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My paper 20 years later: cerebral venous oxygen saturation studied with bilateral samples in the internal jugular veins

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Abstract *Introduction:* Jugular oxygen saturation monitoring was introduced in neurointensive care after severe traumatic brain injury (TBI) to explore the adequacy of brain perfusion and guide therapeutic interventions. The brain was considered homogeneous, and oxygen saturation was taken as representative of the whole organ. We investigated whether venous outflow from the brain was homogeneous by measuring oxygen saturation simultaneously from the two jugular veins. *Methods:* In 32 comatose TBI patients both internal jugular veins (IJs) were simultaneously explored using intermittent samples; hemoglobin saturation was also recorded continuously by fiber-optic catheters in five patients. In five cases long catheters were inserted bilaterally upstream, up to the sigmoid sinuses. *Main findings:* On average, measurements from the two sides were in agreement (mean and standard deviation of the differences between the saturation of the two IJs were respectively 5.32 and 5.15). However, 15 patients showed differences of more than 15 % in hemoglobin saturation at some point; three others showed differences larger than 10 %. No relationship was found between the computed tomographic scan data and the hemoglobin saturation pattern. *Discussion/conclusion:* Several groups have confirmed differences between oxygen saturation in the two jugular veins. After years of enthusiasm, interest for jugular saturation has decreased and more modern methods, such as tissue oxygenation monitoring, are now available. Jugular saturation monitoring has low sensitivity, with the risk of missing low saturation, but high specificity; moreover it is cheap, when used with intermittent sampling. Monitoring the adequacy of brain perfusion after severe TBI is essential. However the choice of a specific monitor depends on local resources and expertise.

Keywords Jugular oxygen saturation · Cerebral blood flow · Traumatic brain injury

Introduction: historical background

Management of traumatic brain injury (TBI) improved profoundly at the end of the 1970s, when surgical removal of intracranial masses was complemented with prevention and treatment of secondary insults in the intensive care setting [1–3].

The first physiological parameters monitored, and targeted with specific therapies, were intracranial pressure (ICP) and cerebral perfusion pressure (CPP) [4–6].

Unfortunately, the adequacy of cerebral perfusion and oxygen delivery for the metabolic needs could not be explored. Normal brain function, assessed by a comprehensive neurological examination, could indirectly indicate adequate perfusion, but was obviously not feasible in deeply comatose and/or sedated patients.

Cerebral blood flow (CBF) and oxygen metabolic rate (CMRO2) were studied in selected series, first in 1955 [7], but could not be monitored at the bedside.

In general intensive care, systemic hemodynamic parameters and oxygen-related variables, including arteriovenous oxygen differences, were increasingly studied during the 1980s, and served as potential therapeutic goals for patients after major surgery [8].

The arteriojugular O_2 difference ($AJDO_2$), inversely proportional to the ratio of CBF to $CMRO_2$, had been investigated in humans in 1942 [9], but was rarely used in clinical practice in the following decades. For instance, it was reported as a possible indicator of cerebral oxygenation during carotid surgery, with temporary carotid occlusion [10], but was not widely used outside research.

In 1984 a large series of patients was studied in the first days after severe TBI [11]. CBF was measured using intravenous xenon-133 and $AJDO_2$ was repeatedly measured in 55 cases. This pioneering publication was followed 5 years later by a report on 100 comatose patients, with TBI or other pathologies [12]. These two papers showed that the traditional approach, focused on ICP, was clearly changing: maintenance of cerebral perfusion sufficient to meet metabolic demand became the main goal of investigations.

Two main concerns were the risk of ischemia or, at the other extreme, of hyperemia. Ischemia could jeopardize tissue integrity requiring increased blood flow. Hyperemia, conversely, could raise ICP because of the high cerebral blood content. Tailored reduction of an overabundant CBF, for instance by inducing vasoconstriction with hyperventilation, could be a targeted therapy. Both hyperemia and ischemia, however, required a precise definition, not based solely on CBF, but on the relationship between flow and metabolism. It was increasingly documented that comatose patients had reduced metabolic activity, with low oxygen consumption. In this situation normal CBF could be excessive for the metabolic need, representing a "luxury perfusion". These two papers made the central role of flow/metabolism relationships clear, and $AJDO_2$ qualified as an essential parameter.

