Published in final edited form as:

Adv Exp Med Biol. 2014 ; 812: 43–49. doi:10.1007/978-1-4939-0620-8_6.

Role of Microvascular Shunts in the Loss of Cerebral Blood Flow Autoregulation

Edwin M. Nemoto

Department of Neurosurgery, University of New Mexico, 1101 Yale Blvd, NE,

Domenici Hall, Brain Center, RM 1131B, Albuquerque, NM 87131, USA

Denis E. Bragin

Department of Neurosurgery, University of New Mexico, 1101 Yale Blvd, NE,

Domenici Hall, Brain Center, RM 1131B, Albuquerque, NM 87131, USA

BRaIN Imaging Center, University of New Mexico, Albuquerque, NM 87106, USA

Gloria Statom, Mark Krasberg, Suguna Pappu, Bobby Sena, Tracey Berlin, Kim Olin, and Howard Yonas

Department of Neurosurgery, University of New Mexico, 1101 Yale Blvd, NE,

Domenici Hall, Brain Center, RM 1131B, Albuquerque, NM 87131, USA

Abstract

Historically, determination of the critical cerebral perfusion pressure (CPP) was done in animals by a progressive lowering of arterial pressure yielding a nominal critical CPP of 60 mmHg. Subsequently, it was shown that if the CPP was decreased by increasing intracranial pressure (ICP), critical CPP fell to 30 mmHg. This discrepancy was unexplained. We recently provided evidence that the decrease in critical CPP was due to microvascular shunting resulting in maintained cerebral blood flow (CBF) at a lower CPP. We demonstrated by a progressive increase in ICP in rats using two-photon laser scanning microscopy (2PLSM) that the transition from capillary to microvascular shunt flow is a pathological process. We surmise that the loss of CBF autoregulation revealed by decreasing arterial pressure occurs by dilation of normal cerebral blood vessels whereas that which occurs by increasing ICP is due to microvascular shunting. Our observations indicate that the loss of CBF autoregulation we observed in brain injured patients that changes on an hourly or daily basis reflects an important pathophysiological process impacting on outcome that remains to be determined.

Keywords

Brain; Cerebral blood flow; Edema; Intracranial pressure; Microvascular shunts; Thoroughfare channels

1 Introduction

Intracranial pressure (ICP) was first measured clinically more than 60 years ago [1]. With the measurement of ICP, the concept of cerebral perfusion pressure (CPP) or mean arterial pressure minus ICP evolved [2]. Simultaneously, methods to measure cerebral blood flow (CBF) were developed along with the concept of CBF autoregulation [3]. With these developments, the question arose as to the minimum cerebral perfusion pressure (CPP) or the “critical CPP” where CBF would begin to fall and brain perfusion compromised. This was especially relevant to brain injured patients in whom CPP may fall due to either a *decrease* in mean arterial pressure (MAP) or an *increase* in ICP.

Historically, critical CPP has been determined in animals by a progressive reduction of arterial pressure in the *normal, uninjured*, brain to decrease CPP while measuring CBF yielding a value of about 60 mmHg [3, 4]. This was applied clinically. The recommended CPP in the Brain Trauma guidelines is 50–70 mmHg [5].

However, Miller et al. [6] showed in dogs, that when CPP was reduced by *increasing ICP* as opposed to *decreasing arterial pressure*, the critical CPP fell to 30 mmHg (Fig. 6.1). Their observations were subsequently reproduced in non-human primates [7, 8] and rats [9]. The reason for the decrease in CPP to 30 mmHg by increasing ICP remained unexplained. We recently tested the *hypothesis* that the reduction in critical CPP by high ICP was due to microvascular shunting resulting in a sustained high CBF at a lower CPP by using two-photon laser scanning microscopy (2PLSM) [10] and examined the effect of increasing CPP on the transition from capillary to micro-vascular shunt flow [11].

2 Methods

2.1 Two Photon Laser Scanning Microscopy Studies

All procedures used in these studies were previously described [10]. Briefly, laboratory acclimated, male, Sprague-Dawley rats weighing 250–300 g body weight were studied by 2PLSM under 2 % isoflurane/70 % nitrous oxide/28 % oxygen anesthesia via a craniotomy over the left parietal cortex.

Fluorescent serum was visualized using an Olympus BX 51WI upright microscope and water-immersion LUMPlan FL/IR 20×/0.50 W objective. Excitation was provided by a PrairieView Ultima multiphoton microscopy laser scan unit powered by a Millennia VI 6 W diode laser source pumping a Tsunami Ti:sapphire laser (Spectra-Physics, Mountain View, CA) tuned to 810-nm center wavelength. Bandpass-filtered epifluorescence (560–660 nm) was collected by the photomultiplier tubes of the Prairie View Ultima system. Images (512 × 512 pixels, 0.15 μm/pixel in the x- and y-axes) or line scans were acquired using Prairie View software. Red blood cell flow velocity was measured in microvessels ranging from 3 to 25 μm diameter up to 500 μm below the surface of the parietal cortex as previously described [8].

