

Oxygen and Carbon Dioxide in the Cerebral Circulation during Progression to Brain Death

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Background: The authors propose that for a moderate reduction of perfusion during progressive irreversible ischemia, oxygen extraction increases to maintain aerobic metabolism, and arteriojugular oxygen difference (AJDO₂) increases. Because of reduced carbon dioxide washout, venoarterial difference in carbon dioxide tension (DPco₂) increases, with no change in the DPco₂/AJDO₂ ratio. With further reduction of cerebral perfusion, the aerobic metabolism will begin to decrease, AJDO₂ will decrease while DPco₂ will continue to increase, and the ratio will increase. When brain infarction develops, the metabolism will be abated, no oxygen will be consumed, and no carbon dioxide will be produced.

Methods: The authors studied 12 patients with acute cerebral damage that evolved to brain death and collected intermittent arterial and jugular blood samples.

Results: Four patterns were observed: (1) AJDO₂ of 4.1 ± 0.7 vol%, DPco₂ of 6.5 ± 1.9 mmHg, and a ratio of 1.55 ± 0.3 with cerebral perfusion pressure of 62.5 ± 13.4 mmHg; (2) a coupled increase of AJDO₂ (5.8 ± 0.7 vol%) and DPco₂ (10.1 ± 1.0 mmHg) with no change in ratio (1.92 ± 0.14) and cerebral perfusion pressure (57.9 ± 5.8 mmHg); (3) AJDO₂ of 4.7 ± 0.4 vol% with an increase in DPco₂ (11.8 ± 1 mmHg) and correspondingly higher ratio (2.7 ± 0.2); in this phase, cerebral perfusion pressure was 39.7 ± 10.5 mmHg; (4) immediately before diagnosis of brain death (cerebral perfusion pressure, 17 ± 10.4 mmHg), there was a decrease of AJDO₂ (1.1 ± 0.1 vol%) and of DPco₂ (5.3 ± 0.6 mmHg) with a further ratio increase (5.1 ± 0.8).

Conclusions: Until compensatory mechanisms are effective, AJDO₂ and DPco₂ remain coupled. However, when the brain's ability to compensate for reduced oxygen delivery is exceeded, the ratio of DPco₂ to AJDO₂ starts to increase.

ISCHEMIA is a common pathway of damage after acute cerebral injury.^{1,2} Different techniques have been used to detect ischemia at the bedside, including continuous cerebral perfusion pressure (CPP) monitoring and measurements of the arteriojugular oxygen difference (AJDO₂). CPP is the physiologic variable that defines the pressure gradient driving cerebral blood flow (CBF). AJDO₂ provides information about the ratio between the cerebral metabolic rate of oxygen and CBF. High AJDO₂ (> 8.5 vol%) is indicative of ischemia. However, cerebral ischemia and infarction can develop even at a low AJDO₂,³ highlighting the need for better bedside measurements. Studies in the systemic circulation have

shown that ischemia can also be revealed by changes in the venoarterial carbon dioxide tension difference, because when blood flow decreases, the difference between mixed venous and arterial carbon dioxide tension (Pco₂) increases.^{4,5} Progression to brain death represents a condition of progressive irreversible global cerebral ischemia. Combining the measurements of venoarterial Pco₂ (DPco₂) and AJDO₂, various phases can be hypothesized in the progression to brain death. For moderate cerebral perfusion reduction, aerobic metabolism will be preserved; oxygen extraction will increase, with a subsequent increase in AJDO₂. Similarly, because the same amount of carbon dioxide will be cleared by less flow, DPco₂ will increase proportionally; in this phase, AJDO₂ and DPco₂ changes should therefore remain coupled, and their ratio should remain stable. With a further decrease in cerebral perfusion, the aerobic metabolism will begin to fail, so AJDO₂ will start to decrease while DPco₂ will continue to increase, and the ratio will increase. When brain death develops, a condition of CBF arrest identified with the irreversible cessation of all brain functions, the metabolism will be abated, no oxygen will be consumed, and no carbon dioxide will be produced, and in this state, because there is no CBF, we hypothesize that jugular sampling will no longer be indicative of the venous cerebral drainage.

