TRAUMATIC BRAIN ISCHEMIA DURING NEURO INTENSIVE CARE

Myth rather than fact

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ABSTRACT - In non-missile severe acute brain trauma, brain ischemia was a frequent finding in cadavers. Studies during neuro intensive care, however, have failed to disclose brain ischemia under most circumstances, except when cerebral hemodynamic and metabolic parameters have been misinterpreted, or when cerebral blood flow (CBF) alone has been addressed in a biased fashion, without mandatory metabolic data. Indeed, comprehensive and unbiased studies focusing on global cerebral metabolic activity have invariably revealed a condition of normal coupling between reduced CBF and oxygen consumption in the early postinjury hours, which is then followed by a prolonged, sustained pattern of relative cerebral hyperperfusion (the opposite of ischemia). Accordingly, traumatic brain ischemia during intensive care represents myth rather than fact.

KEY WORDS: head injury, cerebral metabolism, cerebral blood flow, brain ischemia.

Isquemia cerebral tráumatica durante neuro terapia intensiva: mito ao invés de fato

RESUMO - Em traumatismo cerebral agudo grave excluindo-se ferimentos por arma de fogo, isquemia cerebral foi achado frequente em cadáveres. Entretanto, estudos durante neuro terapia intensiva não têm revelado isquemia cerebral, exceto quando parâmetros hemodinâmicos e metabólicos cerebrais tem sido mal interpretados, ou quando fluxo sanguíneo cerebral (FSC) sozinho tem sido enfocado de forma tendenciosa, sem dados metabólicos mandatórios. De fato, estudos abrangentes e não tendenciosos enfocando a atividade metabólica cerebral têm invariavelmente revelado uma condição de ajustamento normal entre FSC e consumo cerebral de oxigênio reduzidos nas primeiras horas após o traumatismo, um padrão seguido de prolongada hiperperfusão relativa (o oposto da isquemia). Assim sendo, isquemia cerebral traumática durante terapia intensiva representa um mito ao invés de um fato.

PALAVRAS-CHAVE: traumatismo cerebral, metabolismo cerebral, fluxo sanguíneo cerebral, isquemia cerebral.

Previously reported neuropathological findings from cadavers have revealed a high rate of ischemic brain damage in severe acute non-missile brain trauma [1]. Because of these findings, several investigators have attempted to detect cerebral ischemic abnormalities during neuro intensive care. Unfortunately, a comprehensive and unbiased approach to brain ischemia has been frequently hampered by publications focusing on reduced cerebral blood flow (CBF) alone, without mandatory metabolic information. Even more upsetting are previous reports where cerebral metabolic data have been misinterpreted. The present work therefore represents the first attempt to critically and comprehensively clarify previously addressed bias and misinformation in this topic.

Cadaver studies

Postmortem findings from Scotland [1] have emphatically addressed ischemic brain damage in non-missile severe acute brain trauma. Such findings from dead brains, however, were documented under circumstances that do not reproduce physiological parameters in alive brains, such as during intensive care.

Indeed, as a general rule in neurotrauma acute care, prolonged periods of hours or even days will have elapsed between the moment when clinical signs of brain death are first documented and the time when supportive measures are finally discontinued. Accordingly, the brains evaluated by neuropathologists will have almost invariably sustained ultra-prolonged periods of very low or even absent

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cerebral perfusion, because of very high intracranial pressure (ICP), low blood pressure, or a combination of both; that is, cerebral perfusion pressure (CPP) will have approached zero for prolonged periods.

Accordingly, it is not surprising that postmortem studies in severe acute brain trauma may frequently disclose ischemic damage. In alive brains, however, adequate ICP and blood pressure levels are frequently found during intensive care and, therefore, factors other than CPP are expected to play a relevant role, insofar as cerebral hemodynamics and metabolism are concerned. From the above discussion, extrapolation from cadaver brains to alive patients during most of the acute phase of injury is largely inappropriate.

Cerebral perfusion pressure

First proposed in the 1960s [2], CPP (the difference between mean arterial pressure and mean ICP) has been erroneously assumed as a marker of cerebral hemodynamic and metabolic adequacy in acutely brain injured patients. While some investigators [3] have empirically claimed without proof that CPP levels above 70 mmHg are hemodynamically beneficial, we [4] did prove, and for the first time, that normal-to-increased CPP levels hold absolutely no correlation with CBF or oxygen metabolism (both oxygen extraction and consumption). Cerebral vascular resistance is the key variable [4].

