Witness Statement Ref. No. 235/1

NAME OF CHILD: Adam Strain

Name: Leslie Dyer

Title: Dr

Present position and institution:

Previous position and institution:
[As at the time of the child's death]

Membership of Advisory Panels and Committees:
[Identify by date and title all of those between January 1995- January 2012]

Previous Statements, Depositions and Reports:
[Identify by date and title all those made in relation to the child's death]

OFFICIAL USE:
List of previous statements, depositions and reports:

Ref:	Date:	

Witness Statement Ref No

NAME OF CHILD: ADAM STRAIN

Name: Leslie Gordon Dyer

Title: Dr Leslie Gordon Dyer

Present position: Retired since 1999

Previous positions and institutions:

Staff Anesthesiologist Marquette General Hospital, Michigan, 1976-1999
Resident in Anesthesia at the University of Michigan, 1974-1976
Senior House Officer in the Ulster Hospital, Dundonald, 1973-1974
House Officer in Craigavon Area Hospital, 1972-1973
Graduate of the Queen`s University of Belfast, 1972 – MB

Marquette General Hospital is a small community hospital in Northern Michigan, U.S.A. I was not involved in any research or any academic studies. Much of what I did was cardio-vascular anesthesia and the remainder was supervising nurse anesthetists performing anesthesia for general cases.

A. Introduction

1. In 2005 I was asked by the family of Adam Strain to review the Anesthetic Record of Adam Strain. I agreed.

2. I raised various issues at that time (see 094-219-1010a), namely:

   (a) my belief that Adam`s fluid management was poor.

   (b) my concern that the RVH`s inquiry by Doctor Fiona Gibson MD FFARCSI concluded (at 011-005-017) that Adam had received a very carefully thought out and well managed anesthetic with great care to fluid management, that no untoward episode took place, when the ultimate untoward episode, ie Adam's brain death had occurred, and that that death was related to fluid management.

B. The Anesthetic Records Relating to the Operation on Adam Strain

1. I compared the electronic record (058-008-023) to the written one (058-003-005) and found them to be compatible.

2. The electronic record (058-008-023) shows the Mean Arterial Pressure ["MAP"] from 0730 to 0900 to be 70 -75mmHg.

3. The electronic record (058-008-023) shows that from 0830 onwards the Central Venous Pressure ["CVP"] was 22 mm Hg. or higher.

4. As the tip of the catheter was in the neck this means that it was in effect reading Jugular Venous Pressure. "]. Dr Taylor has clearly stated that there were both cardiac and respiratory patterns to the waveform confirming correct intra-vascular placement: see 011-002-006 and 011-014-099. This means that the reading at the tip of the catheter was correct.

5. Adam was in a head down position so that the Intracranial Pressure ["ICP"] would be slightly higher, namely, in the region of 25mmHg.

C. Interpretation of the Anesthetic Records

1. The first step is to identify the Cerebral Perfusion Pressure ["CPP"].

2. I agree with Dr Taylor [at 059-036-072] that the CPP is ascertained by subtracting the ICP from the MAP.

3. In Adam`s case, the ICP was 25 and the MAP was 75.

4. The CPP was, therefore, 50mmHg.

D. Interpretation of the CPP

1. Many authorities believe that children need a CPP of at least 60mmHg [see, for example, the Medscape article at TAB "1"].

2. However, more recently, a paper in Neurology Neurosurgery suggested a critical threshold for CPP of 48mmHg in children aged 2-6 years [see, for example, Chambers (2005) – TAB "2"].

3. As the CPP falls, oxygen extraction increases. The normal brain extracts more oxygen from the blood than any other organ with the exception of the heart. Thus this protective mechanism is of limited scope. This means that if one of the other factors in oxygen delivery is compromised, then there is little room for further extraction: see www.vascularneurosurgery.com/cbf.html at TAB "3".

4. Dr. Sumner in his report to the Coroner stated:

> "A CVP of 22mm Hg. is difficult to achieve" (059-054-117)

5. Unfortunately, "achieving" this level of CVP is extremely dangerous.

6. Its effect on CPP is significant.

7. The most significant effects are:

   (a) a high CVP in the supine patient means that the pressure in the superior saggital sinus will be equally high: see diagrams at TAB "4" and "5".

   (b) Cerebral Spinal Fluid ["CSF"] is absorbed into the superior saggital sinus. The superior saggital sinus is part of the central venous system. The CSF cannot be adequately absorbed if the CVP in the superior saggital sinus is high.

   (c) a high CVP resulting in a high ICP places the patient in a situation where small increases in volume will result in large increases in ICP [see, for example, Physiology, Issue 8 (1998) Article 4: page 2 entitled "Intracranial Pressure and Cerebral Blood View" at TAB "6"].

8. Absorption of CSF is necessary to prevent a marked increase in ICP when the brain's blood vessels dilate [see Walters (1998) at TAB "7".]

9. These vessels dilate in response to low CPP in a process called auto-regulation, ie the brain causes the blood vessels in the brain to dilate. A CPP of 50 mmHg means that the blood vessels have reached the point at which they can no longer dilate [see Phsyiology, Issue 8 (1998) Article 4, page 3 – TAB "8"].

10. Cerebral blood vessels routinely dilate in response to anemia.

11. Adam was anemic. Normally, his cerebral blood vessels would respond to the anaemia by dilating. This protective mechanism was, however, not available to Adam because his cerebral blood vessels were already maximally dilated as a result of the low CPP.

12. During the anesthetic Adam`s haematocrit had fallen to 18%: see 058-003-003. The normal reading for a child of Adam`s age is between 33% and 39%.

13. Acute anemia has been shown to cause both cerebral infarction and renal failure [see Neurol (2010) at TAB "9" and Karkouti *et al* (2005) at TAB "10" and Chapter Two of Cerebral Ischemia and Stroke – www.neuropathology-web.org/chapter2/chapter2aHIE.html at TAB "11".

14. These factors combined to make cerebral hypoxia inevitable.

E. Principal Concerns about Dr Taylor`s Anesthetic Management of Adam

1. His pre-operative behaviour.

2. His fluid management of Adam.

3. His response to the high CVP reading of 17.

4. His failure to obtain laboratory data once the arterial line had been placed.

5. His apparently unconventional use of Dopamine: see 011-014-100 and "Dopamine Clinical Pharmacology" at www.rxlist.com/dopamine-drug.htm at TAB "12".

F. The CVP Reading of 17

1. Such a reading is extremely high.

2. I am firmly of the belief that it is mandatory for the clinician to investigate the cause.

3. Possible diagnoses of such a high reading include:

   (a) equipment failure (easily excluded by swapping the transducers);

   (b) fluid overload;

   (c) cardiac failure;

   (d) pneumothorax (a potentially rapid fatal complication).

G. The Element of Hyponatremia

1. My original notes from 2005 appear at 094-192-936.

2. I made these notes during a meeting with the family of Adam Strain. They were done for the purpose of explaining, in layman`s terms, the CVP, the risks associated with it and some basic fluid considerations.

3. I note that Adam`s Serum Sodium had fallen to 123mmol/L. Hyponatremia is defined as a Serum Sodium less than 135mmol/L. Minor degrees of hyponatremia are common and cause no significant problems. The massive extent of Adam`s hyponatremia meant that water flowed into Adam`s brain. This was a brain that had been compromised by other aspects of Adam`s anesthetic management as detailed above.

4. A level of 123mmol/L means that the water will flow into the brain from the blood as a result of osmosis. Even a small flow could have caused a massive increase in ICP. It should be emphasized that any increase in ICP would have the effect of lowering the CPP even further.

H. Conclusions

1. On the information currently available to me [and I understand that there are further reports, statements and evidence to come], I believe that Adam died as a result of cerebral hypoxia and/or an osmotic fluid shift.

2. I believe that cerebral hypoxia was the dominant cause.

3. Both cerebral hypoxia and osmotic fluid shift are a result of fluid mismanagement.

4. I am concerned that the Public Inquiry does not have access to a general purpose paediatric anesthetist, ie an anesthetist, who does not specialize in cardio-vascular anesthesia.

5. I am surprised that Dr John Alexander did not address the cerebral effects of a high CVP in his report to the Coroner: see 011-030-153. I would be interested in knowing what his response to the following questions would be:
   (a) What is a normal C.V.P.?
   (b) What is his differential diagnosis for a C.V.P. of 17 mm. Hg.?
   (c) What is the normal range for intra-cranial pressure?
   (d) What is the minimum safe cerebral perfusion pressure?
   (e) What is the oxygen saturation of venous blood leaving the brain?
   (f) At what level of venous oxygen saturation does cerebral hypoxia occur?
   (g) At what haematocrit would he worry about hypoxia?
   (h) Has he ever had or heard of a patient survive who had a cerebral perfusion pressure of 50mm. Hg. coupled with a haematocrit of 18% without concomitant hypothermia?
   (i) Why did he not include cerebral hypoxia in a differential diagnosis of Adam's death?
   (j) Did he consider the effects of the high C.V.P. on Adam's intra-cranial pressure?

6. I am very concerned that CVP is being used to make clinical decisions regarding fluid management when meta analysis is definitive that it should not [see, for example, Marik *et al* (2008) at TAB "13"].

7. In addition, I am also extremely concerned that the effects of rapid infusion of fluid on the brain are being ignored and children are still dying in Northern Ireland as a result of fluid mismanagement.

This Statement is true to the best of my knowledge and belief

Signed:  Dated: 24 January 2012

TAB 1

Initial Evaluation and Management of CNS Injury

- Author: Christos Tolias, MBBS, PhD, FRCS; Chief Editor: Allen R Wyler, MD

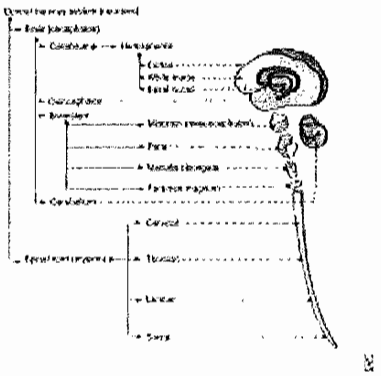
Updated: Sep 12, 2011 *Medscape* Reference

http://emidicine.medscape.com/artcile/434261-overview

Relevant Anatomy/Pathophysiology

Relevant anatomy

The brain and the spinal cord make up the CNS and is illustrated in the image below. The brain, surrounded by its 3 membranes (also known as meninges), is encased in the skull. The scalp covers the bone of the top of the skull or vault, while the facial bones and muscles and the neck muscles cover the base of the skull. A deep projection of the dura (the outer and hardest of the brain meninges) known as the falx cerebri divides the brain into the cerebral hemispheres. Another projection, known as the tentorium, divides the cerebral hemispheres from the posterior fossa, which contains the cerebellum.



Initial evaluation and management of CNS injury. Schematic representation of the brain and the spinal cord.

The brain stem arises from the middle of the cerebral hemispheres, descends through an opening of the tentorium (tentorium hiatus), and continues as spinal cord after the foramen magnum. The spinal cord exits the cranial cavity through an opening at the base of the skull and the top of the cervical spine (foramen magnum). In adults, it extends down to the level of the 12th thoracic or first lumbar vertebra. In children, the spinal cord terminates much lower, depending on the age of the child.

Relevant pathophysiology

Consciousness is defined as the ability to be aware of oneself and one's surroundings. The reticular formation, a very complicated and poorly defined collection of nerve cells in the brain stem, continuously maintains the activity of the rest of the brain and is considered responsible for maintaining consciousness. Intracranial pressure (ICP) is the normally positive pressure present in the cranial cavity. It ranges from 5 mm Hg in an infant to 15 mm Hg in an adult. Cerebral perfusion pressure (CPP) equals mean blood pressure (BP) minus ICP. CPP should be maintained at higher than 70 mm Hg in adults and at higher than 60 mm Hg in children.

Maintaining adequate circulation in the brain is of vital importance. If cerebral perfusion falls below 12 mL/mg/min, then irreversible damage to neuronal cells occurs. Cerebral blood flow is kept stable under normal conditions due to linear changes in cerebrovascular resistance. This phenomenon is called cerebral autoregulation and means that changes in CPP between 50 mm Hg and 150 mm Hg do not cause significant changes in the cerebral blood flow. However, under traumatic conditions, autoregulation is lost, resulting in a linear relationship of BP to cerebral blood flow. Therefore, maintenance of adequate BP is of vital importance for brain survival.

Because the cranium is a closed space, the sum of the intracranial volumes of brain, blood, cerebrospinal fluid (CSF), and other components (eg, hematomas, mass lesions) are constant. This is called the Kellie-Monro principle and implies that changes in one of the intracranial components will result in compensatory alteration in the others. Because the amount of blood and CSF that can be pushed out of the cranium is limited, increases of ICP above a certain level cause herniation of the brain matter through natural openings such as the tentorium hiatus (uncal herniation) or the foramen magnum (hindbrain herniation). Both herniations can result in brain stem compression and death (conning).

Uncal herniation compresses the ipsilateral III cranial nerve (oculomotor), resulting in dilatation of the ipsilateral pupil. This is a well-known localizing sign of intracranial pathology causing mass effect.

Disclosure: Nothing to disclose.