It was a simple measurement, requiring reverse cannulation (pointing cranially) of an internal jugular vein; not too expensive if fiber-optic catheters for continuous jugular oxygen saturation were used, or definitely cheap using regular venous catheters for intermittent sampling. Interest in $AJDO_2$ in TBI grew fast, as indicated by the steep growth of publications (Fig. 1). $AJDO_2$ was measured for targeted therapies, such as hyperventilation or mannitol [13, 14] and for assessing cerebral autoregulation [12]. Jugular desaturation was identified as a second insult to the injured brain, potentially related to the long-term outcome. Profound and repeated episodes of desaturation, in fact, were strongly associated with poor neurological outcome [15]. $AJDO_2$ was proposed for routine monitoring in severe TBI care [16].

Most publications relied on the assumption that $AJDO_2$ accurately reflected the ratio of flow to metabolism in the brain, considered as a homogeneous organ. This assumption, however, had not been properly tested. Therefore we decided to investigate whether venous outflow from the brain was in fact homogeneous, by measuring oxygen saturation simultaneously from the two jugular veins [17].

The original paper: methods and findings

In 32 comatose TBI patients we simultaneously explored both internal jugular veins (IJs) using intermittent samples; the hemoglobin saturation was also recorded continuously with fiber-optic catheters in five patients. In five cases long catheters were inserted upstream bilaterally, up to the sigmoid sinus. This maneuver confirmed that the data collected with regular catheters, with the tip at the superior jugular bulb, was the same as in samples collected more cranially.

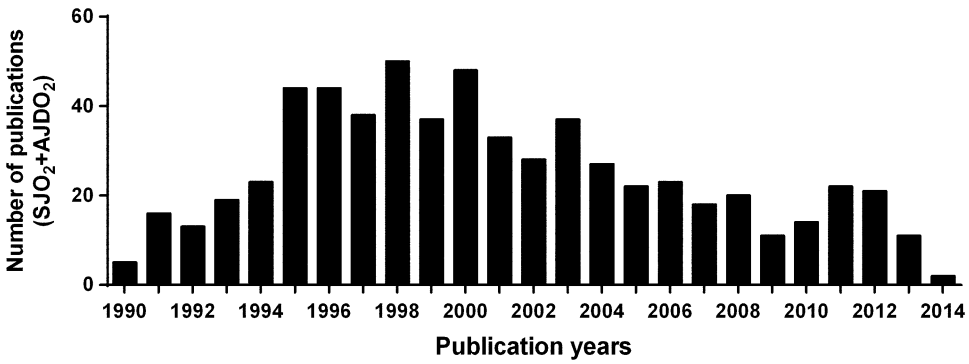

Fig. 1 Indexed papers on jugular venous oxygen saturation (15 November 2014). *Bars* indicate the number of indexed papers added to Pubmed in each year since 1990. Pubmed query: ("Jugular saturation" AND Humans[Mesh]) OR ("Arteriojugular oxygen content difference" AND Humans[Mesh])

The mean and standard deviation of the differences between the saturation of the two IJs were respectively 5.32 and 5.15, on average an acceptable agreement. However, 15 patients showed differences larger than 15 % in hemoglobin saturation at some point; three others had differences greater than 10 %. Ultimately, only eight patients had differences less than 5 %. This enabled us to work out the limits of agreement, which were −4.77 and 15.41. In other words, assuming a normal distribution, we would expect 95 % of the differences to fall within these limits. The 95 % confidence limits for the patients with a difference of more than 15 % were between 30 and 64 % and between 39 and 73 % for those with more than 10 % difference. No relationship was found between the computed tomographic scan data and the patterns of hemoglobin saturation. Therefore we could not establish which side was more appropriate for monitoring in patients with bilateral or predominantly monolateral, cortical, or deeply located lesions.

