Original Article

The predominance of metabolic regulation of cerebral blood flow and the lack of “Classic” autoregulation curves in the viable brain

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Abstract

Background: The influence of cerebral perfusion pressure (CPP) on real-time focal cerebral blood flow (fCBF) is not fully understood, in either intact or injured brain. We wanted to evaluate that relationship, and by implication investigate the relative importance of perfusion pressure versus metabolism in the regulation and control of cerebral blood flow. Our hypothesis was that metabolic needs dominated over a physiologic range of blood pressure.

Methods: This was an observational study of 23 patients, most of them with closed head injury, three with subarachnoid hemorrhage, one with a gunshot wound to the brain, and one monitored after craniotomy for unruptured aneurysm. Arterial lines, ventriculostomies, and fCBF monitors were placed. CPP (mean arterial pressure – intracranial pressure) and fCBF were measured and recorded to a computer database every minute. The relationship between CPP and fCBF was graphed and correlation coefficients were compared between survivors and non-survivors.

Results: Graphs of CPP versus fCBF did not show any linearity over a range of 50–150 mm Hg in patients who survived. In those who died, four of seven showed some indication of linearity. The difference in the correlation coefficients between survivors and non-survivors was statistically significant (P < 0.05), with survivors having essentially no correlation, as expected with autoregulation intact, and non-survivors having a mean correlation of 0.311.

Conclusions: In the functioning and viable brain, metabolic regulation of cerebral blood flow (CBF) predominates, leading to the lack of an obvious relationship between perfusion pressure and flow. This predominance of metabolic regulation is robust and preserved over a wide range of brain injury, with pressure autoregulation necessary but not clinically apparent in the metabolically active brain. This robust and constantly varying relationship of pressure and flow shown by our real-time measurements of fCBF has important implications for interpreting clinical measurements of autoregulation. Perhaps most importantly, the development of a correlation between pressure and flow may indicate and be an early warning of deterioration.

Key Words: Brain/blood supply, brain perfusion, cerebral perfusion pressure, cerebral vascular autoregulation, head injuries, intracranial pressure
INTRODUCTION

A dichotomy exists between the theoretic understanding and clinical application of human cerebral blood flow (CBF) concepts. While it is widely acknowledged that blood flow is responsive to the brain’s constantly varying metabolic needs (metabolic regulation or flow metabolism coupling), flow is often portrayed as being constant between 50 and 150 mm Hg. Such invariance, termed pressure autoregulation, is the theoretic underpinning for diagnostic tests of “autoregulation” and clinical decision making in the patient with an injured brain, whether traumatic, hemorrhagic, or ischemic. However, the linear constant flow concept, literally presented, conflicts with the logical expectation that regions of the brain, varying over time in function and hence metabolic needs, have variation in blood flow as well.

Cerebral autoregulation in humans was initially investigated with global, static methods of CBF determination. The idealized concept of a constant CBF over a range of cerebral perfusion pressure (CPP) was based on information from these methods. More recently, methods of determining focal cerebral blood flow (fCBF) in real time have been developed, which may shed light on important aspects of cerebrovascular physiology not apparent with static global methods. Lessons drawn from such an analysis have implications for diagnostic technologies such as transcranial Doppler (TCD) and could influence the concepts used to guide therapies for the injured brain.

In an effort to evaluate the relationship between CPP and fCBF, we utilized thermal diffusion fCBF probes in patients with head injury and subarachnoid hemorrhage (SAH) to determine and record focal real-time CBF, while recording CPP as well. We entered the data into a computer file and graphically analyzed CPP versus fCBF in each patient to evaluate the individual CPP-fCBF relationship.

We then looked at the correlation between CPP and fCBF in those patients who died as compared with those who survived to gain an insight into the effect of brain injury on the relationship.