References

1. Orledge JD, Pepe PE. Out-of-hospital spinal immobilization: is it really necessary?. *Acad Emerg Med.* Mar 1998;5(3):203-4. [Medline].
2. Hadley MN, Walters BC, Grabb PA, Oyesiku NM, Przybylski GJ, Resnick DK, et al. Guidelines for the management of acute cervical spine and spinal cord injuries. *Clin Neurosurg.* 2002;49:407-98. [Medline].
3. Lockey D, Davies G, Coats T. Survival of trauma patients who have prehospital tracheal intubation without anaesthesia or muscle relaxants: observational study. *BMJ.* Jul 21 2001;323(7305):141. [Medline].
4. Cooper A, DiScala C, Foltin G, Tunik M, Markenson D, Welborn C. Prehospital endotracheal intubation for severe head injury in children: a reappraisal. *Semin Pediatr Surg.* Feb 2001;10(1):3-6. [Medline].
5. Winchell RJ, Hoyt DB. Endotracheal intubation in the field improves survival in patients with severe head injury. Trauma Research and Education Foundation of San Diego. *Arch Surg.* Jun 1997;132(6):592-7. [Medline].
6. Gabriel EJ, Ghajar J, Jagoda A, Pons PT, Scalea T, Walters BC. Guidelines for prehospital management of traumatic brain injury. *J Neurotrauma.* Jan 2002;19(1):111-74. [Medline].
7. Stern SA, Zink BJ, Mertz M, Wang X, Dronen SC. Effect of initially limited resuscitation in a combined model of fluid-percussion brain injury and severe uncontrolled hemorrhagic shock. *J Neurosurg.* Aug 2000;93 (2):305-14. [Medline].
8. Rotstein OD. Novel strategies for immunomodulation after trauma: revisiting hypertonic saline as a resuscitation strategy for hemorrhagic shock. *J Trauma.* Oct 2000;49(4):580-3. [Medline].
9. Tolias CM, Wasserberg J. Critical decision making in severe head injury management. *Trauma.* 2002;4:211-221.
10. Greenberg MS. *Handbook of Neurosurgery.* 4th ed. Lakeland, Fla: Greenberg Graphics; 1997.
11. Roberts I, Yates D, Sandercock P, Farrell B, Wasserberg J, Lomas G, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet.* Oct 9-15 2004;364(9442):1321-8. [Medline]. [Full Text].
12. Shackford SR, Zhuang J, Schmoker J. Intravenous fluid tonicity: effect on intracranial pressure, cerebral blood flow, and cerebral oxygen delivery in focal brain injury. *J Neurosurg.* Jan 1992;76(1):91-8. [Medline].
13. Garretson HD, McGraw CP, O'Connor C. Effectiveness of fluid restriction, mannitol and furosemide in reducing ICP. In: Ishii S, Naghai H, Brock M, eds. *Intracranial Pressure V.* Berlin: Springer-Verlag; 1983:742 -745.
14. Schrot RJ, Muizelaar JP. Mannitol in acute traumatic brain injury. *Lancet.* May 11 2002;359(9318):1633-4. [Medline].
15. Ritter AM, Muizelaar JP, Barnes T, et al. Brain stem blood flow, pupillary response, and outcome in patients with severe head injuries. *Neurosurgery.* May 1999;44(5):941-8. [Medline].
16. Cruz J, Minoja G, Okuchi K. Improving clinical outcomes from acute subdural hematomas with the emergency preoperative administration of high doses of mannitol: a randomized trial. *Neurosurgery.* Oct 2001;49(4):864-71. [Medline].
17. Cruz J, Minoja G, Okuchi K. Major clinical and physiological benefits of early high doses of mannitol for intraparenchymal temporal lobe hemorrhages with abnormal pupillary widening: a randomized trial. *Neurosurgery.* Sep 2002;51(3):628-37; discussion 637-8. [Medline].
18. Rotstein OD. Novel strategies for immunomodulation after trauma: revisiting hypertonic saline as a resuscitation strategy for hemorrhagic shock. *J Trauma.* Oct 2000;49(4):580-3. [Medline].

19. Bayir H, Clark RS, Kochanek PM. Promising strategies to minimize secondary brain injury after head trauma. *Crit Care Med*. Jan 2003;31(1 Suppl):S112-7. [Medline].

20. Fisher B, Thomas D, Peterson B. Hypertonic saline lowers raised intracranial pressure in children after head trauma. *J Neurosurg Anesthesiol*. Jan 1992;4(1):4-10. [Medline].

21. Shackford SR, Bourguignon PR, Wald SL, Rogers FB, Osler TM, Clark DE. Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial. *J Trauma*. Jan 1998;44(1):50-8. [Medline].

22. Kamel H, Navi BB, Nakagawa K, Hemphill JC 3rd, Ko NU. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials. *Crit Care Med*. Mar 2011;39(3):554-9. [Medline].

23. Chadwick D. Seizures and epilepsy after traumatic brain injury. *Lancet*. Jan 29 2000;355(9201):334-6. [Medline].

24. Perron AD, Brady WJ, Huff JS. Concussive convulsions: emergency department assessment and management of a frequently misunderstood entity. *Acad Emerg Med*. Mar 2001;8(3):296-8. [Medline].

25. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med*. Aug 23 1990;323(8):497-502. [Medline].

26. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. *Epilepsia*. Apr 2001;42(4):515-24. [Medline].

27. Alderson P, Roberts I. Corticosteroids for acute traumatic brain injury. *Cochrane Database Syst Rev*. 2000;CD000196. [Medline].

28. Bracken MB. Pharmacological interventions for acute spinal cord injury. *Cochrane Database Syst Rev*. 2000;CD001046. [Medline].

29. CRASH Trial Management Group. Possible explanations for the results of CRASH - Author's reply. *Lancet*. Jan 15-21 2005;365(9455):213-214.

30. Gupta AK, Bullock MR. Monitoring the injured brain in intensive care: present and future. *Hosp Med*. Sep 1998;59(9):704-13. [Medline].

31. King BS, Gupta R, Narayan RK. The early assessment and intensive care unit management of patients with severe traumatic brain and spinal cord injuries. *Surg Clin North Am*. Jun 2000;80(3):855-70, viii-ix. [Medline].

32. Kushwaha VP, Garland DG. Extremity fractures in the patient with a traumatic brain injury. *J Am Acad Orthop Surg*. Sep-Oct 1998;6(5):298-307. [Medline].

33. Langham J, Goldfrad C, Teasdale G, Shaw D, Rowan K. Calcium channel blockers for acute traumatic brain injury. *Cochrane Database Syst Rev*. 2000;CD000565. [Medline].

34. Marion DW. Management of traumatic brain injury: past, present, and future. *Clin Neurosurg*. 1999;45:184-91. [Medline].

35. Mattera CJ. Spinal trauma: new guidelines for assessment and management in the out-of-hospital environment. *J Emerg Nurs*. Dec 1998;24(6):523-34; quiz 535-8. [Medline].

36. Meyer P, Legros C, Orliaguet G. Critical care management of neurotrauma in children: new trends and perspectives. *Childs Nerv Syst*. Nov 1999;15(11-12):732-9. [Medline].

37. Mueller FO. Fatalities from head and cervical spine injuries occurring in tackle football: 50 years' experience. *Clin Sports Med*. Jan 1998;17(1):169-82. [Medline].

38. Choux M, Di Rocco C, Hockley AD, Walker ML, eds. *Paediatric Neurosurgery*. London UK: Churchill-Livingstone; 1999.

39. Petri R, Gimbel R. Evaluation of the patient with spinal trauma and back pain: an evidence based approach. *Emerg Med Clin North Am.* Feb 1999;17(1):25-39, vii-viii. [Medline].

40. Rekate HL, Theodore N, Sonntag VK, Dickman CA. Pediatric spine and spinal cord trauma. State of the art for the third millennium. *Childs Nerv Syst.* Nov 1999;15(11-12):743-50. [Medline].

41. Roberts I. Barbiturates for acute traumatic brain injury. *Cochrane Database Syst Rev.* 2000;CD000033. [Medline].

42. Scher AT. Rugby injuries to the cervical spine and spinal cord: a 10-year review. *Clin Sports Med.* Jan 1998;17(1):195-206. [Medline].

43. Schierhout G, Roberts I. Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. *Cochrane Database Syst Rev.* 2000;CD000173. [Medline].

44. Schierhout G, Roberts I. Hyperventilation therapy for acute traumatic brain injury. *Cochrane Database Syst Rev.* 2000;CD000566. [Medline].

45. Schierhout G, Roberts I. Mannitol for acute traumatic brain injury. *Cochrane Database Syst Rev.* 2000;CD001049. [Medline].

46. Stiefel MF, Spiotta A, Gracias VH. Reduced mortality rate in patietns with severe traumatic brain injury treated with brain tissue oxygen monitoring. *J Neurosurgery.* 2005;103:805-811.

47. Suarez JI, Ulatowski JA. Narcotics for brain-injured patients? At what cost?. *Crit Care Med.* Feb 1999;27 (2):262-3. [Medline].

48. Swann IJ, McCarter DH. Investigation of the head injured patient. *J Accid Emerg Med.* Sep 1998;15(5):337-43. [Medline]. [Full Text].

49. Talbert S, Talbert P. Summary of strategies for managing severe traumatic brain injury during the early posttraumatic phase. *J Emerg Nurs.* Jun 1998;24(3):254-8. [Medline].

50. Teasdale GM, Graham DI. Craniocerebral trauma: protection and retrieval of the neuronal population after injury. *Neurosurgery.* Oct 1998;43(4):723-37; discussion 737-8. [Medline].

51. Tolias CM, Reinert M, Seiler R, Gilman C, Scharf A, Bullock MR. Normobaric hyperoxia--induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: a prospective historical cohort-matched study. *J Neurosurg.* Sep 2004;101(3):435-44. [Medline].

52. National Center for Injury Prevention and Control. Centers for Disease Control and Prevention. In: *Traumatic Brain Injury.* Atlanta, Ga: [Full Text].

53. Working Party of the Royal College of Surgeons of England. *Report of the working party on the management of patients with head injuries.* London, UK: Royal College of Surgeons of England; 1999:[Full Text].

54. Wright MM. Resuscitation of the multitrauma patient with head injury. *AACN Clin Issues.* Feb 1999;10(1):32-45. [Medline].

TAB 2

Journal of NEUROLOGY, NEUROSURGERY & PSYCHIATRY with Practical Neurology urgery

Journal of Neurology, Neurosurgery & Psychiatry
jnnp.bmj.com
J Neurol Neurosurg Psychiatry 2006;**77**:234-240 doi:10.1136/jnnp.2005.072215

Paper

Critical thresholds of intracranial pressure and cerebral perfusion pressure related to age in paediatric head injury

I R Chambers[1], P A Jones[5], T Y M Lo[5], R J Forsyth[2], B Fulton[3], P J D Andrews[6], A D Mendelow[4], R A Minns[5]

+ Author Affiliations

Correspondence to: Dr Iain R Chambers Regional Medical Physics Department, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE, UK; i.r.chambers@ncl.ac.uk

Received 16 May 2005
Accepted 10 August 2005
Revised 10 August 2005
Published Online First 15 August 2005

Abstract

Background: The principal strategy for managing head injury is to reduce the frequency and severity of secondary brain insults from intracranial pressure (ICP) and cerebral perfusion pressure (CPP), and hence improve outcome. Precise critical threshold levels have not been determined in head injured children.

Objective: To create a novel pressure–time index (PTI) measuring both duration and amplitude of insult, and then employ it to determine critical insult thresholds of ICP and CPP in children.

Methods: Prospective, observational, physiologically based study from Edinburgh and Newcastle, using patient monitored blood pressure, ICP, and CPP time series data. The PTI for ICP and CPP for 81 children, using theoretical values derived from physiological norms, was varied systematically to derive critical insult thresholds which delineate Glasgow outcome scale categories.

Results: The PTI for CPP had a very high predictive value for outcome (receiver operating characteristic analyses: area under curve=0.957 and 0.890 for mortality and favourable outcome, respectively) and was more predictive than for ICP. Initial physiological values most accurately predicted favourable outcome. The CPP critical threshold values determined for children aged 2–6, 7–10, and 11–15 years were 48, 54, and 58 mm Hg, respectively.

Conclusions: The PTI is the first substantive paediatric index of total ICP and CPP following head injury. The insult thresholds generated are identical to age related physiological values. Management guidelines for paediatric head injuries should take account of these CPP thresholds to titrate appropriate pressor therapy

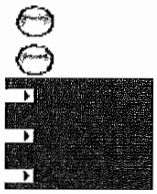
Articles citing this article

Continuous Monitoring of Cerebrovascular Pressure Reactivity After Traumatic Brain Injury in Children
Pediatrics 2009;**124**:e1205-e1212
[Abstract] [Full text] [PDF]

Blood pressure in head-injured patients
J. Neurol. Neurosurg. Psychiatry 2007;**78**:399-402
[Abstract] [Full text] [PDF]

TAB 3

[redacted]



CEREBRAL BLOOD FLOW

The brain is the most demanding organ and it needs 50ml/100gm/minute of continuous blood supply.

