Published in final edited form as:

Acta Neurochir Suppl. 2013 ; 118: 205–209. doi:10.1007/978-3-7091-1434-6_38.

Microvascular Shunts in the Pathogenesis of High Intracranial Pressure

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Abstract

Hyperemia in the infarcted brain has been suggested for years by “red veins” reported by neurosurgeons, shunt peaks in radioactive blood flow clearance curves, and quantitative cerebral blood flow using stable xenon CT. Histological characterization of infarcted brain revealed capillary rarefaction with prominent microvascular shunts (MVS). Despite abundant histological evidence, the presence of cerebrovascular shunts have been largely ignored, perhaps because of a lack of physiological evidence demonstrating the transition from capillary flow to MVS flow. Our studies have shown that high intracranial pressure induces a transition from capillary to microvascular shunt flow resulting in cerebral hypoperfusion, tissue hypoxia and brain edema, which could be delayed by increasing cerebral perfusion pressure. The transition from capillary to microvascular shunt flow provides for the first time a physiological basis for evaluating the optimal cerebral perfusion pressure with increased intracranial pressure. It also provides a physiological basis for evaluating the effectiveness of various drugs and therapies in reducing intracranial pressure and the development of brain edema and tissue hypoxia after brain injury and ischemia. In summary, the clear-cut demonstration of the transition from capillary to MVS flow provides an important method for evaluating various therapies for the treatment of brain edema and loss of autoregulation.

Keywords

Brain edema; Cerebrovascular shunts; Cerebral perfusion pressure; Intracranial pressure; Microvascular shunts; Rats

Introduction

Determination of the critical cerebral perfusion pressure (CPP) to maintain adequate cerebral blood flow (CBF) has been historically defined by definition of the CBF autoregulation curve by progressive reduction of CPP by phlebotomy to decrease arterial pressure [1, 2]. Thus defined, the critical CPP was determined to be approximately 60 mmHg. However, clinically, compromised CPP is often due to an increase in intracranial pressure (ICP) rather than a decrease in arterial pressure. Hence, the question arises as to whether the critical CPP

Conflict of Interest We declare that we have no conflict of interest.

measured by decreasing arterial pressure is equivalent to that obtained by increasing ICP. Comparisons were made between the two methods in the CBF autoregulation curve, which showed that the critical CPP determined by increasing ICP was actually lower and about 50 % lower at 30 mmHg compared with 60 mmHg [1, 2]. The lower critical CPP suggests that CBF autoregulation was better preserved when CPP was decreased by increasing ICP. However, we hypothesized that the higher CBF maintained at a lower CPP with increasing ICP was caused by pathologically maintained CBF due to microvascular shunting, resulting in an apparently lower critical CPP.

To test the hypothesis, we measured flow velocity in capillaries (3–8 μm in diameter) and larger microvessels (9–45 μm), NADH (hypoxia), Doppler flow, and water content with decreasing CPP by either increasing ICP or decreasing arterial pressure [3].

Materials and Methods

The procedures used in these studies have been previously described [3]. Briefly, male Sprague–Dawley (SD) rats weighing between 300 and 350 g were intubated and mechanically ventilated on 2 % isoflurane/30 % oxygen/70 % nitrous oxide. Measured variables were: microvascular red blood cell (RBC) flow velocity; nicotinamide adenine dinucleotide (NADH) fluorescence as an indicator of tissue oxygenation; cortical Doppler flux and cortical water content. Rectal and temporal muscle temperatures, arterial pressure, and intracranial pressure were continuously monitored.

Velocity of RBC flow was measured using in vivo two-photon laser scanning microscopy (2PLSM) of microvessels in the parietal cortex. Blood plasma was labeled with fluorescein isothiocyanate dextran (20 kDa) in physiological saline (5 % wt/vol). The selection of capillary microvessels was based on tortuosity, degree of branching, and diameters ranging from 3 to 8 μm . Multiple recordings were made from the same vessel and mean microvessel RBC velocity and SEM were determined. Approximately 100 microvessels were scanned at each CPP and the diameter of each scanned vessel was measured. Tissue NADH autofluorescence was measured by 2PLSM imaging at each CPP level. Cortical Doppler flux was performed using a single-fiber surface Doppler probe measuring 0.8 mm in diameter (DRT4; Moor Instruments, Axminster, UK). Parietal cortex water content was measured by wet/dry weight.