When continuous recording was used, the intermittent sampling data were confirmed; however, in two cases the side with lower saturation at some point increased more than the contralateral saturation. The main conclusions of the investigation were:

- Hemoglobin saturation of the blood flowing from the brain may be different in the two jugular veins.
- These differences are not due to contamination from extracranial sources, since they are detectable in the sigmoid sinuses.
- Differences between the two sides can be clinically important in a significant proportion of patients (30–64 %).

How these findings have been confirmed

Simultaneous sampling from the two jugular veins was first done in 1945 in 25 schizophrenic or epileptic patients, 18 of whom were felt to have unilateral cerebral pathology [18]. Differences greater than 5 % were detected in eight cases, half of them with unilateral pathology. With the diagnostic limitations of the time, no clear identification of brain lesions was possible.

After the publication of our paper, some groups replicated bilateral measurements in TBI patients. A German group studied 22 TBI patients [19]. The mean and maximum bilateral jugular saturation differences varied between 1.4 and 21.0 %, and 8.1 and 44.3 %, respectively. The bias and limits of agreement (mean differences ± 2SD) between paired samples were 0.4 ± 12.8 %.

A Spanish group confirmed differences of more than 10 % in a significant proportion of 35 TBI patients; the differences varied with time [20]. A Japanese group collected 195 pairs of samples from 19 comatose patients. The overall mean difference in jugular saturation was 9.75 ± 11.4 %. They detected a difference of more than 15 % in 37 % of patients [21]. An Italian group collected 222 samples from 19 TBI cases, whose saturation was also continuously monitored with fiber-optic catheters [22]. The authors found in 32 % of samples a difference of more than 10 % between the two sides.

Causes of differences in jugular saturation

Differences in jugular saturation have both pathophysiological and anatomical explanations. Under normal conditions flow is well coupled with metabolism in the brain, so delivery varies with the energy demand, keeping $AJDO_2$ in the normal range. Flow and metabolism are altered by trauma, more markedly where there are structural lesions such as contusions, but also where tissue appears morphologically intact. TBI may, in fact, disrupt autoregulation [23]. In comatose patients with severe head injuries, it was shown, using intravenous xenon-133 [24], that 65 % of patients had significant hemispheric and/or regional CBF differences.

The venous drainage of the normal brain is asymmetrical, with most of the blood (more than 60 %) flowing from the superior sagittal sinus draining into one transverse sinus, and finally into the dominant jugular vein (Fig. 2). Taking account of the venous asymmetries studied in healthy volunteers, a model of jugular saturation was built assuming the presence of a supratentorial lesion; the model predicted significant asymmetry in jugular venous oxygen saturation (more than 10 %) in 65 % of cases [25].

Implications for clinical practice

The obvious consequence of this investigation was that the interpretation of $AJDO_2$ in TBI was more complex than previously believed. Even if no clear relation was found between lesions detected in the CT scan and the $AJDO_2$ findings, the likely explanation of differences between the two jugular veins was that after TBI the brain was often not homogeneous, in terms of flow and metabolism.

Since the publication of our original paper investigations have tended to take two directions: some seek a better understanding of $AJDO_2$, while in others skepticism gained momentum, and jugular saturation measurement became less popular.

The side of jugular cannulation became an important methodological aspect. Several groups preferred the right side, where the jugular vein is usually bigger [26, 27].