Materials and Methods

Demographic Characteristics

Patients (n = 12) admitted to the Neuroscience intensive care unit of the Ospedale Maggiore Policlinico of Milan, Italy, from August 1998 to December 2003 whose cases evolved to brain death were studied. Brain death was identified as the irreversible cessation of all brain functions and was diagnosed according to national law, which requires the following criteria: (1) deep coma (Glasgow Coma Scale score of 3); (2) absence of brainstem reflexes; (3) positive apnea test result (absence of respiratory drive with Pco₂ > 60 mmHg and pH < 7.4); and (4) electroencephalography documenting the absence of spontaneous or induced brain electric activity in a normothermic, nonsedated patient. Brain death was confirmed over a 6-h interval, by a committee consisting of a neurologist with special expertise in electroencephalography, a forensic medicine doctor, and an anesthesiologist.⁶

Patient characteristics are shown in table 1.

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Table 1. Patient Characteristics

Patient	Sex	Age, yr	Injury
1	M	29	SAH
2	M	51	SAH
3	M	72	TBI
4	M	49	ICH
5	M	35	TBI
6	M	60	SAH
7	M	23	TBI
8	M	69	TBI
9	F	66	SAH
10	F	56	SAH
11	M	62	SAH
12	M	75	ICH

ICH = intraparenchymal hematoma; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury.

This study was approved by the local human studies committee (Institutional Review Board, Milan, Italy), and patients' relatives were informed that the data collected would be used for research purposes.

Clinical Management

All patients were treated according to a predefined protocol.⁷ Space-occupying lesions were evacuated promptly by surgery; serial computerized tomography scans were repeated every 2 days or in case of clinical deterioration. All patients were intubated and mechanically ventilated. Neurologic examinations were performed hourly by nursing personnel and at least three times daily by the medical staff. Intracranial pressure, mean arterial pressure, and CPP were continuously monitored in all except two patients. During the study, none of the patients were given sedatives.

Catecholamines (noradrenaline up to $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and dopamine up to $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) were used in euvolemic patients to avoid hypotension. Anemia (hemoglobin $< 9 \text{ g/dl}$) was corrected by erythrocyte transfusions.

Data Collection

All patients had an arterial line (usually radial), and cerebral venous blood was obtained through a catheter inserted into the superior jugular bulb, usually on the side of the main brain lesion.^{8,9} In patients with diffuse injury, the right side was preferred.¹⁰ In case of bone decompression (two patients), the jugular vein contralateral to the bone flap was cannulated. The proper position of the catheter was always checked by x-ray in the anteroposterior and lateral positions.

Arterial and jugular blood was sampled intermittently (mean interval, $125 \pm 9 \text{ min}$) and analyzed by an IL-1620 Blood Gas Analyzer and an IL-682 Co-Oximeter (both from Instrumentation Laboratory, Lexington, MA). The following parameters were measured for arterial (a) and jugular (j) samples: (1) pH (apH/jpH), (2) oxygen tension ($\text{PaO}_2/\text{PjO}_2$), (3) carbon dioxide tension ($\text{PaCO}_2/\text{PjCO}_2$),

and (4) oxygen saturation ($\text{Sao}_2/\text{Sjo}_2$). The following parameters were calculated: $\text{AJDO}_2 = [(\text{Sao}_2 - \text{Sjo}_2) \times \text{hemoglobin} \times 1.34 + (\text{PaO}_2 - \text{PjO}_2) \times 0.003]$, $\text{DPco}_2 = \text{Pjco}_2 - \text{Paco}_2$, ratio = $\text{DPco}_2/\text{AJDO}_2$.