Results

Reduction of CPP by a progressive increase in ICP caused a shift in MVS flow relative to CAP flow, whereas decreasing CPP by decreasing mean arterial pressure did not (Table 1). Decreasing CPP by increasing ICP decreased the percentage of capillaries (<1.0 mm/s), whereas the percentage of microvessels (>1.0 mm/s) increased with decreasing arterial pressure. The ratio of CAP/MVS also decreased with increasing ICP, whereas the opposite was true with decreasing arterial pressure. These results suggest that the reduction in the critical CPP when ICP was increased in the CBF autoregulation curve was due to a pathologically maintained elevated CBF as a result of microvascular shunting. The distribution of microvascular diameter with increasing ICP versus decreasing mean arterial

pressure (MAP) to reduce CPP also verifies the fact that the increase in flow velocities with increasing ICP is attributable to flow through larger “shunts” or arterioles and not capillaries measuring 3–7 μm in diameter (Fig. 1).

The increase in MVS with increasing ICP raises another question, which is whether an increase in CPP at a given elevated ICP could prevent or delay the transition from CAP to MVS flow (Fig. 1). We have also shown that this increase in MVS flow with increasing ICP can be prevented by increasing CPP (unpublished results) [4]. The increase in MVS flow with increasing ICP is accompanied by increased tissue hypoxia, i.e., increased tissue NADH, and decreased cortical Doppler flow, which is less marked in the MAP as opposed to the ICP group (Fig. 2). The increase in brain tissue water also occurred in the ICP group, but not in the MAP group. These results clearly show the detrimental effects of increasing ICP and its relation to the shift from CAP to MVS flow. The interaction between ICP and CPP in relation to MVS flow could lead to better understanding in the management of high ICP in patients.

Conclusion

Our demonstration of the transition from CAP to MVS flow with increasing ICP provides for the first time, to our knowledge, documentation of this process. Up to now, MVS flow has been observed in infarcted brain [5] combined with capillary rarefaction, but only described as two different states. Without documentation of the transition process, the existence of cerebrovascular shunts was ignored except for a small group of investigators [5]. Now that we have observed and documented this transition between the two states, we now have a measureable and quantitative basis for evaluating the interaction between CPP and ICP and thereby the optimal CPP for a given ICP. We recently showed that MVS can be circumvented at high ICP by increasing CPP. We have also shown that the CPP required to reduce ICP depends upon the degree of elevated ICP (unpublished).

The Brain Trauma Guidelines based on level III evidence suggests that CPP be kept between 50 and 70 mmHg without aggressive measures to increase CPP above 70 mmHg using vasopressors and fluid loading [6]. There is also an ongoing debate on the methods of managing patients with high ICP based upon the recommendations of the “Lund concept” for ICP-targeted therapy, largely by the use of various drugs, as opposed to CPP-targeted therapy [4, 7]. Thus, clinicians, lacking a standard of care (SOC) are left to manage their patients with high ICP using methods based largely on individual bias.

What light can be shed on the problems confronting clinicians with responsibility for caring for these severely brain injured patients suffering from high ICP and resolve the debate regarding ICP versus CPP targeted therapy according to our observations? Based on the hypothesis that in traumatic brain injury (TBI) where high ICP and thereby brain edema is an issue, is characterized by MVS. Thus, in an animal model of TBI resulting in elevated ICP with documentation of MVS, the efficacy of various clinical therapies prescribed by the Lund concept such as beta blockade, sedation with benzodiazepines, and barbiturates while maintaining CPP at 50–60 mmHg can be studied. The dose response and in reducing or counteracting MVS can also be tested. The same can be done in evaluating the effectiveness

of increasing CPP on MVS in the brain after TBI. We have already shown in the brain injured with artificially elevated ICP that MVS can be reduced or prevented by increasing CPP (unpublished data). It is important to note that historically, the determination of the critical CPP based on CBF autoregulation curves was carried out in animals with normal brains and was translated to clinical use. Later studies in humans seem to indicate that patients with CBF autoregulation do better with a higher CPP of 60–70 mmHg, whereas if there is no CBF autoregulation patients do better with lower CPP within the range 50–60 mmHg, as promoted by the Lund concept [6]. However, other studies have suggested that higher CPP of 70–80 mmHg improves outcome after TBI [8–11]. The above-mentioned are all animal studies that can be carried out to address clinical problems encountered by clinicians in managing patients with high ICP after brain injury.

There is already substantial evidence suggesting that patients without CBF autoregulation might fare better if maintained at a lower CPP within the range of 50–60 mmHg [6], whereas those with CBF autoregulation fare better at high CPP [8–11]. It is also notable that with the advent of multimodal neuromonitoring, the presence or absence of CBF autoregulation, whether based on CBF measurements or brain tissue PO₂ (Licox; Fig. 3) varies in each patient from day to day. These data suggest that therapy in these patients might need to be tailored on a daily basis, depending upon their status on any given day rather than standardized therapeutic intervention protocols. Thus, the patient suffering from high ICP with evidence of no CBF autoregulation may be better maintained at a lower CPP of 50–60 mmHg, whereas patients with high ICP and with CBF autoregulation may respond better with high CPP within the range 70–80 mmHg. Whether this is the case, remains to be determined in future randomized clinical trials.