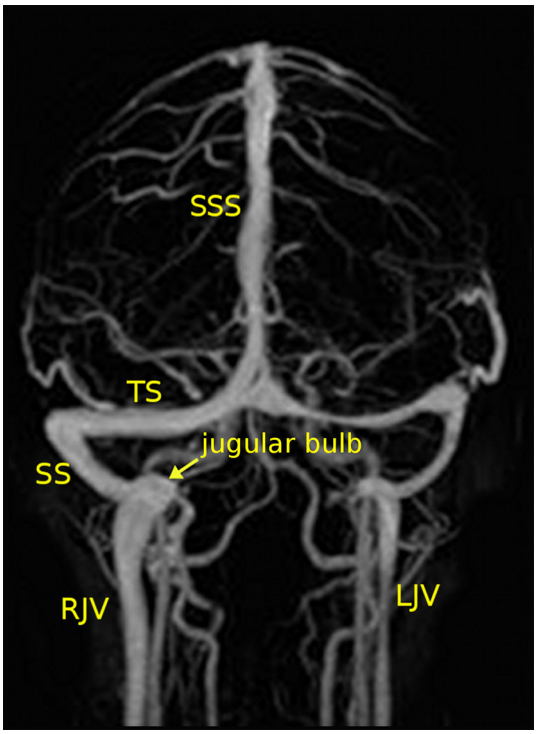

Fig. 2 The anatomy of cerebral venous drainage. Significant asymmetry of the cerebral venous drainage in healthy individuals [25, 39]. As shown in the figure, one jugular vein (commonly the right one) has a larger diameter than the contralateral vein. The jugular bulb (indicated by the *arrow*) is the position for correct jugular venous sampling and jugular venous oxygen saturation measurements. *RJV* right jugular vein, *LJV* left jugular vein, *SS* sigmoid sinus, *TS* transverse sinus, *SSS* superior sagittal sinus (figure modified from http://clinical.netforum.healthcare.philips.com)

Venous drainage from the brain being normally asymmetrical, one jugular vein drains more blood, so its diameter is bigger; in most patients this dominant vein is on the right (Fig. 2). The dominant jugular vein was identified by different methods: looking at the jugular foramina in the CT scan [28, 29], using ultrasound to measure the jugular diameter [30], or compressing the veins one at a time and checking which side caused the greater rise in ICP [21]. Some groups separated global cerebral damage from focal injuries. In cases with diffuse global damage, it was felt that sampling from the dominant jugular vein could be informative on the "average" $AJDO_2$ [12]. In patients with focal injuries some groups concentrated on venous drainage from the most affected hemisphere, and took the jugular vein preferentially draining that side [12, 29].

The insertion of the jugular catheter was not without risks; carotid artery puncture and transient ICP rise were documented but rare (less than 5 %) and not clinically significant [31, 32]. Notably, subclinical internal jugular vein thrombosis was detected, even after short-term monitoring (lasting on average 3 days), in 40 % of 20 patients investigated with ultrasonography [31].

Efforts were then devoted to integrating jugular saturation with emerging new technologies, such as the measurement of brain tissue partial oxygen tension ($PtiO_2$) [33, 34], near-infrared spectroscopy [35], or microdialysis [36].

The main difficulty with jugular saturation was its interpretation. Having demonstrated that a substantial proportion of patients could display clinically important differences, depending on the side investigated, the risk that $AJDO_2$ measurement could miss important regional disturbances was worrying. New investigation methods, such as positron emission tomography (PET), confirmed that $AJDO_2$ in the normal range could coexist with clearly hypoperfused areas of the brain [37].

In contrast with initial enthusiasm some groups became skeptical. After reviewing the differences between jugular saturation measured simultaneously in the two sides, and noting that these measurements did not help in decision-making, one group announced it would discontinue this monitoring [22].

Brain oxygenation monitoring today

In October 2014 we circulated a two-page questionnaire among colleagues with a long record of TBI research. Answers were received from 37 of the 49 centers contacted: 25 in Europe, 9 in the USA, 3 in South America, and 2 in Australia. The main findings are shown in Fig. 3. Jugular saturation monitoring is used in less than half the centers, even in research-oriented environments. Interestingly, many centers are focusing on brain oxygenation, CBF, and/or brain metabolism, regardless of whether or not they use $AJDO_2$.

As a result of the extremely selected, limited sample, this figure does not claim to illustrate current clinical use, but it does suggest that brain pathophysiology and especially parameters linked to oxygen delivery are a vital part of advanced neurointensive care.

Conclusions

Intensive care after severe TBI has progressed in the last few decades from emergency surgical removal of intracranial masses and ICP monitoring to a comprehensive attempt to prevent and manage second insults. Attention has focused on the adequacy of brain perfusion, and $AJDO_2$ monitoring was part of this.