MATERIALS AND METHODS

Patient population

Twenty-three patients, ranging in age from 8 to 82 years, underwent analysis over a 5-year period [Table 1]. Patients with a closed head injury (CHI) and Glasgow Coma Score (GCS) <8 formed the largest group, 11 living and 7 dying. Three patients presented with SAH. One patient with an unruptured aneurysm (UA) had intracranial pressure (ICP) and fCBF monitoring after craniotomy for treatment of a gunshot wound (GSW). GCS on presentation ranged from 3 to 15. As only two beds were available for computer recording, the patients included here were a subset of all monitored patients presenting to our institution with CHI, SAH, GSW, intracerebral hemorrhage (ICH), or UAs. The fCBF probe placement and computer recording of a monitored patient (and thus inclusion of the patient in this study) were based on availability of appropriate beds and the interest of the on-call neurosurgeon. Therefore, bias in patient selection was possible, although no potential cause of bias was obvious.

Monitoring

Ventriculostomies and fCBF monitors were placed according to our usual clinical practice. For head injury patients, the decision to monitor was based on clinical examination and computed tomography (CT) findings. Arterial lines were placed for blood pressure monitoring. No deviation from our usual monitoring, therapy, or care was made for this study. Because the study was purely observational with no change in care, hospital policy did not require Institutional Review Board (IRB) approval.

Monitoring continued for as long as it was judged clinically necessary by the attending neurosurgeon.

Table 1: Patient demographics and outcome

| Pathology | Age | GCS on admission | Outcome |
|-----------|-----|------------------|---------|
| CHI       | 24  | 3                | Alive   |
| CHI       | 75  | 7                | Dead    |
| CHI       | 16  | 7                | Alive   |
| CHI       | 50  | 7                | Dead    |
| UA        | 38  | 15               | Alive   |
| SAH       | 75  | 15               | Alive   |
| CHI       | 15  | 3                | Alive   |
| CHI       | 8   | 6                | Alive   |
| CHI       | 70  | 6                | Alive   |
| CHI       | 82  | 6                | Dead    |
| SAH       | 46  | 5                | Alive   |
| CHI       | 25  | 3                | Dead    |
| GSW       | 30  | 3                | Alive   |
| CHI       | 11  | 5                | Alive   |
| SAH       | 73  | 8                | Alive   |
| CHI       | 20  | 5                | Alive   |
| CHI       | 45  | 3                | Dead    |
| CHI       | 19  | 6                | Dead    |
| CHI       | 78  | 9                | Alive   |
| CHI       | 19  | 3                | Dead    |
| CHI       | 24  | 5                | Alive   |
| CHI       | 49  | 7                | Alive   |
| CHI       | 34  | 3                | Alive   |

GCS: Glasgow coma score, CHI: Closed head injury, SAH: Subarachnoid hemorrhage, UA: Unruptured aneurysm
Standard frontal ventriculostomies were used, as well as thermal diffusion fCBF monitors (Flowtronics, Inc., Phoenix, AZ, USA). If a patient needed monitoring only, the fCBF monitor was slid under the dura next to the ventriculostomy, over the frontal cortex. For patients after craniotomy, the fCBF monitor was tunneled out of a separate small incision after being placed over an accessible portion of the brain, next to but not necessarily on the traumatized cortex.

Treatment goals were a CPP greater than 60–70 mm Hg and an ICP less than 20–25 mm Hg. When treatment was indicated, mannitol was the initial step, followed by mild–moderate hyperventilation in the initial years of the study and ventricular drainage more commonly in the later years. Pressors were also used to improve CPP, and if ICP stayed elevated, barbiturate coma was employed in those patients judged salvageable. When the Guidelines for Management of Severe Head Injury became available, treatment was standardized to those recommendations with emphasis on initial use of ventricular drainage.[1]

A custom data acquisition system was designed to continuously monitor up to 32 parameters from two beds in the neurosurgical intensive care unit.[3] Analog outputs of bedside monitors and ventilators were connected via shielded cables to this monitoring station for continuous display of all data. Signals were digitized using a multiplexer and analog-to-digital board (National Instruments, Austin, TX, USA). Data were sampled at 1-minute intervals for 5 seconds at a rate of 30 samples/second. The mean value of these samples was saved to hard disk. CPP was calculated from the difference between mean arterial pressure (MAP) and ICP. Data were graphed and analyzed with Statistica software (Statsoft, Tulsa, OK, USA). Data were visually screened, and isolated values obviously far out of the general trend for that local segment were removed.

