

Cerebral Blood Flow Thresholds for Cerebral Ischemia in Traumatic Brain Injury. A Systematic Review.

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ABSTRACT

Background. Reduction of cerebral blood flow (CBF) plays a crucial role in causing post-traumatic cerebral ischemia (PTCI). However, the methodological adequacy of studies from which currently used CBF thresholds in traumatic brain injury (TBI) have been derived has not been evaluated.

Objective. To systematically evaluate the evidence available on CBF thresholds and its methodological adequacy in adults with TBI.

Methods. Included were primary studies on adults with TBI in which CBF thresholds were evaluated and reported, and follow-up brain CT or MRI was used as gold standards for diagnosing the finally infarcted area.

Results. Among the 53 diagnostic studies identified, 31 did not report any threshold value, while 20 studies used thresholds derived from the literature, mainly animal or clinical studies on ischemic stroke. One study measured CBF thresholds, but did not use accepted neuroradiological criteria for the diagnosis of PTCI. The remaining study fulfilled all methodological inclusion criteria, but was restricted to 14 patients with severe TBI and cerebral contusion. This study proposed a CBF threshold of 15ml/100ml/min, with sensitivity and specificity of 43% and 95%, respectively.

Conclusions. CBF thresholds for the diagnosis of PTCI are based on weak evidence, and cannot be recommended.

Key words. Systematic review; cerebral blood flow; cerebral ischaemia; cerebral infarction, traumatic brain injury.

Introduction

Cerebral ischemia is a frequent complication after traumatic brain injury (TBI) (1,2). Post-traumatic cerebral ischemia (PTCI) is present in 90% of fatal cases, and in some is the only cause of death (1,3). Measures of cerebral oxygenation and perfusion are therefore of paramount importance in the management of TBI. Cerebral perfusion pressure (CPP) is a major determinant of cerebral perfusion in the injured brain, and targeted CPP management is widely advocated for TBI patients (4). However, the optimal CPP target remains elusive, and may vary substantially in different patients or in the same patient over time (4). Hence, direct measurement of cerebral blood flow (CBF) plays a crucial role in the diagnosis of PTCI (5). To our knowledge, the methodological adequacy of studies from which currently used CBF thresholds in traumatic brain injury (TBI) have been derived has not been evaluated. We, therefore, systematically reviewed the medical literature to evaluate the evidence available on CBF thresholds and its methodological adequacy in adults with TBI.

Material and Methods

Identification of Studies

Studies were identified by electronically searching Medline (January 1966 through June 2007), Embase (January 1982 through June 2007), and the Cochrane Library (January 1993 through June 2007). The following words were used both as text words and keywords: brain ischemia, cerebral ischemia, brain blood flow, cerebral blood flow, blood flow measurement, brain injury, brain trauma, head injury, head trauma. The electronic search was complemented by cross-checking of reference lists of all relevant studies and contact with authors and experts in the field. Study selection was performed independently by 2 authors (MB, EB), and disagreements resolved through discussion with a third reviewer (NL).

Study selection

Included were primary studies on adults with TBI in which CBF thresholds were evaluated and reported, and either follow-up brain CT or MRI were used as diagnostic gold standards for diagnosing the finally infarcted area.

Data extraction

Two reviewers (EB, MB) independently extracted the data and disagreements were resolved through discussion with a third author (NL). Study quality was assessed based on the Standards for Reporting of Diagnostic Accuracy (7) and the Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews (8). Information extracted included: CBF thresholds; number of patients; study design; study population (demographics, Glasgow Coma Scale Score); reference and index tests; independent and blind comparison between reference and index tests; co-registration of the index and reference test.

Results

The whole process of inclusion and exclusion of studies is shown in the Figure.

Fifty-three out of 253 articles reviewed for inclusion were primary studies on CBF in adult patients with TBI.

Thirty-one studies were excluded because they did not evaluate the diagnostic performance of CBF measurement. In particular, 22 studies simply described CBF values observed in different types of post-traumatic brain lesions (e.g. brain edema, cerebral contusions) or in particular conditions associated with TBI (e.g. anemia, hyperventilation), while 9 studies evaluated the prognostic, rather than diagnostic, value of CBF measurement in predicting clinical outcomes (e.g. Glasgow Outcome Scale, mortality).

Twenty studies were further excluded because they evaluated the diagnostic performance of CBF using CBF thresholds derived from the literature. The Table shows the literature sources used, the majority of which indicates threshold values of 18-20 ml/100ml/min derived from either animal experiments (monkeys and pigs) or studies on carotid surgery in patients with acute ischemic stroke.

Only two studies were left which evaluated CBF thresholds for PTCI (9,10), one of which was further excluded since the diagnosis of PTCI was based on cerebral atrophy measured by ventricle size (9), which is not an accepted diagnostic criterion for PTCI.