Tissue hypoxia was assessed by measurement of NADH concentration by autofluorescence and blood brain barrier (BBB) permeability by fluorescein dye transcapillary extravasation.

In offline analyses using NIH ImageJ software, three dimensional anatomy of the vasculature in regions of interest was reconstructed from two-dimensional (planar) scans of the fluorescence intensity obtained at successive focal depths in the cortex (XYZ stack). Attenuation of the signal along the Z-direction was corrected by multiplication of each XY image by factors determined empirically from plots of the intensity variation of background fluorescence as a function of depth.

Doppler flux was measured via a lateral temporal window using a 0.9 mm diameter probe (DRT4, Moor Inst., Axminster, UK) in the same region of the brain studied by 2PLSM. Brain and rectal temperatures were monitored and controlled at 38 ± 0.5 °C. Arterial blood gases and pH were monitored intermittently.

2.1.1 Microvascular Shunting by Increasing Intracranial Pressure—The rats were studied at CPP of 70 (baseline), 50 and 30 mmHg by increasing ICP or decreasing arterial pressure as previously described [10]. Arterial blood gases and all monitored variables were recorded during the 30 min duration at each CPP and ICP or mean arterial pressure (MAP). ICP was increased by the height of a fluid reservoir of artificial CSF at different levels through a catheter sealed into the cisterna magna. Arterial pressure was decreased by phlebotomy through a femoral venous catheter.

2.1.2 Increasing CPP Attenuates the Transition from Capillary Flow to Microvascular Shunts with Increasing ICP—In a second series of studies with the aim of studying the effects of increasing CPP on microvascular shunting with increasing ICP, rats were subjected to a 10 mmHg stepwise increase in ICP from a baseline normal of 10–60 mmHg with CPP maintained at 50, 60, 70 and 80 mmHg by titrated i.v. dopamine infusion throughout the increase in ICP [11].

2.2 Multimodal Monitoring System in Patients

We also report on the results of our multimodality monitoring system in our Neurosurgical Intensive Care Unit (NSICU) using the Component Neuromonitoring System (CNS) (Moberg Research, Inc., Philadelphia, PA). The CNS monitor enables the simultaneous acquisition of brain monitored variables such as tissue PO_2 (Licox), cerebral blood flow (CBF) (Bowman, Inc.), near infrared cerebral oximetry, temperature and intracranial pressure time-locked with vital signs including arterial pressure, pulse oximetry, and EKG. The data are collected de-identified and stored on a server. We currently have data from about 300 patients and are in the process of analyzing these data to explore for significant correlations and relationships that may reveal useful predictors of adverse patterns in these physiological variables to correlate with patient outcome. One of these variables is the correlation between pulsatile arterial pressure and pulsatile changes in CBF and ICP with respect to phase and amplitude both of which would provide information on CBF and ICP autoregulation.

3 Results

Increasing ICP to decrease CPP resulted in increased microvascular shunt flow at higher velocity and larger microvessel diameters of 8–25 μm (Fig. 6.2) which did not occur when CPP was decreased by reducing arterial pressure [10].

Progressively increasing ICP from baseline to 60 mmHg was accompanied by a decrease in the ratio of capillary (CAP)/microvascular shunt (MVS) reflecting a gradual transition from capillary to MVS shunt flow (Fig. 6.3) [11].

The loss of CBF autoregulation observed clinically is especially important if ICP is increased which would lead to a pressure-passive relationship between arterial pressure and ICP. With the development of clinical multimodality monitoring with the Component Neuromonitoring System (CNS) developed by Moberg and colleagues and with the development of various brain tissue monitors such as brain tissue PO_2 (PbtO_2), blood flow (CBF), temperature, and intracranial pressure all time locked with vital signs, has enabled the acquisition of data to illustrate variations in CBF and ICP autoregulation with spontaneous fluctuations in arterial pressure. Acquisition of pulsatile waveforms by AD converters of arterial pressure, intracranial pressure and high frequency CBF allows the continuous assessment of CBF and ICP autoregulation by CVRx and PRx, respectively.

The relationships between CBF and arterial pressure in patients in whom arterial pressure, CBF and ICP were monitored showed CBF and ICP autoregulation varied on a daily if not an hourly basis (Fig. 6.4).