CPP versus fCBF was graphed for each patient and visually examined for linear trends such as the classic “autoregulatory” appearance.

The correlation coefficient for CPP versus fCBF over a CPP of 50–150 mm Hg was calculated for each patient and the correlation coefficients for alive versus dead patients were evaluated with a t-test. Average fCBF, standard deviation (STD) fCBF, average CPP, and CPP STD were also compared using t-tests.

RESULTS

The time of monitoring ranged from 12 to 240 hours, with 191–13,633 CPP observations and 887–15,991 fCBF observations. Average CPP varied from 24 to 100 torr and average fCBF from 25 to 139 ml/100 g/min, both having substantial variability over time.

In general, graphs of CPP versus fCBF in patients who lived did not show a linear relationship over a CPP of 50–150 torr, the range for classic linearity [Figure 1]. In those patients who died, graphs of CPP versus fCBF showed some indication of linearity in four of seven patients [Figure 2].

A comparison of the CPP–fCBF correlation coefficients in the dead versus alive patients showed a statistically significant difference between those groups. The mean correlation in survivors was −0.006 versus 0.311 in non-survivors [Figure 3].

It was also noted that the STD of CPP was higher in those expired (20.7 vs. 11.5, \( P < 0.05 \)), possibly indicating greater peripheral vasomotor or intracranial hemodynamic instability. The average CPP was higher in survivors versus non-survivors (78 vs.55, \( P < 0.05 \)). Whether this was an effect of the severe brain injury or a difference in therapy is uncertain. Since a sizable number of measurements in the non-survivors was below the range of autoregulation (50 torr), CBF measurements would be expected to show a linear relationship to pressure.

DISCUSSION

Surface thermal diffusion flowmetry measures blood flow in the most superficial 2–3 mm of cortex in units of milliliter/100 g tissue/minute.[4] Several authors attest to a good correlation between thermal diffusion fCBF determinations and other focal and global methods,[6,8,10,14,24,26] although not all agree.[21]

While thermal diffusion CBF determination is a focal and real-time method, this may be an advantage, as autoregulation and metabolic demand can vary regionally, segmentally, and temporally.[2] It may be that only by analyzing autoregulation at the local level can global characteristics be understood.

The lower average CPP in non-survivors means more CBF values were on what is thought to be the ascending limb of the pressure autoregulatory curve, where metabolic control may be less effective and the more passive pressure–flow relationship therefore is more apparent. It is interesting to note, however, that in the survivors even when CPP was below 50 mm Hg, there was often a non-linear relationship present, perhaps indicating continued metabolic control.

The observation that CPP in survivors had a minimal correlation with fCBF indicates that other influences, most likely metabolic needs, predominate in the viable brain, and passive pressure mechanisms are uncovered only in the dying brain. In fact, in the surviving patients, the mean correlation coefficient was very close to zero, providing quantitative documentation of the lack of influence of CPP on fCBF in viable brain.
Metabolic regulation, also termed flow–metabolism coupling, is likely the most important factor in the control of the cerebral circulation over a functional CPP range, connecting the changing metabolic needs of the brain with the delivery of substrate by blood flow. Pressure autoregulation, frequently just referred to as autoregulation, is less visible as it is masked by metabolic needs.[25] Other influences on blood flow include the partial pressures of carbon dioxide and oxygen, and viscosity.

A control hierarchy for CBF likely exists, with the functioning pressure autoregulation capability a necessary precondition to allow metabolic regulation to occur.[7,13,18] Our results support such a hierarchy, with pressure autoregulation being uncovered after metabolic regulation ceases operation due to tissue death.