Understanding the relationship between cerebral circulation and cerebral function has evolved through refinements in the delineation of cerebral anatomy and physiology.
Ischemic injury may be a final common pathway in many types of cerebral insults. During cerebrovascular procedures, ischemic injury may result from an unanticipated complication of planned permanent or temporary vessel occlusion. An understanding of the physiologic controls of normal cerebral blood flow and the pathophysiology of ischemic injury is necessary for planning effective strategies to minimize the consequences of cerebral ischemia.
The effects of an interruption of cerebral circulation on brain function have also been recognized for centuries. Leonardo da Vinci described the vessels of the neck and recognized that cervical compression would produce unconsciousness. A more modern demonstration and quantification of this relationship (from a technological if not an ethical viewpoint) was offered by Rossen and coworkers. Pneumatic compression of the neck in normal volunteers revealed that a loss of consciousness followed interruption of cerebral blood flow within 10 s.

Normal Cerebrovascular Control

The brain is unique in that it is supplied by four major arteries that join in an equalizing manifold, the circle of Willis. The carotid arteries each supply approximately 40 percent of the total perfusion requirements of the brain. The traditional view of the cerebral circulation saw the arterial supply as being functionally and morphologically separated into two distinct categories: the extracerebral vessels, including the major arteries at the base of the brain and the pial vessels. and the intracerebral vessels, or the penetrating arteries. Subsequent morphologic and functional studies have not confirmed this assumption. and these two groups of vessels are in fact similar.

Four major, interdependent mechanisms are involved in the control of cerebral blood flow: metabolic coupling: neural control, involving both extrinsic and intrinsic neural pathways: P_{CO_2} and autoregulation. Although this division may be somewhat artificial and these control mechanisms probably operate in concert, it is useful to consider each separately.

Metabolic Control

Local cerebral blood flow (CBF) is regionally heterogeneous. The varied pattern of CBF is neither random nor related to the anatomic organization of the cerebral vasculature or to known differences in the innervation patterns of the cerebral vessels. Neuronal activity is the principal energy-consuming process in the brain. Local cerebral blood flow adjusts to the level of energy generation; therefore, it is the activity in the neuronal circuits that is the major determinant of variations and regional patterns of cerebral blood flow. Normally there is exquisite coupling between the regional cerebral metabolic demand for oxygen and glucose generated by local neuronal activity and the volume of blood flowing through that tissue. This coupling, termed metabolic regulation, was first demonstrated by simultaneous measurements of regional glucose metabolism and local blood flow in 1975, although indirect evidence supporting this mechanism had existed for many years. From their classic experiments in 1890, Roy and Sherrington noted that, the chemical products of cerebral metabolism contained in the lymph which bathes the wall of the arterioles of the brain can cause variations of the calibre of the cerebral vessels. In this reaction the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity. While this doctrine was undisputed for nearly a century. the precise mechanisms responsible for this coupling have remained elusive. Alterations in the concentrations of local metabolites may lead to changes in regional CBF. Several chemical species capable of altering local vascular tone generated during periods of enhanced neuronal or glial activity have been considered as mediators of the coupling between flow and metabolism. These include extracellular pH, P_{CO_2} adenosine, glycolytic intermediates, and extracellular potassium (indirectly, through its role in neuronal and smooth muscle cell membrane function, even though it is not directly involved in energy metabolism).

Silver has shown that local blood flow increases as soon as 1 s after neuronal excitation and that the zone of increase is limited to 250 μm around the site of the increased activity. These results indicate that flow can be adjusted very rapidly at the microvascular level according to metabolic demands in discrete functional subunits. There are a number of examples of increases in flow that are disproportionate compared to metabolism during activation. Such overcompensation has been demonstrated at both cellular and macroscopic levels.

A review of the information indicates that (1) the metabolic hypothesis of Roy and Sherrington does not fully explain the phenomenon of metabolic coupling. since CBF may increase out of proportion to metabolic demands: (2) to date, none of the candidates suggested as mediating this coupling demonstrates the necessary temporal profile between its accumulation in the perivascular space and the flow increase: and, finally, (3) these metabolites may be involved in the maintenance of flow and metabolism levels after this relationship has been set at a different level by a yet undetermined rapid initiator. such as a neurogenic stimulus.

Neurogenic Control

The association of metabolism and flow does not prove that metabolism determines flow. The two variables may be governed by a common third factor. The perivascular innervation is a candidate for playing such a role. It is important to consider not only the extrinsic nerve supply from the cranial ganglia to the cerebral arteries. arterioles, and veins, but also the role of intracerebral neurons serving the intracerebral vasculature. A dense plexus of nerve fibers in the walls of cerebral vessels. forming a "minibrain" or regulatory center. Given this arrangement, neurons could form the coupling mechanism between metabolism and flow. Although systemic administration of various neurotransmitter agonists and antagonists may not produce dramatic effects on cerebral blood flow, in experiments where the blood-brain barrier has been circumvented, marked changes are seen, again suggesting a more prominent role for neurotransmitter action from nerves that synapse directly on the cerebral vasculature. Extrinsic nerves, intrinsic nerves, and intrinsic brain regions all may bring their influence to bear on the cerebral vessels.

Theories of neurogenic control of the cerebral vasculature have focused on the role of efferent nerves that follow large arteries to innervate the cerebral vessels. Three types of extrinsic nerve systems, with distinct origins and neurotransmitters. have been identified. One consists of sympathetic neurons arising principally from the superior cervical ganglion. These neurons contain norepinephrine (NE) and neuropeptide-Y (NPY), which are both vasoconstrictors. A second system consists of parasympathetic neurons in the sphenopalatine and otic ganglia. which contain acetylcholine (ACh) and often coexpress vasoactive intestinal peptide (VIP). The third consists of sensory fibers originating in the trigeminal ganglion. These contain substance P (SP) and calcitonin generelated peptide (CGRP), both of which are vasodilators.

Most of the neuron fibers investing the cerebral vasculature are sympathetic. They appear to function by reducing CBF under conditions where it has been increased by metabolic demand. and they may raise the threshold for the breakthrough of autoregulation that occurs with arterial hypertension. Attempts to manipulate CBF by either stimulation or ablation of sympathetic innervation have been largely unsuccessful. The parasympathetic nerves do not appear to play an important role in the tonic control of flow, but they may have some effect in pain-mediated vasodilatory responses.

Trigeminal nerves appear to become important only under special circumstances, such as hypertension and seizures, when their stimulation can effect a substantial increase in CBF. Despite the abundance of these nerve fibers, CBF appears to be primarily regulated by local metabolism with only minor modulation by extrinsic nerves. It is unclear how these peripheral neurons may contribute to the moment-by-moment governance of the cerebral circulation during normal activity.

The possibility that the brain could regulate its own blood flow was recognized by several early researchers in the field, though for many years most investigators did not consider this to be a significant regulatory mechanism. With the advent of both autoradiographic methods for the determination of regional CBF and positron emission tomography (PET) studies of cerebral circulation and metabolism in humans. as well as an explosion of techniques and knowledge in biochemical neuroanatomy, a growing body of evidence supports the concept that the brain can regulate its own blood flow through intrinsic neural networks. Cerebrovascular control may in part be regulated by intrinsic neural systems within the medulla oblongata and may not (as traditionally believed). depend entirely on responses by vessel walls and/or endothelium.

Carbon Dioxide (C02)

It has been well established that alterations in Pa_{CO_2} result in marked vasodilation. There is an exponential relationship between Pa_{CO_2} and CBF within a Pa_{CO_2} range of 25 to 60 mmHg, with a CBF change of approximately of 4 percent per millimetre of mercury.

Flow changes induced by alterations in Pa_{CO_2} occur within 2 min and reach a new plateau within 12 min. This regulatory mechanism has been shown to be a function of changes in the perivascular pH in the vicinity of the vascular smooth muscle cells, rather than a direct effect of CO2 per se. In addition to the direct effects of hydrogen ions on the vascular smooth muscle, local changes in pH can modulate the vasomotor responses to other agents that affect vessel calibre, such as norepinephrine. Since changes in systemic Pa_{CO_2} are detected by carotid artery chemoreceptors, this regulatory mechanism can be effected by reflex pathways. In support of this. it has been observed that a lesion of the tegmental reticular formation diminishes the cerebrovascular response to alterations in Pa_{CO_2}. Investigations has suggested that the powerful effects of CO2 on the cerebral circulation are mediated by endothelium-derived relaxing factor.

Prolonged alterations in Pa_{CO_2} result in chronic adaptation, and after approximately 36 h the blood flow changes tend to return to prealteration levels. At Pa_{CO_2} levels of 70 mmHg, maximal vasodilation has occurred and CBF does not increase as Pa_{CO_2} increases further. Similarly, Pa_{CO_2} levels less than 20 mmHg cause no further decrease in CBF. These low Pa_{CO_2} levels should be avoided in the clinical setting, since the ensuing blood flow reductions can lead to tissue ischemia.

Autoregulation

Autoregulation is defined as the physiologic maintenance of a constant flow over a moderate range of perfusion pressures. This restricted use of the term autoregulation, in contrast to the broader meaning of the term - the capacity of an organ to regulate its blood supply in accordance with its underlying functional or metabolic needs - avoids confusion with other mechanisms involved in cerebrovascular regulation, such as metabolic coupling.

According to the general equation of flow, CBF can be described by the relationship between cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR):

CBF = CPP/CVR

Cerebral perfusion pressure is equal to mean arterial blood pressure (MABP) [where MABP = 1/3(systolic pressure - diastolic pressure) + diastolic pressure] minus intracranial pressure and sagittal sinus pressure. In the absence of pathologic conditions, intracranial pressure and sagittal sinus pressure are negligible compared to systemic arterial pressure, and CPP is roughly equivalent to MABP. According to the previous equation, autoregulation must be mediated by changes in CVR. The Hagen-Poiseuille equation, which describes the flow of Newtonian fluids in rigid tubes, offers an approximation of the factors that govern CVR and suggests that resistance is inversely proportional to blood viscosity and proportional to the fourth power of eheradius of the vessel. Thus, changes in the radius of cerebral blood vessels can produce marked alterations of CVR. A decrease in CPP produces dilation of the precapillary resistance vessels, whereas an increase produces constriction. Largely by variation in the degree of constriction of the cerebral resistance vessels, average hemispheric CBF is maintained at a fairly constant level, near 50 ml/100 g per minute in the adult human brain at rest.

Although myogenic, neurogenic, and metabolic mechanisms have been postulated, the precise control of the autoregulatory response remains unknown. Pioneering work done by Bayliss on the myogenic basis of autoregulation showed that reflex changes in the tone of arteriolar smooth muscle are elicited by changes in transmural pressure. According to this hypothesis, an increase in the transluminal pressure leads to stretching of smooth muscle within the vessel wall. Reflex contraction of radial fibers then results in constriction of vessel diameter, and an opposite effect is seen with a decrease in transluminal pressure.

A growing body of evidence suggests that endothelium-dependent mechanisms function as the primary mediating factor of vascular tone, and they are now considered as a facet of the myogenic hypothesis of autoregulation. The endothelium acts as a transducer of hemodynamic forces that lead to the release of vasoactive substances. Synthesis of the endothelium-derived relaxing factor, either nitric oxide (EDRF/NO) or a closely related molecule derived from the amino acid L-arginine, appears to affect vascular tone, both under basal conditions and in response to the application of specific agonists. The proposed mechanism for this effect is that stimulation of soluble guanylate cyclase by EDRF/ NO raises the level of cyclic guanosine monophosphate (cGMP) in vascular smooth muscle and results in vascular relaxation. Dilation of large cerebral arteries and pial arterioles in response to the application of acetylcholine in vivo is dependent on the formation of NO by nitric oxide synthase and can be blocked by a competitive antagonist of that enzyme, *N*-monomethyl-L-arginine (L-NMMA). Intravenous administration of a similar NO synthase antagonist in rats caused a 40 percent increase in MABP and a 60 percent reduction in the lumen diameter of pial arteries. This L-arginine/NO/cGMP pathway appears to be critical in the control of vascular tone and is increasingly accepted as the dominant mediator of the autoregulatory response.

In the brain, autoregulation is manifest as the lack of major fluctuation in CBF despite changes in mean arterial blood pressure
between 60 and 150 mmHg. Cerebral autoregulation may be thought of as a homeostatic mechanism that is superimposed on the baroceptive reflexes. It is important to stress that both the upper and the lower limits of autoregulation can be affected by many factors, including sympathetic nerve activity, Pa_{CO_2} and pharmacologic agents. The most important factor that can affect autoregulation is chronic arterial hypertension. As a result of thickening of the cerebral arteries, the upper and lower limits of autoregulation are both displaced to higher levels in patients with chronic hypertension. The consequence of these alterations is that symptoms of cerebral hypoperfusion can occur at higher values of mean arterial pressure in patients with chronic hypertension than in normotensive individuals.

A knowledge of the cerebrovascular status of the patient with respect to hypertension may also be a consideration in the planning of temporary vessel occlusion during cerebrovascular surgery. Some experimental evidence suggests that intermittent temporary occlusion is less damaging than a single sustained episode. Other experimental work directed specifically at determining the response in both normotensive and hypertensive animals demonstrates that in the latter group, intermittent occlusion was associated with a greater degree of ischemic injury.