As is often the case in medicine, disappointment has followed the initial surge of enthusiasm, and our paper

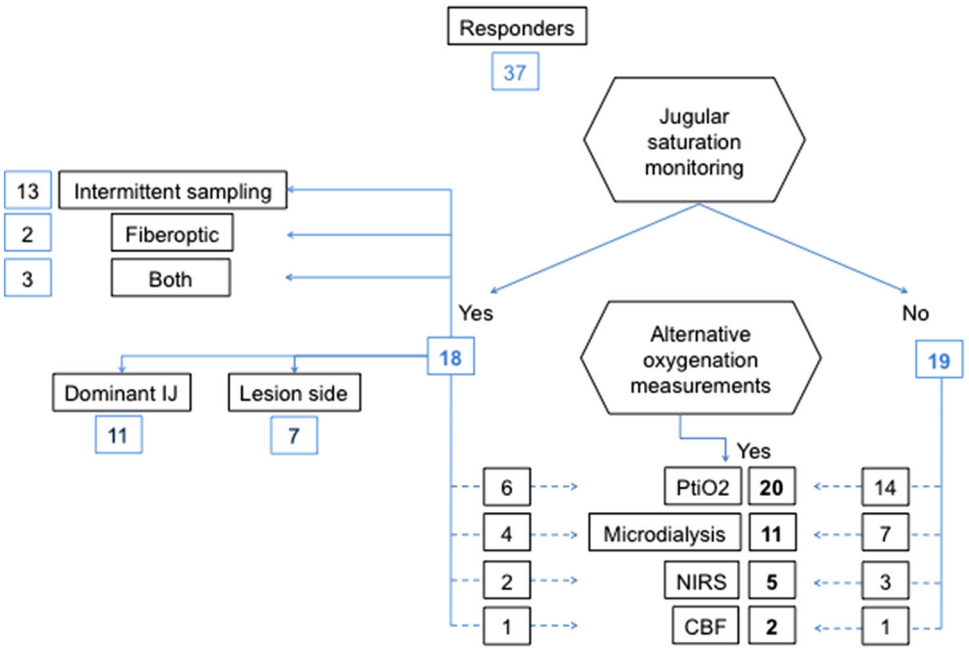

Fig. 3 Results of a survey concerning current use of jugular saturation monitoring and/or alternative brain oxygenation/flow measurements. Centers using $AJDO_2$ ($n = 18$) mainly measure saturation with intermittent sampling through catheters on the side of the dominant jugular vein. Centers with or without $AJDO_2$ monitoring use alternative methods (relative contributions are indicated by *dotted lines*). *Dominant IJ* dominant jugular vein, PtO_2 tissue oxygen tension monitor, *NIRS* near-infrared spectroscopy, *CBF* local invasive CBF monitor

20 years ago noted the complexities and inaccuracies of $AJDO_2$ monitoring; admittedly, it may have significantly contributed to this disappointment.

$AJDO_2$ monitoring has low sensitivity, with the risk of missing low saturation, an important signal of inadequate oxygen delivery. It has, however, high specificity; low saturation, when detected, clearly indicates the presence of regions with inadequate CBF to satisfy the brain metabolic needs. Furthermore, jugular saturation monitoring has the added advantage of being cheap (intermittent sampling requires a normal intravenous catheter) and applicable everywhere, while alternative methods such as tissue $PtiO_2$ or microdialysis are expensive, and extremely focal, exploring only a few cubic millimeters of brain tissue. Similar to all invasive methods, unfortunately, $AJDO_2$ monitoring has complications, even if rare and of limited clinical relevance.

Brain oxygenation is an essential parameter in severe TBI, and should be monitored. A recently published consensus [38] reinforces this concept, especially for severe patients at risk of ischemia/hypoxia; however it does not identify, as a result of scarce evidence, the brain oxygen monitor of choice.

We are still far from a reliable and simple method for continuously assessing the adequacy of brain perfusion, globally and in areas of interest, after TBI.

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Conflicts of interest The authors do not have conflicts of interest to declare.

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