Because brain metabolism varies over time and space, CBF can be expected to vary as well.[20,27] Yet, many clinical conceptions of CBF refer only to pressure autoregulation in that they depict an invariant fCBF over a range of perfusion pressure.[9]

A reason for this oversimplification may be found in the original CBF curves developed by Lassen. An important graph in his original paper that shows a level CBF with MAP greater than 50 is based on “mean values of 11 groups of subjects reported in 7 studies…,” that is, averaged global CBF determinations, which are themselves averages over time and space.[16] Lassen himself says, “…it seems likely that both mechanical and chemical factors are of importance for the autoregulation of CBF, the latter factor, however, having the final regulatory effect.”[17] Therefore, the seminal depiction of CBF and CPP utilized averages over individual brain volumes, different brains, different lengths of time, and different groups. Relevant to the pooling of points, Paneri comments, “Pooling data relies on the assumption that the autoregulatory curve is a population characteristic. Evidence against this assumption is provided by many studies….”[19] More recent papers documenting real-time measurement of individual CPP versus CBF are surprisingly sparse. One useful paper is by Kimme et al., using laser Doppler perfusion imaging in pigs.[12] Varying CPP, they found “classic autoregulatory flow pressure graphs” were present only when all values sampled...
were clustered together.” With a different non-real time technique, positron emission tomography (PET) scanning, Steiner et al. found no relationship between CPP and CBF in normal appearing and abnormal appearing pericontusional brain.[23] Our findings would be consistent with preservation of autoregulation even in injured brain.

The development of new methods for real-time evaluation of fCBF allows a reevaluation of the CPP–CBF relationship in individual patients. Using one method, thermal diffusion, we have shown that there is no relationship between CPP and fCBF in surviving patients, as would be expected with intact autoregulation. The wide variation in flow at any given pressure is presumably due to variation in metabolic demand and other factors. The fCBF flow is dynamic, and this has importance for cerebrovascular physiology in general as well as the interpretation of tests of “autoregulation” in particular.

The evaluation of autoregulation in CHI and cerebrovascular disease are two areas of current interest, but the concept of autoregulation in this context frequently uses the idealized model of invariant blood flow between 50 and 150 as a theoretic underpinning. We have shown that such invariance exists only in the terminally ill brain.

These findings have implications for transcranial Doppler interpretation. Parameters such as mean velocity index and pressure reactivity index involve correlation coefficients between spontaneous slow waves of CPP and mean flow velocity of the middle cerebral artery, or correlation of MAP versus ICP, and are used to try and gain an insight into the state of autoregulation.[11,22] Important to the interpretation of these indices is the assumption that normally CBF is constant over a range of CPP. As we have seen, that is generally not the case. These findings lead to the conclusion that the clinical evaluation of cerebral autoregulation needs to include measuring the adequacy of metabolic substrate delivery and utilization in conjunction with CBF information.

Our patient population was heterogeneous and placement of fCBF monitors was not necessarily consistent. While not ideal, such variation may possibly add to the robustness of our findings. The fCBF tracing likely closest to normal, from the patient with the unruptured aneurysm, was very similar to many of the brain injured patients who survived. Only in dying patients does linearity appear; in all surviving patients (with varied pathophysiologies), there is no linearity.

The concept that metabolic needs dominate the control of CBF in the functional brain implies that changes in perfusion pressure over a range of roughly 50–150 mm

Figure 2: Cerebral perfusion pressure versus focal cerebral blood flow in patients who died. The number at the top of each graph corresponds to the patient number listed in Table 1. A linear relationship can be seen in patients 12, 17, 18, and 20.

Figure 3: A comparison of the correlation coefficients for cerebral perfusion pressure (CPP) versus focal cerebral blood flow (fCBF) over a CPP of 50–150 mm Hg grouped by survival. Mean CPP–fCBF correlation for surviving patients was –0.006 and for non-survivors was 0.311. The difference was significant (P < 0.05).
Hg have a very limited effect on cerebral hemodynamics in viable tissue. Pressure autoregulation, a relatively invariant CBF over a range of perfusion pressures, is necessary but not clinically apparent in the metabolically active brain.

The lack of correlation between CPP and CBF is robust over a wide range of non-fatal injury. If a strong correlation is established in a particular patient, severe brain damage may be present. Importantly, for patient care at the bedside, the transition between no correlation to correlation may be an early indicator of physiologic brain deterioration.