Cerebral Blood Flow and Ischemic Thresholds

The unique metabolic requirements of the brain form the central basis for understanding the relationship between blood flow and ischemic tolerance. Although the brain represents only 2 percent of the total body weight, it receives 18 percent of the cardiac output and uses 20 percent of the oxygen supply. Its high metabolic demand and lack of appreciable energy reserves render the central nervous system uniquely susceptible to alterations of blood supply. The use of PET has greatly enhanced our understanding of the pathophysiologic alterations that occur in focal cerebral ischemia in humans. The simultaneous measurement of regional CBF, oxygen metabolism (CMRO2), oxygen extraction fraction (OEF, or amount of oxygen extracted from the blood as it travels from artery to vein), and cerebral blood volume (CBV, or the volume of blood in the cerebral parenchyma) has permitted the identification of three successive stages of severity in an ischemic injury to the brain. As CPP initially falls, autoregulation occurs and vasodilation of precapillary resistance vessels causes an increase in CBV while maintaining both CBF and CMR_{O_2} At the lower limit of autoregulation, maximal compensatory dilation of cerebral resistance vessels has occurred. Further reductions in CPP lead to a fall in CBF. The oxygen extraction fraction (OEF) then increases to maintain CMR_{O_2}. If CBF reduction is modest, the increased extraction of oxygen and glucose by the brain from remaining blood flow can maintain normal brain metabolism and function. A leftward shift of the oxygen-haemoglobin affinity curve, which is produced by the decreased local pH. results in an increased transfer of oxygen from blood to tissue and is largely responsible for the increased OEF. When the OEF reaches its maximum (approximately 90 percent). no further compensation can occur. As CBF falls further, the metabolic demands of the brain can no longer be satisfied, and CMR_{O_2} decreases.

The alterations of cerebral function that occur as these compensatory systems become overwhelmed in the face of increasingly severe ischemia may be best understood in the context of ischemic thresholds and the ischemic cascade.

Flow Thresholds

Electrophysiologic techniques and accurate cerebral blood flow determinations have refined our understanding of the relationship between neuronal function, tissue viability and critical levels of regional cerebral blood flow.

Experimental studies of middle cerebral artery occlusion in various species have demonstrated a blood flow gradient from normal flow in areas outside the affected territory, to modest decreases in the adjacent perifocal region, to a profound drop in the ischemic core. The slope of this gradient depends on the extent and functional capacity of collateral blood supply.

While some authors have attempted to make a distinction between the events occurring in the ischemic core and those that occur in tissue affected by a global ischemic insult, on a biochemical basis it is difficult to clearly dissociate the events occurring in these two environments. The tissue in the border zone between normal perfusion and the ischemic core-the perifocal region-may be subjected to unique challenges to its homeostatic mechanisms, however.

Different cellular functions, which require specific minimum levels of blood flow, are affected in these regions depending on the level of blood flow reduction. Certain functional perturbations occur once blood flow decreases below these thresholds. Critical values for loss of synaptic transmission, corresponding to loss of neuronal function, are between 15 and 18 ml/100 g per minute. The threshold for membrane pump failure. and thus for loss of cellular integrity, is approximately 10 ml/100 g per minute. The level of blood flow reduction for ion pump failure appears to be similar to that for energy failure. The presence of these two distinct thresholds implies that some regions in the perifocal area contain cells that are electrophysiologically quiescent but nonetheless viable. These regions constitute the ischemic penumbra, defined as areas with EEG quiescence and low extracellular K^+. These thresholds were determined in experimental models using both primates and other higher vertebrates. Similar values have been reported in humans. While absolute values may vary somewhat depending on the species and anaesthetic factors, the percent reduction from normal flow to these thresholds appears to be uniform and constant.

Flow reduction is one component that determines the severity of an ischemic insult, but the duration of flow reduction is also of paramount importance. The threshold for infarction in monkeys is approximately 12 ml/100 g per minute, but that the duration as well as the degree of blood flow reduction was important, since infarction developed only if blood flow was reduced to below 12 ml/100 g per minute for periods lasting 2 h or longer. Since the time course for irreversible damage in complete global ischemia models is much shorter-approximately 10 min-it is reasonable to suspect that areas with more profound blood flow reduction in focal ischemia have a shorter tolerance than areas with higher levels of blood flow.

The existence of two distinct thresholds suggests that some areas in the perifocal region contain cells that are electrically silent but nonetheless viable. These cells are the likely targets for prevention of ischemic injury, since they should be the most susceptible to therapeutic rescue. The ability to maintain a low extracellular potassium concentration in the perifocal region implies that sufficient energy stores remain to maintain near-normal electrochemical gradients. but the neuronal paralysis and reduced blood flow suggest that the penumbra is clearly at risk for further damage. SiesjÖ has applied a pragmatic definition to this region by defining a reperfusion penumbra and a pharmacologic penumbra, which represent the tissue that would inevitably become infarcted without the timely institution of either reperfusion or pharmacologic intervention.

Therapeutic Manipulation of Residual Flow and Alteration of Flow Thresholds

The Role of Blood Viscosity

The importance of blood viscosity in the routine regulation of CBF remains controversial. Several studies suggest that in normal brain the effect of blood viscosity on cerebral perfusion is nonexistent or minimal. Under ischemic conditions. however. even small alterations in the rheologic properties of blood may have significant functional relevance.

This selective contribution of viscosity to the regulation of CBF under impaired flow conditions can be explained by the inconstant nature of blood viscosity, which results from erythrocyte deformability and aggregation. Therefore, the relationship between blood flow and viscosity is imprecisely described by the HagenPoiseuille equation. especially at low flow rates. In low-flow states, perfusion pressure is reduced and compensatory vasodilation of the microcirculation occurs. Under these conditions, blood flow is further reduced by an increase in viscosity. Thus, under ischemic conditions an intricate relationship exists between vasomotor compensatory mechanisms and blood viscosity, and even small alterations in the rheologic properties of blood have significant functional relevance.

Blood viscosity is determined by several factors. hematocrit being the most important, especially when shear rates are low. The steep portion of the hematocrit-viscosity curve falls in the physiologic range of hematocrit. Reductions in hematocrit within the physiologic range significantly reduce blood viscosity and this effect is most marked at the low shear rates seen in focal cerebral ischemia.
Experimental studies have shown augmentation of diminished CBF following the acute reduction of hematocrit. Although reduction of hematocrit (and thus haemoglobin content) reduces the oxygen content of blood. relative oxygen transport capacity has been calculated to increase owing to improved CBF with hematocrit reductions to approximately 30 percent. Below this hematocrit level, the decrease in blood oxygen content outweighs the beneficial effect of decreased viscosity on CBF in the microcirculation. This finding is consistent with reports that indicate that a hematocrit range of 30 to 32 percent is optimal for tissue oxygen delivery.

The Role of Reperfusion

The results of experimental work with reperfusion suggest that there is a definite time limit after which such restoration of flow will not be beneficial. Whether such treatment is in fact harmful is a matter of some debate. That reperfusion can lead to aggravation of edema and hemorrhagic transformation has been clearly documented. On a cellular and pathophysiologic level, it has also been shown that "reperfusion injury" occurs in some organs. This type of injury is speculated to occur in the brain. It has nevertheless been shown that reperfusion achieved by the endovascular route in the early evolution of ischemic damage in the clinical setting does improve neurological outcome and offers a promise of revolutionizing the treatment of stroke.

The Role of Calcium Homeostasis

While there are many promising areas of investigation into the pharmacologic control of the cerebral circulation, including adrenergic mechanisms and the roles of dopamine, serotonin, acetylcholine, histamine, prostaglandins, neuropeptides, and glutamate, few have generated as much interest among neurosurgeons as the possible uses of calcium antagonists.
The role of calcium in the control of both cerebrovascular smooth muscle function and intracellular homeostasis offers opportunities for the treatment of ischemia and ischemia-producing disorders. The pharmacologic effects exerted by calcium entry blockers on vascular reactivity through an effect on excitationcontraction coupling involve three main processes: the influx of extracellular calcium or release of calcium from intracellular stores. the transport of calcium out of the cells and

uptake into various cell organelles and the processes that are regulated by the intracellular concentration of free calcium and that affect the activity of contractile proteins themselves or other cellular processes.

The final common pathway for initiating contraction in vascular smooth muscle cells is believed to be an increase in the concentration of free ionized calcium within the cell. The current concept is that vasoconstrictor agents cause a depolarization of smooth muscle cells that in turn increases their spike frequency and ultimately leads to vascular contraction. Of great therapeutic interest is the ability of some pharmacologic agents to induce contraction independent of any change in membrane potential (pharmacomechanical coupling). These effects on smooth muscle function have resulted in the use of calcium antagonists as therapeutic agents in the treatment of cerebral vasospasm. Their precise role in this setting needs further clarification, since it is unclear whether the reported beneficial effects are due to changes in blood flow at the microcirculatory level or are directly related to ischemic cell protection, since dramatic changes in angiographic spasm are not seen with these agents.

Loss of Ca^{2+} homeostasis leading to an elevated level of intracellular Ca_i^{2+} has been implicated as a cause of irreversible cell injury in ischemia. Both voltage-sensitive and agonist-operated calcium channels control the movement of calcium into the cell, and the latter are predominantly involved in the initiation of the pathologic processes resulting from ischemia. Since Ca^{2+} plays an important role as an intracellular messenger, the rise in Ca_i^{2+} may disrupt several intracellular processes and thus compromise the cell's ability to recover from the insult.

The importance of Ca^{2+} as an intracellular messenger can be appreciated by the number of different mechanisms employed by the cells to maintain Ca^{2+} homeostasis. Intracellular Ca^{2+} concentration is maintained around 10^{-7} *M*, while extracellular concentration is in the range of 10^{-3} *M*. This large concentration gradient together with the electrical gradient exerts large inward force on Ca^{2+} ions. This gradient takes energy to maintain, requiring the active extrusion of Ca^{2+} from the cell either by a Ca^{2+}-activated ATPase or by electrogenic (3:1) Na^+/Ca^{2+} exchange, which uses the membrane Na^+ gradient as the energy source. Regulation of intracellular Ca^{2+} over the short term can be achieved by the binding or sequestration of calcium. Virtually all of the intracellular Ca^{2+} is bound to calcium-binding proteins or other molecules. Sequestration of Ca^{2+} also is energy-dependent, and it occurs primarily in the endoplasmic reticulum and mitochondria.

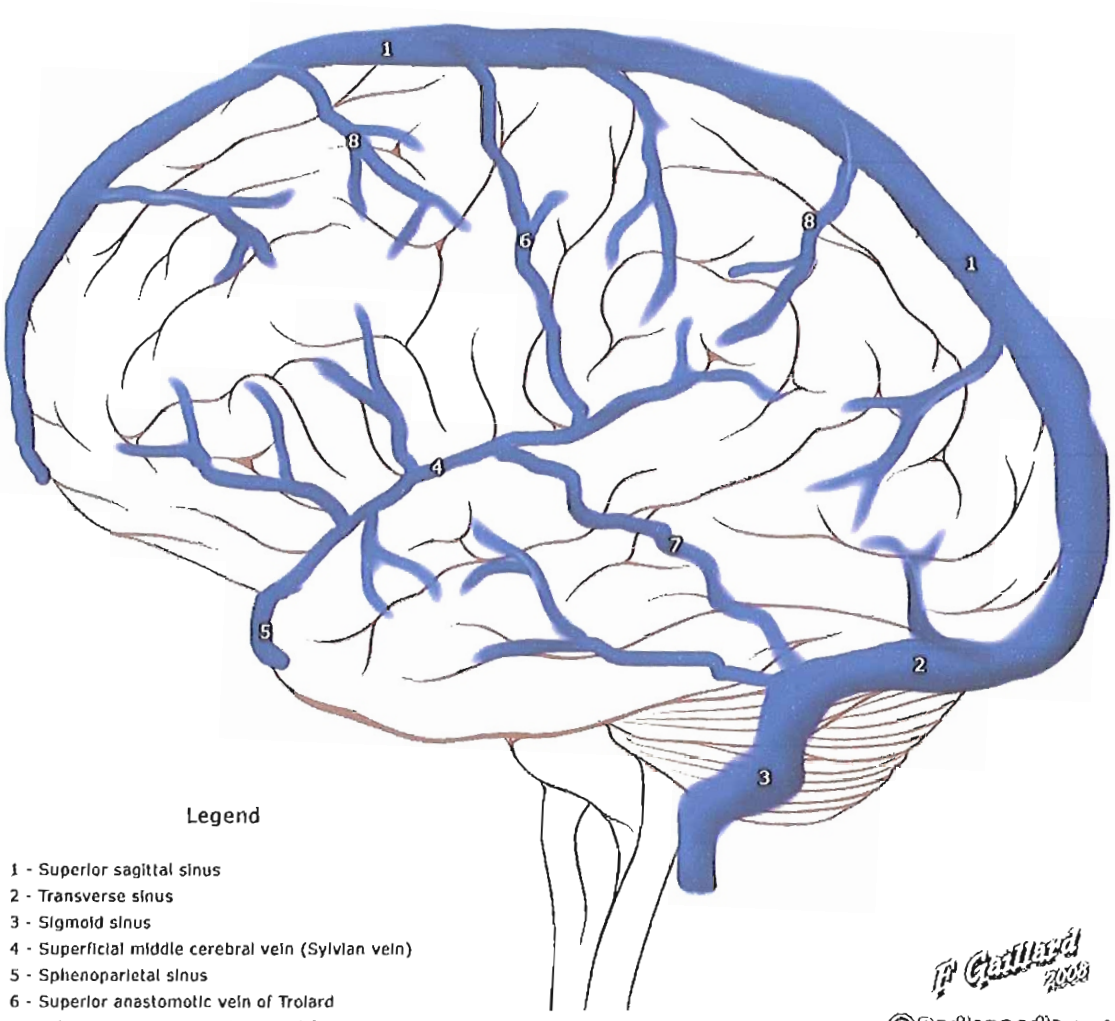
There is substantial evidence that a massive influx of calcium occurs during ischemia. The excessive rise in Ca_i^{2+} that results from an ischemia-induced failure of these homeostatic mechanisms represents a nonphysiologic stimulus that activates a wide array of intracellular receptors, membrane channels and phosphorylases, which lead to compromise of the cells functional and structural integrity.