The only study included in the review was a retrospective cohort study of 14 consecutive patients with severe TBI (Glasgow Coma Scale Score ≤ 8) and focal injury (cerebral contusion) (10). CBF measurement by PET was obtained within 72 hours of TBI (mean=46 h); the

diagnostic gold standard was follow-up MRI at 3-18 months (mean=239 days) after injury. Index test (PET-CBF) and reference test (follow-up MRI) were co-registered and comparison between the two tests was independent and blind. The authors reported a CBF threshold of 15 ml/100ml/min for irreversible ischemic damage (cerebral infarction), which was obtained based on a cumulative probability function for voxels coming from lesion and non-lesion regions of interest (ROI) of the brain. The sensitivity of this threshold (proportion of lesion voxels correctly classified) was 43%, and the specificity (proportion of non-lesion voxels correctly classified) was 95%. In the study population, where lesion voxels represented 4.3% of the entire supratentorial brain volume (i.e., prior probability of lesion of 4.3%), the positive predictive value was only 27%, while the negative predictive value was 96%. The authors also calculated positive and negative predictive values under the hypothetical scenario of a much higher prior probability of lesion, i.e. 50%, which might be more appropriate if the analysis is limited to pericontusional regions. In this scenario, the corresponding positive predictive value became 90% and the negative predictive value 63%.

Discussion

This systematic review on CBF thresholds for the diagnosis of PTCI explored the literature published over the last 62 years, since the first method for measuring CBF in humans became available in 1945 (11). Among the 22 studies identified which assessed the performance of CBF measurements in the diagnosis of PTCI, only two attempted to derive CBF thresholds. The other 20 studies adopted threshold values reported in the literature, which were mainly derived from studies performed in the 70's and early 80's in either animal models of acute ischemic stroke or humans with ischemia during carotid endarterectomy. However, translation of results from animal experiments to mankind can be difficult, as is the extrapolation of results from stroke studies to TBI. Although some pathophysiological mechanisms are common to both the ischemic and traumatized brain -for example, the inflammatory response has detrimental effects

in the acute phase and beneficial effects in the chronic phase of both conditions (12), differences between the two conditions remain substantial. In acute ischemic stroke, persistent CBF impairment eventually leads to neuronal death, particularly at the center of the ischemic focus, where cells die within minutes of ischemic onset. TBI involves a “primary” mechanical impact that abruptly disrupts the brain parenchyma with shearing and tearing of blood vessels and brain tissue. This, in turn, triggers a cascade of events characterized by activation of molecular and cellular responses that lead to “secondary” ischemic injury (5). Cerebral metabolism is often reduced following TBI (1), because of the trauma itself or the associated use of sedatives, so that apparently low CBF, resulting from preserved flow-metabolism coupling, might indeed be normal. Conversely, excitotoxicity may lead to an increase in cerebral metabolism that is not met by apparently normal CBF. Both situations will alter the CBF threshold for tissue survival compared to ischemic stroke. Another important difference with ischemic stroke is that post-traumatic cerebral damage is often diffuse rather than focal. Because of these differences, deriving CBF ischemic thresholds for TBI from ischemic stroke is hardly justified. In addition, CBF thresholds for acute ischemic stroke are themselves based on weak evidence (6).

The fact that only two diagnostic studies on CBF measurements did evaluate CBF thresholds suggests that the importance of the choice of the threshold, as well as its implications for the interpretation of indices of diagnostic performance, is under recognized. Sensitivity and specificity of a test, that is its capability to correctly classify diseased and non-diseased individuals, highly depend on the threshold value used to define positive and negative results so that a test can only be “good” if used with an appropriate threshold. For this reason, the most informative way of presenting the results of diagnostic studies is the ROC curve, where sensitivity and specificity are plotted for different threshold values.

Another crucial methodological point of diagnostic studies is the need to compare the results of the test under evaluation with those of a recognized diagnostic gold standard. Only one study used an accepted gold standard (10). This might be partly explained by the lack of consensus on the imaging method(s) and criteria to diagnose PTCI “antemortem”(2).

The only included study had a sample size of only 14 patients (10). However, the power of the study is difficult to evaluate, since the voxel, not the patient, was the unit of analysis. The pooled set of voxels was analyzed without accounting for the hierarchical nature of the data, where each voxel belongs to a certain brain region of interest within a certain patient. A more appropriate analysis would require the use of a three-level statistical model, which takes into account both the within-ROI and the within-patient correlation. The CBF threshold value of 15 ml/100ml/min for cerebral infarction was derived using the lower 95% confidence limit of CBF values in normal (non infarcted) tissue. Such an approach implicitly favors specificity at the expense of sensitivity, as demonstrated by the results of the study (sensitivity=0.43; specificity=0.95). Hence, while tissue with CBF values below this threshold was highly likely to become infarcted, much lesion tissue had value above this threshold. This means that the use of this threshold would lead to under-diagnose the presence of PTCI in patients with cerebral contusion, as acknowledged by the authors of the study.

