EXPENSIVE CEREBRAL BLOOD FLOW MEASUREMENTS ALONE ARE USELESS AND MISINFORMATIVE IN COMATOSE PATIENTS

A comprehensive alternative

Julio Cruz

ABSTRACT - Since the first report addressing quantification of cerebral blood flow (CBF), concomitant assessment of cerebral oxygen consumption was also carried out. Over the years, however, some investigators have emphatically and mistakenly addressed cerebral ischemia in comatose patients, on the basis of CBF measurements alone. In contrast, we have repeatedly reported that ischemia in these patients must be precisely evaluated based on CBF-metabolism coupling or uncoupling, rather than CBF alone. Based on these previous findings, we therefore propose a comprehensive alternative approach, namely the evaluation of brain ischemia in comatose patients based on cerebral metabolic parameters, such as cerebral extraction of oxygen or cerebral lactate release, without expensive CBF measurements.

KEY WORDS: arteriojugular lactate difference, brain ischemia, cerebral blood flow, cerebral extraction of oxygen, coma.

Since the pioneering work of Kety and Schmidt\(^1\), addressing quantification of cerebral blood flow (CBF), concomitant assessment of the cerebral metabolic rate of oxygen consumption (CMRO\(_2\)) was also established. CBF was precisely quantified as the integrated arteriojugular difference of nitrous oxide over approximately 10 minutes (the “height-over-area” method of quantification), whereas CMRO\(_2\) was calculated as the product of CBF and the arteriojugular oxygen content difference (AVDO\(_2\)). The latter parameter had already been introduced in the pertinent literature by another pioneering work of Gibbs and coworkers\(^2\).

Over the years, nearly all alternative techniques proposed for CBF quantification adopted the normal CBF values reported by Kety and Schmidt for validation, even those involving modern and sophisticated positron emission tomography (PET) scanning. Therefore, arteriojugular measurements have been regarded as highly accurate by most investigators, not only for cerebral metabolic assessment but also for CBF measurements.

In recent years, however, stable xenon computerized tomography (CT) CBF measurements became available, and a number of studies have emphatically and mistakenly addressed global or regional cere-
bral ischemic changes in comatose patients\textsuperscript{5-5}. The most elementary mistake in all these papers is that ischemia was defined as CBF levels of 18 ml/100 g/min or less, based on previously reported work addressing ischemic changes at such CBF levels, but in the awake monkey brain\textsuperscript{6}.

Because the awake brain presents with normal oxygen consumption, it is expected that a reduction in CBF from normal 50 ml/100 g/min to 18 ml/100 g/min may, in fact, lead to cerebral ischemic changes. Unlike the awake monkey brain, however, CBF reductions to approximately 20 ml/100 g/min in awake human brain have not resulted in any neurological deficit\textsuperscript{7}. In this latter study by Finnerty and coworkers, cerebral oxygen extraction increased to compensate for the CBF reduction, but no evidence of cerebral ischemia was found on clinical grounds.

Because cerebral oxygen consumption has been invariably reported as largely decreased in comatose patients\textsuperscript{8-15}, and by simply applying to cerebral physiology the basic notion of proportionality, it therefore became clear to us that ischemic CBF thresholds in the comatose brain must be lower than 20-18 ml/100 g/min. In this respect, we first reported a well documented case where CBF spontaneously dropped to as low as 10 ml/100 g/min in a comatose patient, and excellent neurological recovery could still be observed after 45 days only\textsuperscript{8}. Most recently, Diringer and coworkers\textsuperscript{16} have intentionally dropped regional CBF levels to as low as 8 ml/100 g/min, also in comatose patients, and found no metabolic evidence of ischemia based on sophisticated PET scanning.

From the above discussion, it becomes clear that all studies addressing CBF measurements alone (without concomitant metabolic data) have invariably introduced mistaken, perhaps intentional misinformation in the field of cerebral hemodynamics applied to comatose patients. This is particularly true for studies involving stable xenon CT-CBF measurements\textsuperscript{3-5}, besides less frequently used single photon emission computerized tomography (SPECT) CBF studies, which simply do not provide any metabolic information.