Summary and Conclusions

Although the precise mechanisms remain to be elucidated, it can be appreciated from the material discussed that cerebral blood flow is strictly maintained and controlled. Pathologic conditions. induced by either disease or therapeutic intervention, can disrupt the regulation of blood flow and metabolism and the neurosurgeon must be aware of these alterations to avoid untoward sequelae.

TAB 4

Superficial veins of the brain

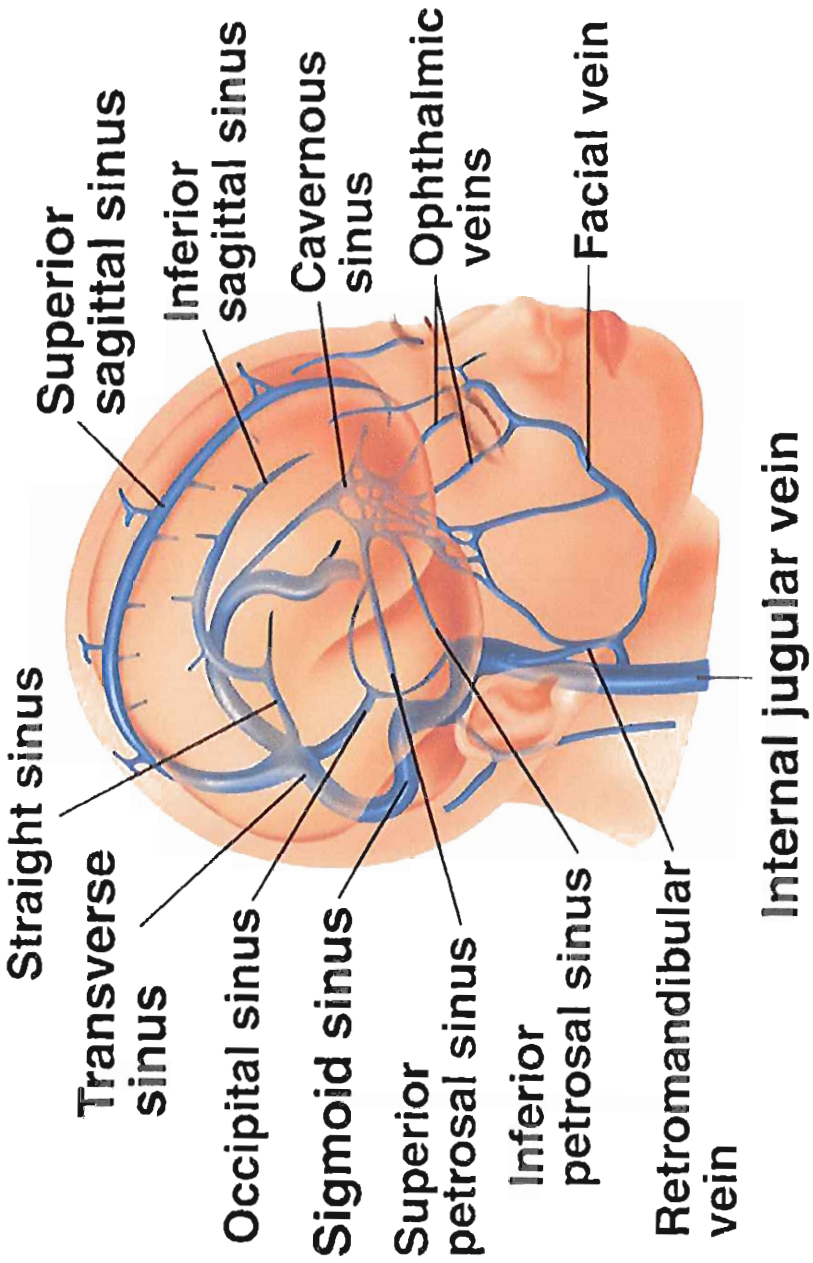


Legend

1 - Superior sagittal sinus
2 - Transverse sinus
3 - Sigmoid sinus
4 - Superficial middle cerebral vein (Sylvian vein)
5 - Sphenoparietal sinus
6 - Superior anastomotic vein of Trolard
7 - Inferior anastomotic vein of Labbé
8 - Superior cerebral veins

Lateral view of brain base image, Creative Commons, Patrick Lynch 2006

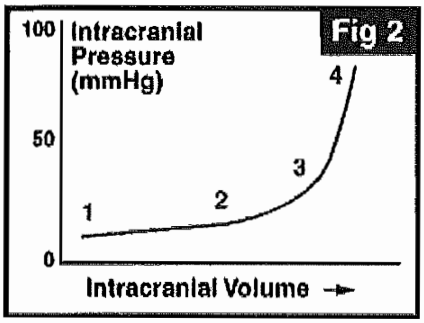
TAB 5



TAB 6

Intracranial Pressure and Cerebral Blood Flow *(Continued)*

The pressure changes within the skull are drawn in the classical curve Fig. 2 which indicates an increase in volume with little change in pressure until a certain point is reached when a further small change in volume results in a large increase in pressure: 1-2 compensation phase; 3-4 decompensation phase.



It is interesting to note that this classic curve represents the alterations in pressure when the volume of a single compartment within the skull, in this case CSF, changes. Therefore it is a CSF-pressure volume curve. In practice when the enlargement of the brain is due to a tumour or haematoma the curve is less steep. Pressure gradients develop within the brain substance and the compliance or "squashiness" of the tumour is different from that of brain leading to this altered curve.

Cerebral swelling leads to herniation of the brain either internally, when the temporal lobe is pushed down onto the mid-brain through the tentorium incisura or externally, with the cerebellar peduncles being forced down through the foramen magnum. This causes torsion of the brain stem and a reduction of local cerebral blood flow as the unrelenting rise in ICP opposes arterial pressure. Ultimately cerebral perfusion pressure falls to a point when there is no cerebral blood flow, no cerebral perfusion and death. The rise in ICP may be accelerated because of acute hydrocephalus. This is caused by brain-stem torsion leading to sudden obstruction of CSF flow.

The volume of blood contained within the venous sinuses is reduced to a minimum as part of the compensatory process. However, should free flow of venous blood be impeded by a number of simple causes (INFO Table 1) then this increase in volume of the venous system in a critically swollen brain will lead to a rapid rise in ICP. In practice, it is imperative to ensure that when the patient is in the supine or lateral position that a head up tilt to a maximum of 30° is obtained. This improves venous drainage with minimal effect on arterial pressure [1]. Venous drainage is passive and thus maximised by ensuring there is no pressure on, or kinking, of the neck veins. In addition the higher the head, the greater the effect of gravity on the flow of venous blood. However, as the head is raised, the gravitational effect on the arterial pressure at the brain is also increased. This is a disadvantage as it reduces the pressure of blood perfusing the brain. The best compromise is the position described above of 30°.

Teaching point. If the patient is lying in the supine position, and it is necessary to turn the head laterally, a sand bag should be placed under the shoulder to reduce the pressure of the sternomastoid on the jugular vein. When patients with severe head injuries are nursed or transported it must be with a 30° head up tilt, and the blood pressure maintained.

The extent of the change in ICP caused by an alteration in the volume of intracranial contents is determined by the compliance or "squashiness" of the brain. In other words if compliance is low, the brain is stiffer or less "squashable". Therefore, an increase in brain volume will result in a higher rise in intracranial pressure than if the compliance were high. Compliance affects the elastance or "stretchiness" of the walls of the ventricles. When the elastance is reduced the walls are stiffer. Therefore there is a greater change in pressure for a given alteration in brain volume. If a catheter is inserted into a lateral ventricle via a burr hole, this can be assessed by injecting 1ml of saline and observing the change in intracranial pressure. After the injection, if the rise in pressure is more than 5 mmHg then the patient has become has become decompensated and is at the right hand end of the pressure-volume curve (Fig 2). ⧗

Cerebral Perfusion Pressure

Cerebral perfusion pressure (CPP) is defined as the difference between mean arterial and intracranial pressures. Mean arterial pressure is the diastolic pressure plus one third of the pulse pressure (difference between the systolic and diastolic). MAP is thus between systolic and diastolic pressures, nearer diastolic. It is used as it is the best value to estimate the "head of pressure" perfusing in the brain:

CPP = MAP - ICP

Normal cerebral perfusion pressure is 80 mmHg, but when reduced to less than 50 mmHg there is metabolic evidence of ischaemia and reduced electrical activity. There have been a number of studies on patients with severe head injuries which have shown an increase in mortality and poor outcome when CPP falls to less than 70 mmHg for a sustained period [2,3]. Continuous monitoring of jugular venous bulb saturation is another tool used to monitor the adequacy of the cerebral circulation when it is at risk. Jugular venous bulb saturation is the oxygen saturation of venous blood in the jugular bulb which is at the base of the skull. The normal range is 65%-75%. If blood flow to the brain is reduced below a critical point there is a fall in venous saturation. As the flow of blood and delivery of oxygen is reduced, the brain, in order to maintain its oxygen supply, extracts more oxygen from the blood, leading to a fall in venous oxygen saturation.

Teaching point. Cerebral perfusion pressure (CPP) = MAP - ICP
Inadequate CPP (less than 70 mmHg) has been shown to be a major factor in the poor outcome of patients with raised ICP. Assessment of CPP is vital and possible either by measurement of both ICP and MAP (mean arterial pressure - see text) or by measuring MAP and making a reasonable estimate of ICP. During anaesthesia therefore, if ICP is raised a fall in blood pressure must be avoided or treated quickly by volume replacement or catecholamines whichever is relevant.

More specifically, when CPP is inadequate the oxygen saturation of jugular venous blood falls (normal range 65%-75%) because of increased oxygen extraction. Does the jugular venous bulb measurement give an indication of the minimum level for CPP? Chan [4] in another study of head-injured patients showed that when CPP was below 70 mmHg, there was a rapid decrease in jugular venous bulb saturation. It was concluded that when CPP was less than 70 mmHg cerebral perfusion was insufficient.

In the head injured patient, CPP should not fall below 70 mmHg.

Therefore continuous consideration of changes in CPP are vital when anaesthetising patients who may have raised ICP and a fall in arterial pressure occurs as a result of anaesthetic agents or blood loss. Ideally ICP should be monitored, but often this is impossible or impractical. However a reasonable estimate can be made in head injured patients who are not sedated:

Drowsy and confused: (GCS 13-15)ICP=20 mmHg,
Severe brain swelling (GCS <8) ICP=30 mmHg

Teaching point. The following example illustrates the point. A 28-year old patient who has had a recent head injury where he was unconscious briefly, requires urgent abdominal surgery. He is confused, restless and drowsy. It would be reasonable to estimate his ICP to be 20 mmHg. Following induction of anaesthesia his systolic arterial pressure (SAP) falls to 80 mmHg. In this situation MAP will have fallen to 65 mmHg and therefore CPP will have fallen to less than 45 mmHg, significantly below the critical value of 70 mmHg with a significant risk of causing cerebral ischaemia and a poor cerebral outcome. ▲

(Continued ...)

Next Page ➡

Issue Index | Section Index | Keyword Search | Download Update | Guidance Notes | Contacts | Home Page

TAB 7

Update in Anaesthesia

Physiology | Next Article | Issue Index | Home Page | Prev Article

Issue 8 (1998) Article 4: Page 1 of 4 Go to page: 1 2 3 4

Intracranial Pressure and Cerebral Blood Flow

Dr FJM Walters,
Consultant Anaesthetist, Frenchay Hospital, Bristol, UK

- Introduction
- Intracranial pressure
- Cerebral perfusion pressure
- Cerebral blood flow
- Applied physiology - Head injury
- References

Introduction

The physiological changes that maintain cerebral blood flow (CBF) and accommodate alterations in brain volume are relatively simple to understand. Following trauma or in the presence of major intracranial disease additional changes occur. Major advances in the care of patients with major neurosurgical problems have been developed over the last 10 years. These advances have evolved from a sound understanding of basic physiological rules and the pathological process of different disease situations as well as the pharmacology of anaesthetic drugs. Successful management of these patients relies on a clear understanding of these physiological mechanisms and of the added effect of anaesthesia and the manipulation of arterial pressure, CO_2 and O_2 tensions.