Accordingly, in this latter study [4], we could rule out "cerebral vasodilatory and cerebral vasoconstrictive cascades" proposed by those who only measured blood pressure and ICP [3], unlike done in our experience where a broad spectrum of pressoric, hemodynamic and metabolic parameters were addressed[4]. Evidently, when CPP is grossly reduced (such as when neuro monitoring and management are felt to no longer benefit the patient), and the condition of brain death is frequently met, one can then expect the brain to undergo gross hypoperfusion and ischemia (which the neuropathologist will finally confirm).

Cerebral blood flow

Studies focusing on CBF alone [5,6] have *invariably* addressed biased information regarding brain ischemia. This is because, in no less than 100% of previous reports covering not just CBF but also cerebral oxygen consumption [4,7-12], this latter parameter has been unequivocally and pathologically reduced in coma, usually by 50% or more.

Accordingly, investigators focusing on reduced CBF alone in the early postinjury hours [5,6] have inadequately and emphatically addressed ischemic patterns when, in fact, concomitant metabolic data would have been mandatory. Furthermore, CBF levels at later points in time during the acute phase have been omitted [5] when, on the other hand, different investigators have demonstrated normal or high blood flow levels in several of these patients[10,13]. This latter condition, defined as posttraumatic cerebral hyperemia, has also been well documented in animal experimentation [14].

Combined cerebral blood flow and metabolism

As described above, CBF alone in comatose patients is frequently misleading and misinformative. This is because reduced CBF is *expected*, as long as it is normally coupled with reduced cerebral oxygen consumption. The critical information regarding coupling or uncoupling is provided by cerebral oxygen extraction, *not* by CBF or oxygen consumption.

In a study where CBF and arteriojugular oxygen content difference ($AVDO_2$) were simultaneously evaluated in 35 acutely brain injured patients [15], biased information was addressed, as follows: in the early hours postinjury, a 33% rate of global brain ischemia was emphatically highlighted, and the entire manuscript only addressed traumatic brain ischemia. The authors, however, failed to properly interpret their own findings, because even when CBF was $\leq$ 18 ml/100 g/min, $AVDO_2$ did not exceed the upper normal limit of 8.3 vol % [16] (Figure 1 in Bouma's paper [15]) and, therefore, the true rate of "potentially ischemic" cerebral oxygen extraction was zero percent.

In contrast with the above-mentioned findings from the first 6 postinjury hours, starting at approximately 12 hours after injury and lasting *throughout the acute phase*, CBF had already increased to levels of relative cerebral hyperperfusion (the opposite of ischemia), as determined by decreased $AVDO_2$ levels below the lower normal limit of 5.1 vol% [16] (Table 1 in Bouma's paper[15]). Unfortunately, the most frequent and sustained pattern of cerebral hemodynamics and metabolism, namely global relative cerebral hyperperfusion, was not even identified and discussed by those authors [15].

Furthermore, combined measurements involving CBF and $AVDO_2$ have clearly disclosed global relative cerebral hyperperfusion (decreased $AVDO_2$ levels) in association with both normal and high CBF values[10,13], a finding expected in the presence of pathologically reduced cerebral oxygen consumption[4,7-12].

Studies involving simultaneous measurements of CBF and cerebral lactate production have also inadequately emphasized global brain ischemia [17,18]. In one of these papers [17], the cerebral metabolic rate of lactate (the product of CBF and arteriojugular lactate difference [AVDL]) was arbitrarily and equivocally defined as ischemic if $\leq$ -6 mMol/100 g/min. In this respect, however, the normal mean CBF value is 50 ml/100 g/min [19], and the normal mean AVDL is -0.17 mMol/L [16], so that the normal (non ischemic) mean cerebral metabolic rate of lactate is -8.5 mMol/100 g/min, far lower than the above-mentioned arbitrarily proposed ischemic threshold of -6 mMol/100 g/min [17]. Accordingly, *false* rather than true brain ischemia was addressed in that manuscript [17].

As an alternative parameter, the same group from Texas later proposed a cerebral lactate-oxygen index (LOI, the ratio of negative AVDL to $AVDO_2$)[18], and ischemic thresholds were arbitrarily established at LOI values $\geq$ 0.08. As previously and unequivocally demonstrated by our team [8,20], however, even in the presence of mild acute anemia (a frequent finding during neuro intensive care), $AVDO_2$ decreases and underestimates cerebral oxygen extraction. Accordingly, in the presence of decreased $AVDO_2$ (the denominator in the LOI calculation), false ischemic LOI values $\geq$ 0.08 will be found even when AVDL is normal (indicative of a normal lactate gradient within the brain). Therefore, until otherwise proven, *false* rather than true global brain ischemia was again reported by those authors, based on LOI measurements [18].

