ICP) in patients other than those suffering from traumatic brain injury**

Conscious patient
- Diagnosis based on suspicious history (new headaches, nausea, vomiting, visual blurring/obscurations, diplopia) with or without papilledema on examination

Any patient with drowsiness or fluctuation in level of consciousness merits emergency referral to neurosurgery
- Definitive investigation by CT scan combined with general medical assessment

Never perform a lumbar puncture in a patient with suspected raised ICP, even if papilledema is absent, until a CT scan has shown no evidence of either a mass lesion or diffuse brain swelling
- Management depends on the presumptive diagnosis after CT and proceeds in consultation with neurosurgery:
  - Tumors: dexamethasone, tissue diagnosis and excision, radiotherapy, chemotherapy, as appropriate
  - Abscess: aspiration/excision
  - Hydrocephalus: CSF shunt with or without prior ICP monitoring and CSF infusion studies
  - Idiopathic intracranial hypertension: referral to combined neurosurgery/neuro-ophthalmology service for CSF monitoring, diuretics/steroids/diet for mild cases. Venous stenting in case of active stenosis (Higgins et al., 2002), CSF shunt/optic nerve sheath fenestration for severe/refractory cases

**Unconscious patient**

Emergency resuscitation for patients no longer obeying commands
- Intubation and ventilation
- Intravenous mannitol (2 mL/kg) if signs of herniation present
- Definitive investigation:
  - CT scan in combination with general medical assessment
- Consider ICP monitoring

Management of raised ICP
- Institute specific treatment for etiology
- Mass lesions: surgical evacuation
- Hydrocephalus: external ventricular drainage
- Cerebral edema and brain swelling:

  Dexamethasone for tumors only, not for trauma, consider for abscesses
- Use generic algorithm (Table 5.1) where and as applicable

CT, computed tomography; CSF, cerebrospinal fluid.

and, preferably, by information derived from its waveform. In encephalitis, acute liver failure, and cerebral infarction after stroke, ICP monitoring is used less commonly. However, an increasing number of reports highlight its importance, including noninvasive ICP monitoring methodology.

In summary, despite a lack of clear evidence, the recommendation to treat raised ICP > 20–25 mmHg is standard practice. However, it is important to realize that treatment of raised ICP is associated with a multitude of potential complications, and stringent clinical judgment is required, particularly when guidelines that are based on data from TBI are adapted for patients with other forms of brain injury. A possible approach to the patient suffering from disease other than TBI is shown in Table 5.3.

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