Poor anaesthetic technique which allows coughing, straining, hypotension, exaggerated hypertension, hypoxia and hypercarbia will seriously damage the brain. Better results can be obtained by careful monitoring of the patient and attention to simple details than by complex pharmacological interventions. It is the purpose of this article to explain these factors and how an understanding of them can be applied to patients following head trauma or intracranial disease.

The brain is only able to withstand very short periods of ischaemia, unlike the kidney, liver or muscle. Thus cerebral blood flow must be maintained to ensure a constant delivery of oxygen and glucose as well as the removal of "waste" products. Maintenance of cerebral blood flow depends on a balance between the pressure within the skull, intracranial pressure (ICP) and the arterial pressure of the blood, mean arterial pressure (MAP). It is important to maintain a constant blood flow. Thus when blood pressure falls, physiological mechanisms attempt to maintain flow to prevent ischaemia. This process is autoregulation and is explained in detail later. Similarly, when blood pressure rises, the same mechanism stops the blood flow from increasing to excessive levels. If this did occur, cerebral oedema could develop and the brain would enlarge because of the increase in cerebral arterial blood volume.

A number of terms will be used in this article and are defined:

- **ICP** intracranial pressure is the pressure within the rigid skull.

- **CBF** cerebral blood flow is the flow of blood through the brain, important for delivery of oxygen and removal of "waste" products

- **CPP** cerebral perfusion pressure is the effective pressure driving blood through the brain. It is discussed in detail later ⧗

Intracranial Pressure

Teaching Point: High intracranial pressure (ICP) will cause internal or external herniation of the brain, distortion and pressure on cranial nerves and vital neurological centres. Cerebral perfusion will be impeded and operating conditions difficult or impossible. Loss of CSF and reduction of venous blood volume act to compensate for increases in brain volume. Once these mechanisms are exhausted, any further increase, however small, will cause a large increase in ICP.

The principle constituents within the skull are brain (80%), blood (12%) and CSF (8%). The total volume is 1600ml. The skull is thus a rigid fluid filled box. If the volume of the contents of a rigid fluid-filled container increase, the pressure inside will rise considerably unless some fluid is able to escape. So it is with the skull and brain within it.

If the brain enlarges, some blood or CSF must escape to avoid a rise in pressure. If this should fail, or be unable to occur there will be a rapid increase in ICP from the normal range (5-13 mmHg). If there is an increase in the volume of either the brain or blood the normal initial response is a reduction in CSF volume within the skull. CSF is forced out into the spinal sac. Thus the pressure within the skull, ICP, is initially maintained. If the pathological process progresses with further increase in volume, venous blood and more CSF is forced out of the skull.

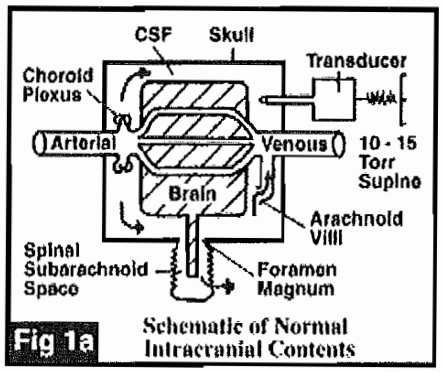


Fig 1a Schematic of Normal Intracranial Contents

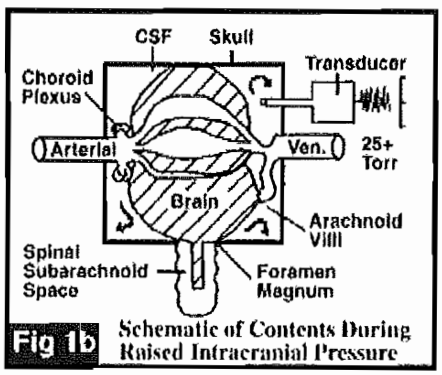


Fig 1b Schematic of Contents During Raised Intracranial Pressure

Ultimately this process becomes exhausted, when the venous sinuses are flattened and there is little or no CSF remaining in the head. Any further increase in brain volume then causes a rapid increase in ICP. This chain of events is represented by the sequence in Fig 1a and 1b.

(Continued ...)

Next Page

Issue Index | Section Index | Keyword Search | Download Update | Guidance Notes | Contacts | Home Page

TAB 8

Cerebral Blood Flow

The normal cerebral blood flow is 45-50ml $100g^{-1}$ min^{-1}, ranging from 20ml $100g^{-1}$ min^{-1} in white matter to 70ml $100g^{-1}$ min^{-1} in grey matter. There are two essential facts to understand about cerebral blood flow. Firstly, in normal circumstances when the flow falls to less than 18-20ml $100g^{-1}$ min^{-1}, physiological electrical function of the cell begins to fail. Secondly, an increase or decrease in CBF will cause an increase or decrease in cerebral arterial blood volume because of arterial dilatation or constriction. Thus in a brain which is decompensated as a result of major intracranial pathology, increases or decreases in CBF will in turn lead to a significant rise or fall in ICP. The physiological factors which can alter CBF and hence ICP are listed in INFO Table 2. There are also a number of drugs which can induce arterial dilatation, the most well known being high concentrations of volatile agents. These will be discussed in detail in a subsequent article.

Teaching Point. There are a number of physiological factors which affect or change cerebral blood flow (CBF). Rises in CBF due to hypoxia, hypercapnia (raised blood CO_2) and high concentrations of volatile agents will cause a rise in ICP once the normal compensating mechanisms have been exhausted. Poor anaesthetic technique during which hypoxia, hypercapnia and hypotension occur will seriously damage the critically ill brain further.

Autoregulation. CBF is maintained at a constant level in normal brain in the face of the usual fluctuations in blood pressure by the process of autoregulation. It is a poorly understood local vascular mechanism. Normally autoregulation maintains a constant blood flow between MAP 50 mmHg and 150 mmHg. However in traumatised or ischaemic brain, or following vasodilator agents (volatile agents and sodium nitroprusside) CBF may become blood pressure dependent. Thus as arterial pressure rises so CBF will rise causing an increase in cerebral volume. Similarly as pressure falls so CBF will also fall, reducing ICP, but also inducing an uncontrolled reduction in CBF.

More recent work has shown that following trauma autoregulation may still be functioning. Bouma reported that it was present in up to 69% patients with head injuries [5].

In this situation if CPP falls below the critical value of 70 mmHg, the patient will have inadequate cerebral perfusion. Autoregulation will cause cerebral vasodilatation leading to a rise in brain volume. This in turn will lead to a further rise in ICP and induce the vicious circle described by the vasodilatation cascade (fig 3a) which results in cerebral ischaemia.

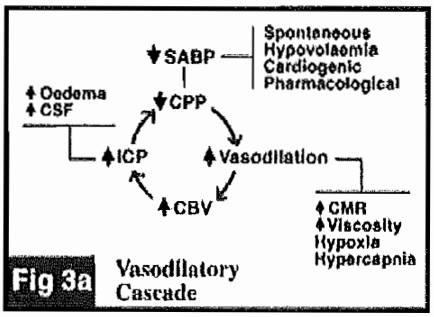


Fig 3a Vasodilatory Cascade

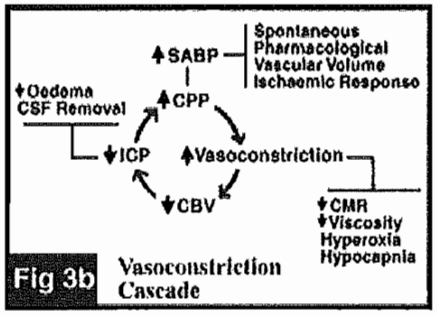


Fig 3b Vasoconstriction Cascade

This process can only be broken by increasing the blood pressure to raise CPP, inducing the vasoconstriction cascade (fig 3b). This explains why the maintenance of arterial blood pressure at adequate level by careful monitoring and rapid correction if it falls is so important.

Carbon dioxide causes cerebral vasodilation. As the arterial tension of CO_2 (fig 4) rises, CBF increases and when it is reduced vasoconstriction is induced.

Thus hyperventilation can lead to a mean reduction in intracranial pressure of about 50% within 2-30 minutes [6]. When $PaCO_2$ is less than 25 mmHg (3.3kPa) there is no further reduction in CBF. Therefore there is no advantage in inducing further hypocapnia as this will only shift the oxygen dissociation curve further to the left, making oxygen less available to the tissues.

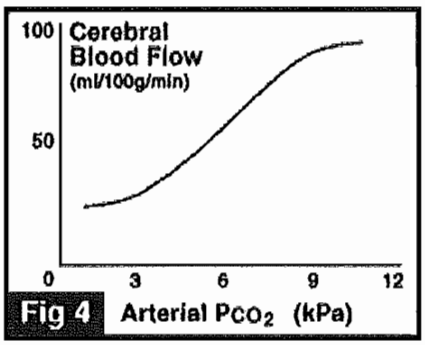


Fig 4

Acute hypocapnic vasoconstriction will only last for a relatively short time (5 hours). While hypocapnia is maintained, there is a gradual increase in CBF towards control values leading which will lead to cerebral hyperaemia (over-perfusion) if the $PaCO_2$ is returned rapidly to normal levels (7). When long term ventilation is required, only mild hypocapnia (34-38 mmHg: 4.5-5.1 kPa) should be induced. Worse outcome was reported in patients after head injuries at 3 and 6 months in those who had been hyperventilated to low $PaCO_2$ levels for long periods [8].

Teaching Point. When there is an acute rise in ICP, for example after an acute head injury ICP can be reduced by hyperventilation to lower arterial CO_2 tension. This technique is used during neurosurgery to reduce brain size to improve access for the surgeon. In CONTRAST only mild hyperventilation should be used for long term ventilation of patients as described above.

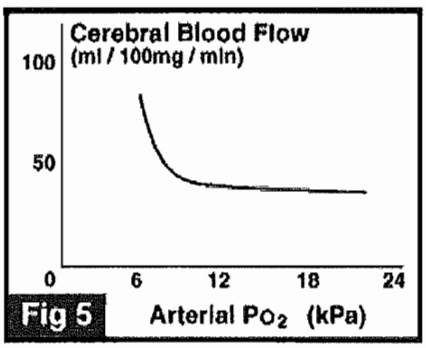


Fig 5

Oxygen. Low arterial oxygen tension also has profound effects on cerebral blood flow (Fig 5). When it falls below 50 mmHg (6.7 kPa), there is a rapid increase in CBF and arterial blood volume.

(Continued ...)

Next Page

Issue Index | Section Index | Keyword Search | Download Update | Guidance Notes | Contacts | Home Page

TAB 9

J Neurol. 2010 Dec;257(12):2044-51. Epub 2010 Jul 16.

Cerebral infarction in acute anemia.

Tsai CF, Yip PK, Chen CC, Yeh SJ, Chung ST, Jeng JS.

Department of Neurology, Cardinal Tien Hospital, Taipei, Taiwan.

Abstract

There are few previous studies on the relationship between cerebral infarction and acute anemia. This study presents patients with cerebral infarction in acute anemia due to marked blood loss and aims to clarify the stroke nature and possible mechanism. Patients with acute cerebral infarction and anemia following marked blood loss without systemic hypotension were recruited from 2001 to 2009. Clinical characteristics, particularly hemoglobin level, and neuroimaging findings were reviewed in detail to analyze the stroke nature and verify the possible pathogenesis. Twelve patients (males 8; mean age 74.9 years) were included. Eleven patients had cerebral infarction after acute massive gastrointestinal bleeding, and one had cerebral infarction following postoperative extensive hematoma during hospitalization. In all patients, borderzone infarction was the most characteristic finding: six had unilateral and six had bilateral borderzone infarction. Mean hemoglobin at infarction after acute blood loss was 5.8 g/dl, with 46% reduction from baseline. Of nine patients receiving detailed extracranial and intracranial vascular studies, none had severe carotid stenosis and six had intracranial stenosis. The arterial borderzones are the most vulnerable regions to a fall in cerebral perfusion. Acute anemia may produce cerebral blood flow insufficiency, reduce oxygen-carrying capacity, and result in distal-field tissue ischemic injury when hemoglobin level decreases below a critical level, especially in patients with intracranial stenosis.

PMID: 20635184 [PubMed - indexed for MEDLINE]

TAB 10

PubMed Search

Display Settings: Abstract

ELSEVIER FULL-TEXT ARTICLE

J Thorac Cardiovasc Surg. 2005 Feb;129(2):391-400.

Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery.

Karkouti K, Beattie WS, Wijeysundera DN, Rao V, Chan C, Dattilo KM, Djaiani G, Ivanov J, Karski J, David TE.

Department of Anesthesia, University Health Network, University of Toronto, Ontario, Canada. keyvan.Karkouti@uhn.on.ca <keyvan.Karkouti@uhn.on.ca>

Abstract

BACKGROUND: This observational study sought to determine whether the degree of hemodilution during cardiopulmonary bypass is independently related to perioperative acute renal failure necessitating dialysis support.

METHODS: Data were prospectively collected on consecutive patients undergoing cardiac operations with cardiopulmonary bypass from 1999 to 2003 at a tertiary care hospital. The independent relationship was assessed between the degree of hemodilution during cardiopulmonary bypass, as measured by nadir hematocrit concentration, and acute renal failure necessitating dialysis support. Multivariate logistic regression was used to control for variables known to be associated with perioperative renal failure and anemia.