To the best of our knowledge, while initially reduced CBF alone has been equivocally addressed as ischemic, there is only one reported case in the pertinent literature where phasic CBF changes were well documented in a comatose patient [7]. In this latter report, CBF initially above 20 ml/100 g/min spontaneously dropped to a markedly low level of 10 ml/100 g/min, while global cerebral oxygen extraction largely increased. That patient had excellent neurological recovery, despite profoundly reduced CBF for several hours [7].

Cerebral extraction of oxygen

As mentioned above, $AVDO_2$ frequently underestimates global cerebral oxygen extraction, thereby overestimating relative cerebral hyperperfusion. Because bedside routine information regarding global cerebral oxygen extraction has played a major role in neuro intensive care in recent years, we [8,21-27] have proposed an alternative physiological parameter,

which was termed cerebral extraction of oxygen (CEO_2, the arteriojugular oxyhemoglobin saturation difference). The normal CEO_2 range used for therapeutic normalization (in conjunction with ICP and CPP treatment) is 24-42% in adults [21,23,24], and 17-35% (estimated) in children [27].

In a study involving CBF, oxygen consumption and extraction, we found CEO_2 to be far more accurate than $AVDO_2$ at levels of total hemoglobin content < 12 g/dl [8]. Yet, such levels represent frequently and routinely found total hemoglobin content during intensive care, so that we have abandoned the use of $AVDO_2$ under most circumstances, and have adopted CEO_2 instead [8,21-27].

Along the same line of fine-tuning bedside physiological assessment, we have also proposed a novel parameter of cerebral oxygen consumption, which was termed cerebral consumption of oxygen (CCO_2)[8], to replace the conventional cerebral metabolic rate of oxygen ($CMRO_2$) [19]. As seen in our previous report[8], $CMRO_2$ underestimates cerebral oxygen consumption even in mild acute anemia, unlike our proposed and more accurate CCO_2.

Invasive brain tissue probes

In recent years, bedside monitoring of cerebral ischemia has been proposed by using invasive, transcranially implanted brain tissue probes for evaluation of *focal* oxygen tension, as well as assessment of microdialitic elements such as lactate and glutamate, among others [28-30]. A major limitation of any acutely implanted brain tissue probe, however, is that focal mechanical microvascular compression and distortion are likely to occur (because these probes measure millimeters in diameter, versus microns in the microcirculation and the blood-brain barrier). Mechanical disruption of the blood-brain barrier is also expected.

Accordingly, until otherwise proven, the finding of ultra-prolonged cerebral hypoxia-ischemia lasting several hours[30] was most likely artifactual and due to mechanical microvascular compression at the tip of the oxygen tension probe, with resulting low oxygen values. Also artifactual may have been the finding of low oxygen and high lactate levels [29], because focal (mechanically-induced) hypoxia may, in fact, generate focally high lactate concentrations. These patterns, however, may have *nothing at all* to do with the rest of the brain that is not under mechanical load.

Furthermore, normal values for all parameters evaluated by focal brain tissue probes are not even known in humans, because healthy human beings

will just never volunteer to have their heads open for invasive brain tissue probes to be placed. Accordingly, just as a general rule in Medicine, one is not supposed to address abnormalities [28-30] when, in fact, normal parameters are not even known.

In contrast with these focal brain tissue probes, normal values in humans have long been known for arteriojugular measurements involving oxygen content, glucose and lactate concentrations [16], so that cerebral hemometabolic evaluation can be accurately carried out from arteriojugular parameters [4,7-13,20-27] (unlike brain tissue probes [28-30]).

CONCLUSION

In non-missile severe acute brain trauma, brain ischemia represents an exception rather than a rule in alive brains, during contemporary neuro intensive care. Global relative cerebral hyperperfusion (the opposite of ischemia) is the most frequent, sustained pattern of cerebral hemometabolism in these patients. Accordingly, insofar as managing intracranial hypertension is concerned, the use of cerebral vasoconstrictive therapies can be further explored and optimized based on cerebral extraction of oxygen (rather than oxygen content differences).

Findings addressing traumatic brain ischemia during neuro intensive care have invariably overestimated hypoxia-ischemia and underestimated the most frequent pattern, namely global relative cerebral hyperperfusion. Therefore, bias and misinformation found in some reports have unfortunately contributed to confused directions in this field of medicine, insofar as patient care is concerned.

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