**CBF–metabolism coupling**

As described earlier, AVDO\textsubscript{2} is the ratio of CMRO\textsubscript{2} to CBF. However, we have found that AVDO\textsubscript{2} frequently underestimates cerebral oxygen extraction in mild or profound acute anemia, a frequent finding during intensive care\textsuperscript{10,17}. We have therefore introduced in the pertinent literature two novel parameters, which were termed cerebral extraction of oxygen (CEO\textsubscript{2}) and cerebral consumption of oxygen (CCO\textsubscript{2})\textsuperscript{18}. CEO\textsubscript{2} (the arteriojugular oxyhemoglobin saturation difference) and CCO\textsubscript{2} (the product of CBF and CEO\textsubscript{2}) are accurate variables in either anemic or non anemic conditions, and therefore became better alternative measurements than the conventional AVDO\textsubscript{2} and CMRO\textsubscript{2}. These interrelationships are expressed by the following equation:

\[
\text{CEO}_2 = \frac{\text{CCO}_2}{\text{CBF}} \times 100
\]

The simple inspection of this equation reveals that, without the need to measure CBF and CCO\textsubscript{2}, a normal (or therapeutically normalized) CEO\textsubscript{2} value will accurately indicate adequate global CBF-metabolism coupling. Accordingly, an increased (widened) CEO\textsubscript{2} will indicate a condition of relative cerebral hyperperfusion, where CBF is reduced in relation to the oxygen demand, consistent with a preischemic or truly ischemic finding, depending on the magnitude of the CEO\textsubscript{2} increase. In our experience, the normal CEO\textsubscript{2} ranges are 24-42% in adults\textsuperscript{10,18-21} and 17-35% in children\textsuperscript{19,22}, so that values above the upper normal limits would require therapies to increase CBF (again, without the need for CBF measurements).

Conversely, a decreased (narrowed) CEO\textsubscript{2} will indicate a condition of relative cerebral hyperperfusion, where CBF is decreased relative to oxygen demand. Under these circumstances, cerebral vasoconstrictive therapies may be indicated, especially in the presence of elevated intracranial pressure (ICP).

**Phasic physiological changes**

Lassen\textsuperscript{23} first reported abnormally increased CBF following clinically suspected cerebral hypoxic or ischemic events, a surprising condition defined as “luxury perfusion syndrome”. Indeed, based on Lassen’s experience, this secondary hyperperfusion state may be expected in patients with acute ischemic stroke, following an initial CBF reduction. The exact underlying mechanism responsible for such phasic changes remains unknown, however.

In comatose patients with severe acute brain trauma, we first reported in recent studies that phasic CEO\textsubscript{2} changes are also frequent, both in adults\textsuperscript{20,21} and children\textsuperscript{22}. Unlike Lassen’s experience with CBF measurements, we did not have clear clinical evidence of an initial hypoxic or ischemic insult, but normal or mildly increased CEO\textsubscript{2} values on the first postinjury day were frequently replaced by decreased CEO\textsubscript{2} during most of the acute phase of illness\textsuperscript{20,22}. These important phasic changes, however, have not even been addressed by those who have only focused on reduced CBF alone (without mandatory metabolic data), and have invariably and mistakenly addressed ischemia in a grossly biased fashion\textsuperscript{3-5}.

**Consciousness versus coma**

The aforementioned controversial findings must
be interpreted on the basis of the patient’s level of consciousness, as well as the disease process. Indeed, if a patient becomes unconscious immediately after the brain insult (such as severe trauma), a global decrease in \( \text{CCO}_2 \) is expected, until the patient recovers consciousness and \( \text{CCO}_2 \) physiologically increases. Under these circumstances, it is just expected that truly ischemic \( \text{CBF} \) thresholds will not be found, at least during intensive care. Indeed, the metabolic parameters involving arteriojugular oxygen (CEO2) and lactate differences have recently essentially ruled out cerebral ischemia in two large series of patients reported by our team\(^{20,21}\).

In the initially conscious patient (such as in ischemic stroke or cerebral vasospasm in aneurysmal subarachnoid hemorrhage), however, ischemic \( \text{CBF} \) thresholds are expectedly higher than in the initially comatose patient, because \( \text{CCO}_2 \) is initially normal. Accordingly, therapies to increase \( \text{CBF} \) are logical in most of these conscious patients. In addition, if there is a clear cause-and-effect relationship between acutely reduced \( \text{CBF} \) and the state of coma or even just focal neurological deficits, manipulating \( \text{CBF} \) upward would always seem advisable. Once the state of coma is diagnosed without clear evidence that reduced \( \text{CBF} \) was the triggering event, however, therapies aiming at upward \( \text{CBF} \) changes would seem to be illogical, because \( \text{CBF} \) would just exceed the globally reduced \( \text{CCO}_2 \) and, in patients with acutely decreased cerebrospinal fluid spaces, increasing \( \text{CBF} \) therapeutically may induce dangerous ICP increases.

Therefore, on practical grounds, it is extremely difficult to make decisions regarding therapeutic upward \( \text{CBF} \) manipulations in a comatose patient, whereas such decision-making process is easy in the conscious patient, especially in the presence of localizing neurological signs and a well established diagnosis showing that reduced \( \text{CBF} \) was the primary adverse event. While this condition is clear in acute ischemic stroke and vasospasm following aneurysmal subarachnoid hemorrhage, the same is not true in many comatose patients who present at the hospital with other disease processes.