PTCI is an extremely complex event (1), and it is unlikely that future studies would use CBF as the sole diagnostic test. Detection of the three components of PTCI, namely sustained global ischemia, transient diffuse ischemia and sustained focal ischemia (1), depends on combined measurement of CBF and cerebral oxygen metabolism made sufficiently *soon*, sufficiently *often*, and with sufficient *resolution* to detect local impairments, respectively. However, the methodological principles of good diagnostic studies remain the same, and future research

evaluating a combination of diagnostic tests for PTCI should consider the results of this systematic review to avoid the limitations we found in the current literature.

At present, diagnosis of PTCI in adults based on CBF measurement alone cannot be recommended. Studies with larger samples from a relevant clinical population, with blind comparison between index test and reference test, would be crucially important to identify thresholds. Adequate multi-level statistical modelling and reporting of results based on ROC curves should also be adopted. Finally, consensus should be reached on what diagnostic method and criteria are to be used as gold standard to diagnose PTCI “antemortem”.

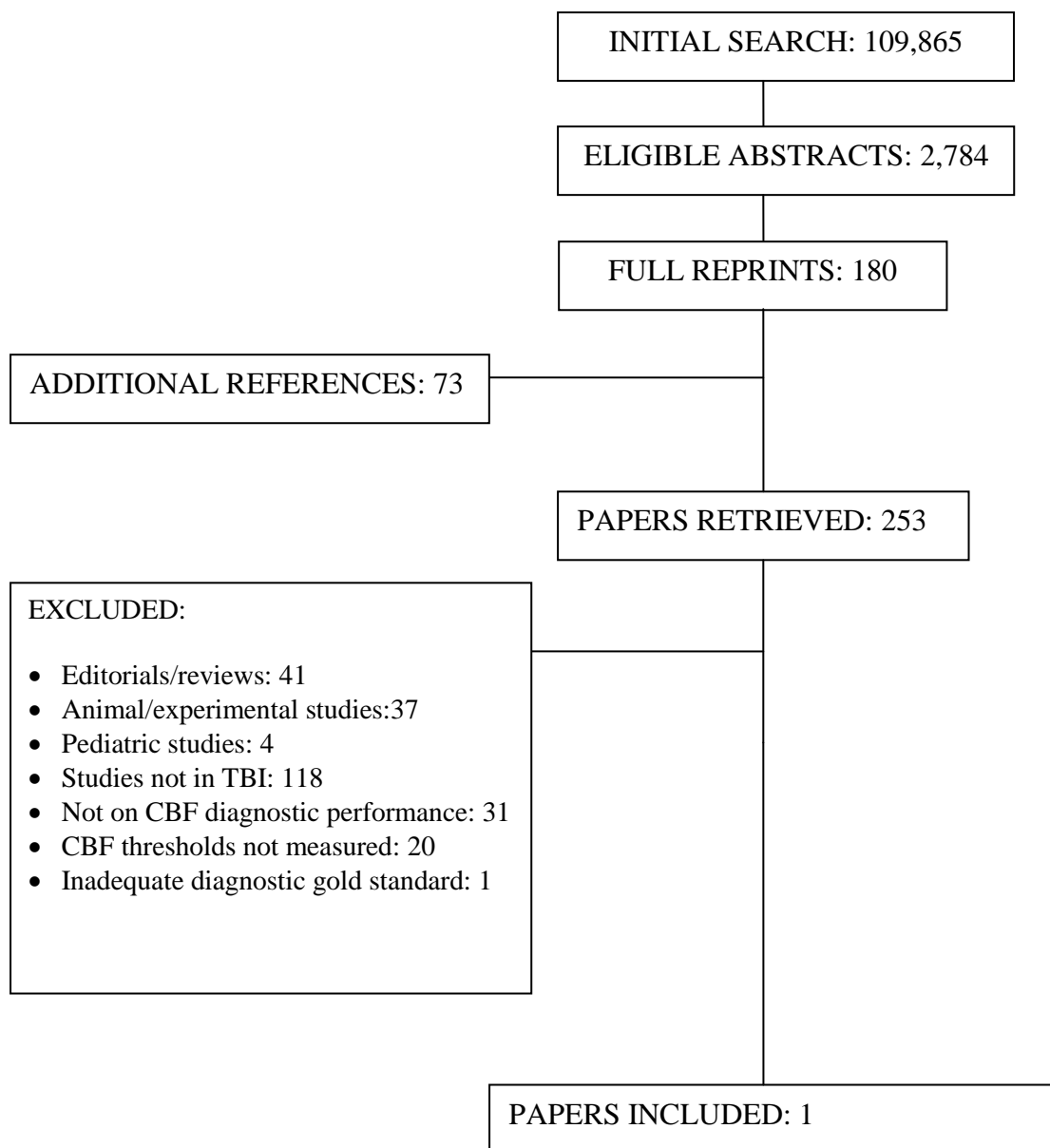


Figure. Flow chart of the inclusion and exclusion of studies in the review. TBI, traumatic brain injury; CBF, cerebral blood flow.