RESULTS: Of the 9080 patients included in the analysis, 1.5% (n = 134) had acute renal failure necessitating dialysis support. There was an independent, nonlinear relationship between nadir hematocrit concentration during cardiopulmonary bypass and acute renal failure necessitating dialysis support. Moderate hemodilution (nadir hematocrit concentration, 21%-25%) was associated with the lowest risk of acute renal failure necessitating dialysis support; the risk increased as nadir hematocrit concentration deviated from this range in either direction (P = .005). Compared with moderate hemodilution, the adjusted odds ratio for acute renal failure necessitating dialysis support with severe hemodilution (nadir hematocrit concentration <21%) was 2.34 (95% confidence interval, 1.47-3.71), and for mild hemodilution (nadir hematocrit concentration >25%) it was 1.88 (95% confidence interval, 1.02-3.46).

CONCLUSIONS: Given that there is an independent association between the degree of hemodilution during cardiopulmonary bypass and perioperative acute renal failure necessitating dialysis support, patient outcomes may be improved if the nadir hematocrit concentration during cardiopulmonary bypass is kept within the identified optimal range. Randomized clinical trials, however, are needed to determine whether this is a cause-effect relationship or simply an association.

PMID: 15678051 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources

TAB 11

CHAPTER TWO
CEREBRAL ISCHEMIA AND STROKE

Page 1 | Page 2 | Page 3| Page 4
HIE General Principles | HIE Pathology | HIE-Clinical Findings | The White Matter in HIE |
Cerebral infarcts-Clinical Findings | Pathology | Hemorrhagic Infarct |Lacunar Infarct | Causes of Ischemic Infarction | Small Vessel Disease | Venous Infarct |Vascular Dementia |
Cerebral Hemorrhage |Hypertensive Hemorrhage |Hypertensive Encephalopathy |Arterial Aneurysms | Arterio-venous Malformation | Cerebral Amyloid Angiopathy | Other Hemorrhagic Strokes | Pathology of Seizures
PRINT E-MAIL THIS PAGE CHAPTER TEST LEARNING OBJECTIVES

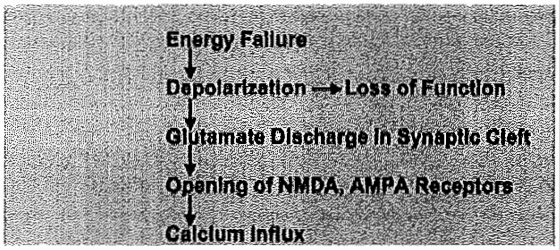
HYPOXIC - ISCHEMIC ENCEPHALOPATHY. GENERAL PRINCIPLES

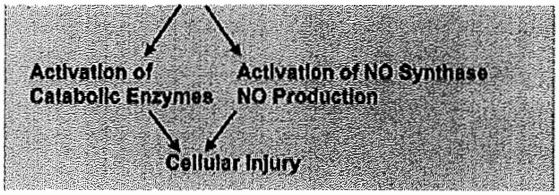
The brain is about 2% of the total body mass but consumes 15% of the energy generated in the body. Most of this energy is used by neurons to maintain ionic gradients that are important for conductivity and synaptic function. Some energy is also needed to support synthetic and catabolic activity of neurons and glial cells and, in young age, for growth. Energy for these functions is derived from hydrolysis of ATP. Thus, the brain is like a chemical battery of ATP which must be constantly recharged. The brain has no energy stores of its own except for a small amount of glycogen in astrocytes. Anaerobic glycolysis of this glycogen is insufficient to meet energy needs. Fatty acids cannot be used because they are not transported across brain capillaries. Brain cells have no back up energy source such as creatine phosphate that muscle cells have. Consequently, energy for recharging the ATP battery is derived exclusively from oxidative phosphorylation of glucose. Thus, the brain depends on a second by second supply of oxygen and glucose by the blood. **A drop in cerebral perfusion, hypoxia, hypoglycemia, and severe anemia** can cause a critical shortage of energy (**energy crisis**). In protracted **generalized seizures**, neurons use up glucose and oxygen faster than they are supplied, and discharge glutamate (see below) with the same result.

The most common cause of energy crisis is a drop of cerebral perfusion (**global ischemia**), usually resulting from cardiac arrest or severe hypotension (shock). Sustained severe hypoglycemia, and seizures lasting 1-2 hours also cause permanent brain damage. Pure hypoxia in clinical settings is unusual. Patients with lung disease are treated with oxygen and the brain can adapt to pure hypoxia, especially if it develops slowly. Hypoxia develops acutely in CO poisoning, which displaces oxygen from hemoglobin. Global ischemia is worse than hypoxia, hypoglycemia, and seizures because, in addition to causing energy failure, it results in accumulation of lactic acid and other toxic metabolites that are normally removed by the circulation.

The mechanism of neuronal damage in hypoxic-ischemic encephalopathy (HIE) is now beginning to be understood. Obviously, lack of energy causes initially electrical failure and, if it lasts long enough, results in arrest of cellular functions and cell death. However, animal experiments and clinical studies show that there are other factors, in addition to energy loss, that account for neuronal damage. Even sublethal HIE can set in motion a series of toxic reactions that finish off injured neurons and kill additional ones that have not been damaged during the initial insult. Thus, following global ischemia, neurons do not die suddenly or all at once. In some of them, damage develops hours or days after the insult. Most neurons undergo necrosis. In some neurons, HIE triggers apoptosis.

The first result of energy depletion is failure of Na^+ and K^+ pumps, leading to **depolarization** of the neuronal membrane (see diagram on left). Synaptic function and conductivity cease at this point. Depolarization causes neurons to release **glutamate** into the synaptic cleft. Glutamate is the most common excitatory neurotransmitter. In small amounts, it is indispensable for neuronal function. In excessive amounts, it is a neuronal poison, a toxin, and has been called **excitotoxin**. Some glutamate receptors are non-selective cation-permeable ion channels. Initially, over-activation of these channels causes a passive influx of Cl^- (and $Na^{+)}$ into cells causing osmotic (cytotoxic) edema and rapid death. Additional structural damage develops hours or days later as a result of **Ca^{++} influx** into neurons. The NMDA and AMPA receptors of glutamate are channels that are permeable to Ca^{++}. Activation of these receptors by excess glutamate causes massive influx of Ca^{++} into neurons. Ca^{++} activates **catabolic enzymes** (proteases, phospholipases,





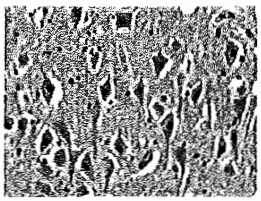
endonucleases). Ca^{++} also activates NO synthase, resulting in formation of the **free radical** NO. Additional free radicals result from the impairment of oxidative phosphorylation. Free radicals and activated catabolic enzymes destroy structural proteins, membrane lipids, nucleic acids, and other cellular contents, causing neuronal necrosis. DNA damage from endonucleases and mitochondrial injury from free radicals trigger apoptosis. Counteracting the action of glutamate is the basis of neuroprotective strategies that are now at an experimental stage.

Incomplete combustion of glucose results in **lactic acidosis**. Lactic acid can get through cell membranes and can damage not only neurons but glial and mesenchymal cells as well. Additionally, lactic acid and hydrogen ions cause cerebral edema by attracting water. Obviously, lactic acidosis is more severe in patients with HIE who are hyperglycemic and is not a significant factor in hypoglycemic encephalopathy or seizures.

Severe HIE is accompanied by cerebral edema and its effects are compounded by increased intracranial pressure. **Cytotoxic (intracellular) edema** develops in the initial phase of the insult. **Interstitial cerebral edema**, which follows, is due to vascular injury and the release in the interstitial space of vasoactive metabolites such as arachidonic and other fatty acids (derived from membrane glycerolipids), lactic acid, electrolytes and other unknown osmoles. Arachidonic acid also has a chemotactic function and induces acute inflammation.

Free radicals, lactic acid, cerebral edema, and inflammation cannot develop in unperfused, completely ischemic tissue. They develop following **reperfusion**. In an ironic sense, the brain has to be alive in order for the changes of neuronal death to develop. Thus, reperfusion is a double-edged sword. Without it, there is no hope for recovery. On the other hand, reperfusion causes additional (delayed) neuronal injury, brings monocytes to the site of injury, and sustains the glial and vascular reactions that follow. Knowledge of the various aspects of HIE and reperfusion injury may open the way to possible neuroprotective interventions.

THE PATHOLOGY OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY

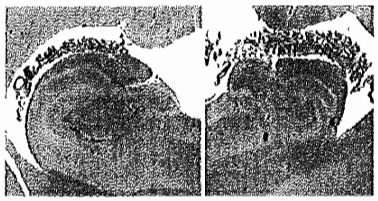


Anoxic neurons

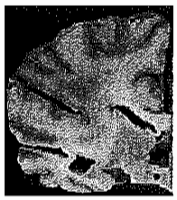
With this background, let us examine what happens with different grades of HIE. Suppose that someone has a brief episode of global ischemia, say from fainting. Within seconds, energy failure causes electrical activity in neurons to cease and the patient loses consciousness. Neurons and glial cells are viable and, if circulation is promptly restored, the patient returns to normal. If, however, ischemia lasts longer, first the integrity of cell membranes will be compromised and then cellular metabolism will cease and neurons will die. Ischemia lasting 4-5 minutes can damage irreversibly hippocampal and neocortical pyramidal cells, striatal neurons, and Purkinje cells. More protracted ischemia can damage thalamic and brainstem neurons.

If a patient dies shortly after the insult, the brain is usually grossly and microscopically normal. If the patient survives and perfusion is restored, changes begin to appear within hours. At first, injured neurons shrink and become eosinophilic. This is due to increased density of damaged mitochondria. Neuronal nuclei condense. The shrunken eosinophilic neuron (**anoxic neuron**) is the hallmark of HIE. Astrocytes swell (Alzheimer type II cells). This is a poorly understood response of astrocytes to metabolic insults. If the patient survives longer, damaged neurons disintegrate and are removed by macrophages. With time, **cortical atrophy and gliosis** develop.

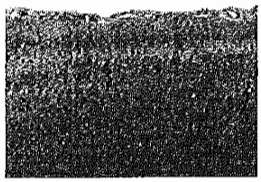
Some cases of HIE, usually after brief insults, cause neuronal death only without damage of glial cells (**selective neuronal necrosis**). Neurons are more sensitive than glial cells because they have higher energy demands and only they produce glutamate. Some neurons are more vulnerable than others (**selective vulnerability**). The hippocampal pyramidal cells of CA1, pyramidal neocortical neurons (layers 3, 5, and 6), Purkinje cells, and striatal neurons have the highest vulnerability.



Hippocampal neuronal loss (right) post-HIE



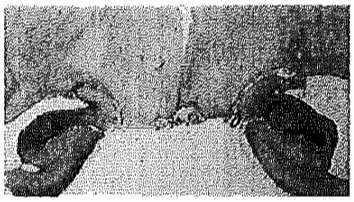
Pseudolaminar necrosis



Pseudolaminar necrosis

Damage of the cortex sometimes causes a band-like lesion, called **pseudolaminar necrosis**. There is also a **regional variation in susceptibility** to HIE. The cerebral cortex and striatum are more sensitive than the thalamus, and the thalamus in turn is more sensitive than the brainstem. The spinal cord may remain uninjured even when all the rest of the CNS is severely damaged. The most likely explanation for this selective vulnerability is that susceptible neurons produce more glutamate. In severe cases of HIE, not only neurons but glial cells are damaged as well. The key factor that converts selective neuronal necrosis to total tissue necrosis is probably lactic acidosis.

Hippocampal sclerosis, left



Hippocampal sclerosis

The term HIE encompasses hypoxia, ischemia, hypoglycemia, and the efects of prolonged seizures. Shock and cardiac arrest develop at some point in most severe HIE cases, and the neuropathology is the same regardless of the initial event. Only rarely it is possible to identify the cause of HIE based on the pathological findings. For instance, bilateral hippocampal neuronal loss and gliosis (**hippocampal sclerosis**) without other lesions is seen in some patients with epilepsy or following cardiac arrest of short duration. Sparing of Purkinje cells suggests hypoglycemic encephalopathy but is also seen in HIE without hypoglycemia. In addition to causing hypoxia, CO binds to iron-rich neurons of the globus pallidus and substantia nigra, damaging these nuclei selectively.

"Respirator brain"

Non-perfused brain

Severe and protracted HIE damages the cortex, deep nuclei, and brainstem, resulting in **brain death**. If such a patient is put on the respirator, the brain (under normal body temperature) undergoes an enzymatic autodigestion which may end in liquefaction. The term"**respirator brain**" that has been applied in such cases is misleading because the autolysis is not caused by the respirator. The term "**non-perfused brain**" is more accurate. Because circulation is arrested and all metabolic activity ceases, the non-perfused brain does not show any reactive changes (inflammation, macrophages, gliosis), only autolysis. Imaging reveals hypodensity due to edema and disintegration of brain tissue without enhancement.

In some instances, global ischemia causes bilateral, symmetric **cerebral infarcts in the border zones** between major arterial territories. Rarely, HIE involves the **white matter**, causing myelin damage and loss. Unravelling of damaged myelin results in vacuolization and a spongy appearance of the white matter in tissue sections. White matter damage is common in CO poisoning but may occur in other forms of HIE.