4 Discussion

Our observation of a progressive increase in microvascular shunting with increasing ICP suggests that the decrease in critical CPP is due to microvascular shunting resulting in a sustained high CBF at a lower CPP. In stark contrast, microvascular shunting did *not* occur when CPP was decreased by reducing arterial pressure. These results suggest that the loss of CBF autoregulation where CPP is manipulated by increasing ICP or decreasing arterial pressure likely differ in the fundamental mechanisms involved.

We surmise that the reduction in CPP by decreasing arterial pressure results in a pressure passive decrease in flow through cerebral capillaries whereas that observed by increasing ICP occurs through a transition from capillary to microvascular shunt flow, i.e. two entirely different processes. This mechanism is supported by the observation of capillary rarefaction in stroke in animal models [11].

These results for the first time show the gradual transition from capillary to microvascular shunt flow where previously only two stable states of capillary and microvascular shunts were known.

5 Conclusions

The loss of CBF autoregulation in the injured brain represents pathological micro-vascular shunt flow whereas that observed by a passive decrease in CPP represents a simple vasodilation of normal cerebrovasculature.

Acknowledgments

Supported in part by: NIH Grants NS061216, NS051639 and UNM HSC COBRE program (P20 RR15636).

References

1. Guillaume J, Janny P (1951) Continuous intracranial manometry; physiopathologic and clinical significance of the method. *Presse Med* 59(45):953–955 [PubMed: 14864407]
2. Ingvar DH (1964) The regulation of cerebral circulation. *Acta Anaesthesiol Scand Suppl* 15(15):43–46
3. Jennett WB, Harper AM, Miller JD et al. (1970) Relation between cerebral blood-flow and cerebral perfusion pressure. *Br J Surg* 57(5):390
4. Waltz AG, Yamaguchi T (1970) Pressure-flow relationships of the cerebral vasculature: autoregulatory responses to changes of perfusion pressure produced without drugs or hemorrhage. *Trans Am Neurol Assoc* 95:326–327 [PubMed: 5514403]
5. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS, Bratton SL, Chestnut RM, Ghajar J et al. (2007) Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds. *J Neurotrauma* 24(1):S1–S116
6. Miller JD, Stanek A, Langfitt TW (1972) Concepts of cerebral perfusion pressure and vascular compression during intracranial hypertension. *Prog Brain Res* 35:411–432 [PubMed: 5009562]
7. Grubb RL, Jr, Raichle ME, Phelps ME et al. (1975) Effects of increased intracranial pressure on cerebral blood volume, blood flow, and oxygen utilization in monkeys. *J Neurosurg* 43(4):385–398 [PubMed: 808593]
8. Johnston IH, Rowan JO, Harper AM, Jennett WB (1972) Raised intracranial pressure and cerebral blood flow: I. Cisterna magna infusion in primates. *J Neurol Neurosurg Psychiatr* 35:285–296 [PubMed: 4624687]
9. Hauerberg J, Juhler M (1994) Cerebral blood flow autoregulation in acute intracranial hyper-tension. *J Cereb Blood Flow Metab* 14:519–525 [PubMed: 8163595]
10. Bragin DE, Bush RC, Müller WS et al. (2011) High intracranial pressure effects on cerebral cortical microvascular flow in rats. *J Neurotrauma* 28(5):775–785 [PubMed: 21395499]
11. Bragin DE, Bush RC, Nemoto EM (2013) Effect of cerebral perfusion pressure on cerebral cortical microvascular shunting at high intracranial pressure in rats. *Stroke* 44(1):177–181 [PubMed: 23204051]

Fig. 6.1.

Effect of altering cerebral perfusion pressure (CPP) by decreasing arterial pressure (*thick line*) and by increasing intracranial pressure (*thin line*) in dogs with intact autoregulation on cerebral blood flow (CBF). Significance between changes assessed by paired *t*-test [11]. * $P < 0.05$ [11]. Reproduced with permission of the Editor of Elsevier Press

Fig. 6.2.

(a) normal CPP (70 mmHg) and by (b) decreased CPP to 30 mmHg by increasing ICP. (c) Decreased MAP to reduce the CPP to 30 mmHg [10]. Reproduced with the permission of the Editor of J Neurotrauma

Fig. 6.3.

Ratio of capillary (CAP) and thoroughfare channel (TFC) shunt flow with increasing intracranial pressure (ICP) and different cerebral perfusion pressure (CPP) in rats. Increasing ICP increases TFC flow [11]. Reprinted with the permission of the Editor of Stroke Journal

Fig. 6.4.

Correlation coefficient plot of mean arterial pressure (MAP) and thermal diffusion cerebral blood flow (CBF) showing daily variations in correlation coefficients reflecting loss and return of CBF autoregulation