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REFERENCES

1. Arbit E, DiResta GR. Application of laser Doppler flowmetry in neurosurgery. Neurosurg Clin N Am 1996;7:741-8.
2. Baumbach GL, Heistad DD. Regional, segmental and temporal heterogeneity of cerebral vascular autoregulation. Ann Biomed Eng 1985;13:303-10.
3. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury. J Neurotrauma 2007;24 Suppl 1:S1-106.
4. Carter LP. Thermal diffusion flowmetry. Neurosurg Clin N Am 1996;7:749-54.
5. Choksey MS. Cortical thermal clearance as a predictor of imminent neurological deterioration. Cerebrovasc Brain Metab Rev 1996;8:230-71.
6. Faraci FM, Baumbach GL, Heistad DD. Myogenic mechanisms in the cerebral circulation. J Hypertens 1989;7:561-4.
7. Gaines C, Carter LP, Crowell RM. Comparison of local cerebral blood flow determined by thermal and hydrogen clearance. Stroke 1983;14:66-9.
8. Goadsby PJ, Edvinsson L. Neurovascular control of the cerebral circulation. In: Edvinsson L, drause DN, editors. Cerebral Blood Flow and Metabolism. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 177.
9. Gopinath SP, Valadka AV, Contant CF, Robertson CS. Relationship between global and cortical cerebral blood flow in patients with head injuries. Neurosurgery 1999;44:1273-9.
10. Hiller M, Czosnyka M, Hutchinson P, Balestrieri M, Smielewski P, Matta B, et al. Predictive value of initial computerized tomography scan, intracranial pressure, and state of autoregulation in patients with traumatic brain injury. J Neurosurg 2006;104:731-7.
11. Kimme P, Ledin T, Sjoberg F. Cortical blood flow autoregulation revisited using laser Doppler perfusion imaging. Acta Physiol Scand 2002;176:255-62.
12. Kontos HA, Wei EP. Oxygen-dependent mechanisms in cerebral autoregulation. Ann Biomed Eng 1985;13:329-34.
13. Kuwayama N, Takaku A, Harada J, Fukuda O, Endo S, Saito T. Modified thermal diffusion flow probe for the continuous monitoring of cortical blood flow. Neurosurgery 1991;29:583-9.
14. Lassen NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev 1959;39:183-238.
15. Lassen NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev 1959;39:197.
16. Lassen NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev 1959;39:198.
17. McPherson R, Koehler R, Trastman R. Effect of jugular venous pressure on cerebral autoregulation in dogs. Am J Physiol 1988;255:H1516-24.
18. Panerai R. Assessment of cerebral pressure autoregulation in humans—A review of measurement methods. Physiol Meas 1998;19:305-38.
19. Raichle M, Edvinsson L. Functional brain imaging. In: Edvinsson L, Drause DN, editors. Cerebral Blood Flow and Metabolism. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 413.
20. Schroder M, Muizelaar JP. Monitoring of regional cerebral blood flow in acute head injury by thermal diffusion. Acta Neurochir Suppl (Wien) 1993;59:5-10.
21. Steiner L, Coles J, Johnston A, Chatfield DA, Smielewski P, Fryer TD, et al. Assessment of cerebrovascular autoregulation in head-injured patients: A validation study. Stroke 2003;34:2404-9.
22. Steiner L, Coles J, Johnston A, Czosnyka M, Fryer TD, Smielewski P, et al. Responses of postrauumatic pericontusional cerebral blood flow and blood volume to an increase in cerebral perfusion pressure. J Cereb Blood Flow Metab 2003;23:1371-7.
23. Vajkoczy P, Roth H, Horn P, Lucke T, Thome C, Hubner U, et al. Continuous monitoring of regional cerebral blood flow: Experimental and clinical validation of a novel thermal diffusion microprobe. J Neurosurg 2000;93:265-74.
24. Vavilala MS, Lee LA, Lam AM. Cerebral blood flow and vascular physiology. Anesthesiol Clin North Am 2002;20:247-64.
25. Voorhees W, DeFord J, Bleyer M. Continuous monitoring of cerebral perfusion by thermal clearance. Neurol Res 1993;15:75-82.
26. Zauner A, Daughtery W, Bullock M, Warner DS. Brain oxygenation and energy metabolism: Part 1—biological function and pathophysiology. Neurosurgery 2002;51:289-302.