**Diagnosing brain ischemia**

Based on our extensive previously published experience\(^{9-11,18-22}\), we hereby propose that \( \text{CBF} \) measurements be definitively abandoned, and replaced by cerebral metabolic parameters. For global assessment, CEO2 has been the most practical and inexpensive option, for both adults\(^{10,18,20,21}\) and children\(^{22}\). The arteriojugular lactate difference (AVDL) may also be used\(^{20,21}\), but it is more expensive and technically more cumbersome. The combination of CEO2 and AVDL measurements certainly and accurately will inform about global brain ischemia or its reciprocal (relative hyperperfusion), as we have recently reported for the first time in adults\(^{20,21}\). AVDL measurements are not yet used for children, because of the lack of normal data in the pertinent literature.

For regional information, PET scanning is the best technique, but it is expensive, involves lengthy procedures, and is formally contraindicated for patients with suspected or confirmed intracranial hypertension, because the patient’s head is placed flat for prolonged periods. The same applies to functional magnetic resonance imaging, which also provides regional cerebral metabolic information, but cannot be used for these unstable patients, because dangerous ICP increases may occur due to lowering the head as well.

Finally, regional information addressing \( \text{CBF} \) alone, as described earlier, should be definitively abandoned, not only because it provides absolutely no information with respect to \( \text{CBF}-\text{metabolism} \) coupling, but also because unstable patients with intracranial hypertension will be at increased risk of developing lethal tentorial herniation, for having the head positioned flat during the CT-CBF studies (as also happens with PET and functional magnetic resonance imaging). Therefore, on practical grounds, regional information regarding brain ischemia is still an “impossible dream” and, besides clinical information and cerebral angiography, true metabolic confirmation of regional cerebral ischemia would appear to be unfeasible under most circumstances, at least for acutely unstable patients.

**Transcranial doppler is not an alternative**

Unlike suggested by some investigators, transcranial doppler (TCD) assessment is not regional, but segmentary, involving only large intracranial vessels. Because cerebrovascular resistance may change at the microcirculatory level, in response to macrocirculatory abnormalities detected by TCD, true tissue ischemia cannot be confirmed by TCD measurements, in any disease process. This is particularly true in comatose patients, because global cerebral metabolic suppression represents a general rule and, therefore, even gross TCD abnormalities may be clinically irrelevant in comatose patients. In conscious or semicomatose patients, however, serial (not single) TCD assessment may allow for better selection of candidates to undergo cerebral angiography and, eventually, angioplasty in cerebral vasospasm associated with aneurysmal subarachnoid hemorrhage. In contrast, TCD diagnosis does not apply to brain trauma or even acute ischemic stroke, where TCD has not been demonstrated as capable of changing therapeutic decisions.
An additional limitation of TCD in comatose patients is that changes in flow velocity, sometimes speculated as indicative of vasospasm, may just represent reduced CBF which, at the microcirculatory level (not assessable by TCD measurements), represents nothing but normal coupling between low blood flow and reduced CO2.

**Dangerous brain tissue probes**

In recent years, acute placement of brain tissue probes has been proposed, focusing on microdialysis (for measurements of brain tissue lactate, glucose, etc), focal oxygen tension monitoring, or even focal brain temperature assessment. Even though these expensive monitoring devices have been approved for clinical use, such approval should never have occurred, because normal values are not even known for any type of brain tissue probe measurement. Indeed, healthy human beings will never volunteer to have their heads open for any type of brain tissue probe to be placed in their brains.

Despite the total lack of knowledge regarding normal physiological values by these probes, focal “brain ischemia” has been reported in terms of “low oxygen” and “high lactate”24. In this respect, it is obvious that any brain tissue probe causes focal microvascular compression and distortion, which may well explain focal microcirculatory compressive hypoxia, with resulting increase in lactate concentration, findings that would be just artifactual, however. Another highly biased report addressed focal “brain ischemia” associated with hyperventilation, even when jugular oxygen values were normal or high, but the brain tissue oxygen probe showed so-called “critically low” levels25. Because this kind of intentional misinformation may have serious implications regarding the total lack of validation of any type of intentional misinformation may have serious implications, they are highly invasive and normal values are not even known, and their use has obviously been recently introduced, because the probe to be placed in their brains.

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**Future prospects**

In light of the aforementioned clinically relevant limitations in assessing regional cerebral metabolic patterns associated with ischemia, it remains for global arteriographic measurements to be further explored as clinically reliable guides for a variety of therapeutic approaches, which may be adopted in a broad spectrum of acute disease processes, whereas truly reliable regional information will still require future alternative methodologies and techniques, especially for acutely unstable patients with suspected or confirmed intracranial hypertension. For more stable patients, however, currently available techniques (such as PET or functional magnetic resonance imaging) are helpful but expensive, so that they have not yet become routine procedures in most hospitals worldwide.

**REFERENCES**