THE CLINICAL CONSEQUENCES OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY

The most common pattern of injury in HIE is **selective loss of sensitive neurons** (pyramidal cells of CA1 of the hippocampus, layers 3, 5, and 6 of the neocortex, Purkinje cells, and striatal neurons). **Mild HIE**, such as a brief cardiac arrest, may affect CA1 pyramidal neurons of the hippocampus only. **Bilateral hippocampal damage** causes **Korsakoff's amnesia.** This is a memory disorder characterized by inability to retain new information (anterograde amnesia) and a less severe defect of recall of old memories (retrograde amnesia). Hippocampal amnesia (Korsakiff's amnesia) affects more severely episodic memory and less so semantic memory (see below)

MEMORY
PROCEDURAL: Learning skills (learning how), e.g., how to write with the left hand, if right -handed.
DECLARATIVE: two types
SEMANTIC: Memory for facts (learning that), e.g., Kabul is the capital of Afghanistan.
EPISODIC: Memory for personally experienced events, e.g., remembering where you parked your car this morning.

Diffuse cortical, thalamic, or combined neuronal loss (with intact brainstem) results in dementia or the **persistent vegetative state** (loss of cognitive functions and emotion with preservation of sleep-wake cycles, autonomic function, and breathing). The medical, legal, and ethical issues revolving around the persistent vegetative state were dramatized in 2005 by the case of Terri Schiavo.

More protracted ischemic insults, which damage also the brainstem, cause **brain death**, a terminal clinical state characterized by **loss of cerebral and brainstem** function. The clinical criteria for brain death are complete unresponsiveness, absence of brain stem reflexes, electrical silence (flat EEG), and absence of cerebral perfusion. The latter is probably due to blockage of capillaries from endothelial swelling and cerebral edema. Brain death can be distinguished clinicallly from the persistent vegetative state and other conditions that cause severe brain damage and coma. In most cases, brain death leads to loss of vital functions. Therefore, for legal purposes, brain death is the equivalent of somatic or cardiorespiratory death.

THE WHITE MATTER IN HIE

Acute HIE damages primarily neurons of the cerebral cortex and deep nuclei. The white matter is only rarely affected. One exception is CO poisoning, in which the white matter is affected, along with but sometimes out of proportion to the pathology in the cortex and basal ganglia. In addition, the white matter, especially in subcortical regions, is involved diffusely in chronic ischemia, leading to a condition called leukoaraiosis. **Leukoaraiosis** (rarefaction of the white matter) is a neuroradiology term describing the loss of density of the white matter on CT and increased signal on T2 or FLAIR MRI. These findings can be explained by loss of myelin and axons and increased interstitial fluid. Leukoaraiosis is probably due to the chronic effect of microvascular disease associated with hypertension, diabetes, and angiopathies (cerebral amyloid angiopathy, CADASIL, Collagen 4A1 mutation-seepage 2 and page 3 further on). Some of these angiopathies also cause intracerebral hemorrhage. Its most common substrate is small vessel disease and patients with leukoaraiosis frequently also have lacunar infarcts. The extent of white matter pathology can be best appreciated by MRI, especially with newer techniques such as **diffusion tensor imaging,** which measures the density of axons traversing the white matter. Pathological examination reveals loss of myelin and axons and expansion of perivascular spaces, a finding known in classical neuropathology as état cribré(a sieve-like state). **Binswanger encephalopathy**, a white matter degeneration that has been linked to hypertension, is a pathological counterpart of some cases of leukoaraiosis. The pathogenesis of leukoaraiosis is unknown and probably has to do with nonspecific axon and myelin damage due to chronic ischemia. In that sense it may be considered as being analogous to periventricular leukomalacia (PVL), however, the term PVL should be restricted to the neonatal condition. Leukoaraiosis and the conditions that cause it are is associated with cognitive decline and dementia, instability and gait abnormality with frequent falls, and bladder dysfunction.

Further reading:

Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci. 1999;22:391-7. ***PubMed***

MacDonald JF, Xiong ZG, Jackson MF. Paradox of Ca2+ signaling, cell death and stroke. Trends Neurosci. 2006;29:75-81. ***PubMed***

O'Sullivan M. Leukoaraiosis. Pract Neurol 2008;8:26-38 ***PubMed***

Updated: August, 2010

Top of Page

TAB 12

Dopamine
Drug Center
Drug Description
Indications & Dosage
Side Effects & Drug Interactions
Warnings & Precautions
Overdosage & Contraindications
Clinical Pharmacology
Medication Guide

« Previous | 1 | 2 | 3 | 4 | 5 | 6 | 7 | next »

Dopamine

Heart Disease Slideshow Pictures
Medical Illustrations of the Heart Image Collection
Take the Heart Disease Quiz!

FONT SIZE A A A

CLINICAL PHARMACOLOGY

Dopamine (dopamine hydrochloride) is a natural catecholamine formed by the decarboxylation of 3,4-dihydroxyphenylalanine (DOPA) It is a precursor to norepinephrine in noradrenergic nerves and is also a neurotransmitter in certain areas of the central nervous system, especially in the nigrostriatal tract, and in a few peripheral sympathetic nerves

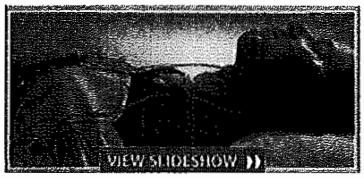
Dopamine (dopamine hydrochloride) produces positive chronotropic and inotropic effects on the myocardium, resulting in increased heart rate and cardiac contractility. This is accomplished directly by exerting an agonist action on beta-adrenoceptors and indirectly by causing release of norepinephrine from storage sites in sympathetic nerve endings.

Dopamine (dopamine hydrochloride) 's onset of action occurs within five minutes of intravenous administration, and with dopamine (dopamine hydrochloride) 's plasma half -life of about two minutes, the duration of action is less than ten minutes If monoamine oxidase (MAO) inhibitors are present, however, the duration may increase to one hour. The drug is widely distributed in the body but does not cross the blood-brain barrier to a significant extent. Dopamine (dopamine hydrochloride) is metabolized in the liver, kidney, and plasma by MAO and catechol-O-methyltransferase to the inactive compounds homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid About 25% of the dose is taken up into specialized neurosecretory vesicles (the adrenergic nerve terminals), where it is hydroxylated to form norepinephrine It has been reported that about 80% of the drug is excreted in the urine within 24 hours, primarily as HVA and its sulfate and glucuronide conjugates and as 3,4-dihydroxyphenylacetic acid A very small portion is excreted unchanged

The predominant effects of dopamine (dopamine hydrochloride) are dose-related, although actual response of an individual patient will largely depend on the clinical status of the patient at the time the drug is administered At low rates of infusion (0 5-2 mcg/kg/min) dopamine (dopamine hydrochloride) causes vasodilation that is presumed to be due to a specific agonist action on dopamine (dopamine hydrochloride) receptors (distinct from alpha and beta adrenoceptors) in the renal, mesenteric, coronary, and intracerebral vascular beds. At these dopamine (dopamine hydrochloride) receptors, haloperidol is an antagonist. The vasodilation in these vascular beds is accompanied by increased glomerular filtration rate, renal blood flow, sodium excretion, and urine flow. Hypotension sometimes occurs. An increase in urinary output produced by dopamine (dopamine hydrochloride) is usually not associated with a decrease in osmolarity of the urine

At intermediate rates of infusion (2-10 mcg/kg/min) dopamine (dopamine hydrochloride) acts to stimulate the beta1-adrenoceptors, resulting in improved myocardial contractility, increased SA rate and enhanced impulse conduction in the heart. There is little, if any, stimulation of the beta2-adrenoceptors (peripheral vasodilation). Dopamine (dopamine hydrochloride) causes less increase in myocardial oxygen consumption than Isoproterenol, and its use is not usually associated with a tachyarrhythmia Clinical studies indicate that it usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure Blood flow to the peripheral vascular beds may decrease while mesenteric flow increases due to increased cardiac output. At low and intermediate doses, total peripheral resistance (which would be raised by alpha activity) is usually unchanged

At higher rates of infusion (10-20 mcg/kg/min) there is some effect on alpha-adrenoceptors, with consequent vasoconstrictor effects and a rise in blood pressure. The vasoconstrictor effects are first seen in the skeletal muscle vascular beds, but with increasing doses they are also evident in the renal and mesenteric vessels At very high rates of infusion (above 20 mcg/kg/min), stimulation of alpha-adrenoceptors predominates and vasoconstriction may compromise the circulation of the limbs and override the dopamine (dopamine hydrochloride) rgic effects of dopamine (dopamine hydrochloride) , reversing renal dilation and natriuresis



Popular Collections

all images »
all slideshows »

Type 2 Diabetes Warning Signs

Recommended Topic Related To

Find it Now

Search the Medical Dictionary for Health Definitions & Medical Abbreviations

SEARCH

Updated & New
News & Features

Identify Your Drugs: Use the RxList Pill Identifier Tool

Pill Identifier: Why & How to Identify Drugs

Vaccine Safety

Last reviewed on RxList: 10/4/2010
This monograph has been modified to include the generic and brand name in many instances

« Previous | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Next »

Next: Medication Guide

Additional Dopamine Information

- Dopamine Drug Center
- Dopamine FDA Approved Prescribing Information including Dosage

Report Problems to the Food and Drug Administration

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit the FDA MedWatch website or call 1-800-FDA-1088.

Dopamine

Heart Disease »

Heart disease facts

- Coronary artery disease is the most common cause of death in the United States. Over a million people each year will have a heart attack and 25% will die before they get to the hospital while or in the Emergency Department.
- Prevention is the key to treatment of heart disease.
- Diagnosis of heart disease is often made by careful history taken by a health care practitioner. Some individuals may have atypical symptoms, including almost none at all.
- The testing strategy to confirm the diagnosis and plan appropriate treatment needs to be individualized for each patient diagnosed with heart disease.
- Treatment of heart disease depends upon the severity of disease, and is often directed by the symptoms experienced by the affected individual.

Introduction to heart disease

The heart is like any other muscle, requiring oxygen and nutrient-rich blood for it t .

Read the Heart Disease article »

See All Slideshows

Causes of Fatigue

How to Fight It

TAB 13

Chest. 2008 Jul;134(1):172-8.

Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares.

Marik PE, Baram M, Vahid B.

Division of Pulmonary and Critical Care Medicine, Thomas Jefferson University, 834 Walnut St, Suite 650, Philadelphia, PA 19107, USA. paul.marik@jefferson.edu

Abstract

BACKGROUND: Central venous pressure (CVP) is used almost universally to guide fluid therapy in hospitalized patients. Both historical and recent data suggest that this approach may be flawed.

OBJECTIVE: A systematic review of the literature to determine the following: (1) the relationship between CVP and blood volume, (2) the ability of CVP to predict fluid responsiveness, and (3) the ability of the change in CVP (DeltaCVP) to predict fluid responsiveness.

DATA SOURCES: MEDLINE, Embase, Cochrane Register of Controlled Trials, and citation review of relevant primary and review articles. Study selection: Reported clinical trials that evaluated either the relationship between CVP and blood volume or reported the associated between CVP/DeltaCVP and the change in stroke volume/cardiac index following a fluid challenge. From 213 articles screened, 24 studies met our inclusion criteria and were included for data extraction. The studies included human adult subjects, healthy control subjects, and ICU and operating room patients.

DATA EXTRACTION: Data were abstracted on study design, study size, study setting, patient population, correlation coefficient between CVP and blood volume, correlation coefficient (or receive operator characteristic [ROC]) between CVP/DeltaCVP and change in stroke index/cardiac index, percentage of patients who responded to a fluid challenge, and baseline CVP of the fluid responders and nonresponders. Metaanalytic techniques were used to pool data.

DATA SYNTHESIS: The 24 studies included 803 patients; 5 studies compared CVP with measured circulating blood volume, while 19 studies determined the relationship between CVP/DeltaCVP and change in cardiac performance following a fluid challenge. The pooled correlation coefficient between CVP and measured blood volume was 0.16 (95% confidence interval [CI], 0.03 to 0.28). Overall, 56+/-16% of the patients included in this review responded to a fluid challenge. The pooled correlation coefficient between baseline CVP and change in stroke index/cardiac index was 0.18 (95% CI, 0.08 to 0.28). The pooled area under the ROC curve was 0.56 (95% CI, 0.51 to 0.61). The pooled correlation between DeltaCVP and change in stroke index/cardiac index was 0.11 (95% CI, 0.015 to 0.21). Baseline CVP was 8.7+/-2.32 mm Hg [mean+/-SD] in the responders as compared to 9.7+/-2.2 mm Hg in nonresponders (not significant).

CONCLUSIONS:

This systematic review demonstrated a very poor relationship between CVP and blood volume as well as the inability of CVP/DeltaCVP to predict the hemodynamic response to a fluid challenge. CVP should not be used to make clinical decisions regarding fluid management.

Comment in

Chest. 2008 Dec;134(6):1352; author reply 1352-3.
Chest. 2008 Dec;134(6):1351-2; author reply 1352-3.

PMID: 18628220 [PubMed - indexed for MEDLINE] **Free full text**

Publication Types, MeSH Terms

LinkOut - more resources