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Fig. 1.

(a) 2-photon laser scanning micrograph showing a region from which microvascular flow was recorded. (b) Line-scan data for red blood cell (RBC) flow velocity in the microvessel shown in a (arrow). (c) Distribution of flow velocity versus vessel diameter in cortical microvessels at normal cerebral perfusion pressure (CPP; 70 mmHg, $n = 10$ rats). CAP capillary, TFC thoroughfare channel. (d) Decrease in CPP to 30 mmHg by increasing intracranial pressure (ICP) reduces capillary (3–6 μm in diameter) and increases thoroughfare channel (8–15 μm in diameter) flow velocities ($n = 10$ rats). (e). Decrease in mean arterial pressure (MAP) to reduce the CPP to 30 mmHg reduces the velocity of all microvessels in the rat parietal cortex ($n = 10$ rats). Blue dashed line indicates a velocity of 1.0 mm/s. Red dotted line indicates a diameter of 8 μm (Reprinted with permission from the *Journal of Neurotrauma*)

Fig. 2.

(a) Hemispheric Doppler flow flux when *CPP* is reduced by increasing *ICP* ($n = 10$) or decreasing *MAP* ($n = 10$). (b) *NADH* reduction during reduction in *CPP* by increasing *ICP* ($n = 10$) or decreasing *MAP* ($n = 10$). Red dashes show levels in the control group at appropriate time points. (c) *CPP* decrease by elevation of *ICP* causes an increase in cortical water content. In the *MAP* group cortical water content was not different from controls ($n = 3$ for each, mean $\pm$ SEM, * $p < 0.05$, ** $p < 0.01$). Cortical tissue water content obtained by rapidly scooping the cortex out of the craniotomy yields a water content consistently lower, 73.52 ± 0.45 % (mean $\pm$ SD, $n = 2$) than that obtained by decapitating the rat, removing the brain, and sampling the cortex, which yields values of 79.91 ± 0.40 % (mean $\pm$ SD, $n = 2$), significantly different ($p = 0.0262$) according to the Shapiro–Wilk test (Reprinted with permission from the *Journal of Neurotrauma*)

Fig. 3. Brain tissue PbtO₂ (Licox probe) versus *CPP* in the white matter of the contralateral hemisphere on days 0 and 3 after traumatic brain injury. Note the absence of correlation between PbtO₂ versus *CPP* on day 0 as opposed to the linear correlation on day 3, suggesting delayed loss of autoregulation on day 3

Table 1

Distribution (mean $\pm$ SEM) of low (<1 mm/s) and high (>1 mm/s) flow velocity capillaries (CAP) and microvascular shunts (MVS), CAP/MVS ratio, average volume flow per microvessel (μ L/s) and normalized Doppler flux in rat cerebral cortex

CPP-mmHg	ICP group (%) $n = 10$					MAP group (%) $n = 10$					$p <$
	CAP <1 mm/s	TFC >1 mm/s	CAP/MVS Ratio	MVS flow μ L/s	Doppler flux	CAP <1 mm/s	TFC >1 mm/s	CAP/MVS ratio	MVS flow μ L/s	Doppler flux	
70	70 $\pm$ 5	30 $\pm$ 2	2.3 $\pm$ 0.7	39 $\pm$ 2	1.0 $\pm$ 0.1	65 $\pm$ 6	35 $\pm$ 4	2.1 $\pm$ 0.7	40 $\pm$ 2	1.0 $\pm$ 0.1	0.145
50	58 $\pm$ 5	41 $\pm$ 3	1.4 $\pm$ 0.5	68 $\pm$ 6	0.9 $\pm$ 0.1	71 $\pm$ 6	29 $\pm$ 4	2.4 $\pm$ 0.8	33 $\pm$ 2	0.8 $\pm$ 0.1	0.001
30	49 $\pm$ 5	51 $\pm$ 5	1.0 $\pm$ 0.1	135 $\pm$ 8	0.7 $\pm$ 0.1	86 $\pm$ 7	14 $\pm$ 3	6.2 $\pm$ 1.5	21 $\pm$ 1	0.5 $\pm$ 0.1	0.001

p values refer to comparisons of the distribution between the groups at each cerebral perfusion pressure (CPP). Note the increase in MVS shunt in the ICP group as CPP was reduced compared with the reverse in the mean arterial pressure (MAP) group