First author, year (reference)	Study on	Type of study	Setting	CBF threshold (ml/100ml/min)	Number of citations
Boysen, 1973 (13)	Human	Observational	Ischemia during carotid endarterectomy	20	2
Trojaborg, 1973 (14)	Human	Observational	Ischemia during carotid endarterectomy	20	2
Sundt, 1975 (15)	Human	Observational	Ischemia during carotid endarterectomy	20	2
Jones, 1981 (16)	Animal (monkey)	Experimental	Model of ischemia: occlusion of MCA	18	9
Astrup, 1981 (17)	/	Editorial paper	/	/	5
Heiss, 1983 (18)	Animal (cat)	Experimental	Model of ischemia: occlusion of MCA	18	1
Schroder, 1996 (9)	Human	Observational	Ischemia after traumatic brain injury	20	1
Sakoh, 2000 (19)	Animal (pig)	Experimental	Model of ischemia: occlusion of MCA	30	1

TABLE. Sources of CBF thresholds. Sources used by those studies (n=20) that evaluated diagnostic performance of CBF based on values reported in the literature. MCA: middle cerebral artery.

References

1. Teasdale GM, Graham DI: Craniocerebral trauma: protection and retrieval of the neuronal population after injury. *Neurosurgery* 1998; 43:723-737; discussion 737-728
2. Marino R, Gasparotti R, Pinelli L , et al.: Posttraumatic cerebral infarction in patients with moderate or severe head trauma. *Neurology* 2006; 67:1165-1171
3. Graham DI, Ford I, Adams JH , et al.: Ischaemic brain damage is still common in fatal non-missile head injury. *J Neurol Neurosurg Psychiatry* 1989; 52:346-350
4. Menon DK: Procrustes, the traumatic penumbra, and perfusion pressure targets in closed head injury. *Anesthesiology* 2003; 98:805-807
5. Coles JP: Regional ischemia after head injury. *Curr Opin Crit Care* 2004; 10:120-125
6. Bandera E, Botteri M, Minelli C , et al.: Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke: a systematic review. *Stroke* 2006; 37:1334-1339
7. Bossuyt PM, Reitsma JB, Bruns DE , et al.: Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *Bmj* 2003; 326:41-44
8. Whiting P, Rutjes AW, Reitsma JB , et al.: The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003; 3:25
9. Schroder ML, Muizelaar JP, Kuta AJ , et al.: Thresholds for cerebral ischemia after severe head injury: relationship with late CT findings and outcome. *J Neurotrauma* 1996; 13:17-23
10. Cunningham AS, Salvador R, Coles JP , et al.: Physiological thresholds for irreversible tissue damage in contusional regions following traumatic brain injury. *Brain* 2005; 128:1931-1942
11. Kety SS, Schmidt CF: The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. *Am J Physiol* 1945; 143:53-66
12. Leker RR, Shohami E: Cerebral ischemia and trauma-different etiologies yet similar mechanisms: neuroprotective opportunities. *Brain Res Brain Res Rev* 2002; 39:55-73
13. Boysen G: Cerebral hemodynamics in carotid surgery. *Acta Neurol Scand Suppl* 1973; 52:3-86
14. Trojaborg W, Boysen G: Relation between EEG, regional cerebral blood flow and internal carotid artery pressure during carotid endarterectomy. *Electroencephalogr Clin Neurophysiol* 1973; 34:61-69
15. Sundt TM, Jr., Sharbrough FW, Trautmann JC , et al.: Monitoring techniques for carotid endarterectomy. *Clin Neurosurg* 1975; 22:199-213
16. Jones TH, Morawetz RB, Crowell RM , et al.: Thresholds of focal cerebral ischemia in awake monkeys. *J Neurosurg* 1981; 54:773-782
17. Astrup J, Siesjo BK, Symon L: Thresholds in cerebral ischemia - the ischemic penumbra. *Stroke* 1981; 12:723-725
18. Heiss WD, Rosner G: Functional recovery of cortical neurons as related to degree and duration of ischemia. *Ann Neurol* 1983; 14:294-301
19. Sakoh M, Ostergaard L, Rohl L , et al.: Relationship between residual cerebral blood flow and oxygen metabolism as predictive of ischemic tissue viability: sequential multitracer positron emission tomography scanning of middle cerebral artery occlusion during the critical first 6 hours after stroke in pigs. *J Neurosurg* 2000; 93:647-657