In a separate group of six brain-injured patients, the external jugular vein was cannulated. Blood samples were taken in triplicate to determine the external jugular (ej) saturation and carbon dioxide and to calculate AejDO_2 , DPejco_2 , and the ej ratio, as for the internal jugular vein.

Observation Time

It is rarely possible to prespecify which patients, despite active treatment, will proceed to brain death. Therefore, we must clarify as we proceed. We collect measurements prospectively in all severely brain-injured patients. Goals of this data collection are oriented to the issue of oxygen consumption and tissue viability¹¹ in survivors while the goals are oriented to define patterns of progressive hypoperfusion in patients who proceed to brain death. Even if this is a prospective data collection, we can study the progression toward brain death only afterward. For the purpose of this study, we only considered samples collected in the 72 h preceding brain death.

Patterns

We established four patterns. Based on previous data, we classified as "normal pattern" the concurrent presence of AJDO_2 of $4.56 \pm 0.20 \text{ vol\%}$, and DPco_2 of $8.05 \pm 0.29 \text{ mmHg}$.¹¹ In the absence of references for numeric ranges, we used qualitative criteria to define "compensated hypoperfusion," "uncompensated hypoperfusion," and "death" pattern as follows: A coupled increase of AJDO_2 and DPco_2 above these values was classified as compensated hypoperfusion. A DPco_2 increase not accompanied by a corresponding increase in AJDO_2 was classified as uncompensated hypoperfusion. The death pattern involved a decrease of both AJDO_2 and DPco_2 .

Statistical Analysis

Continuous variables are expressed as mean \pm SD. Changes in AJDO_2 , DPco_2 , their ratio, and CPP were compared across the normal, compensated, and uncompensated patterns by analysis of variance. Blocks were used to diminish the effect of variance among subjects (SAS System, version 8; SAS Institute, Inc., Cary, NC); the block effect was considered random. In case of significance ($P < 0.05$), the Tukey-Kramer test was used for *post hoc* analysis. We assumed that because of the CBF arrest, jugular sampling during the death pattern would no longer be indicative of the mixed cerebral blood but of extracerebral venous drainage. The death pattern was therefore considered separately, the unpaired *t* test being used to assess differences between the death pattern and external jugular samples.

Results

On average, monitoring started 36 h before brain death (range, 3–72 h). A total of 206 arterial and jugular samples were collected.

AJDO₂, DPco₂, and Their Ratio

We observed four common patterns of AJDO₂, DPco₂, and their ratio: (1) AJDO₂ of 4.1 ± 0.7 vol%, DPco₂ of 6.5 ± 1.9 mmHg, and a ratio of 1.55 ± 0.3 , with CPP of 62.5 ± 13.4 mmHg, corresponding to the normal pattern¹¹; (2) a coupled increase of AJDO₂ (5.8 ± 2.2 vol%) and DPco₂ (10.1 ± 3.5 mmHg) with no change in the ratio (1.92 ± 0.4), obtained with CPP of 57.9 ± 15.4 mmHg, corresponding to the compensated hypoperfusion pattern; (3) AJDO₂ 4.7 ± 1.5 vol% with an increase in DPco₂ (11.8 ± 3.5 mmHg) and a subsequently higher ratio (2.7 ± 0.8) obtained with CPP of 34.7 ± 29.5 mmHg, corresponding to the uncompensated hypoperfusion pattern; (4) immediately before brain death was diagnosed, there was a decrease of AJDO₂ (1.1 ± 0.4 vol%) and (to a lesser degree) DPco₂ (5.3 ± 1.9 mmHg), with a further increase in the ratio (5.1 ± 2.6). In this phase (brain death pattern), CPP was 17 ± 27.6 mmHg.

Distribution of Patterns

Seven of the 12 patients showed at least one normal pattern; compensated hypoperfusion was identified in 10 patients, and all patients experienced uncompensated hypoperfusion. The death pattern was consistently observed immediately before brain death and was detected in all except one patient in whom this drop was missed, probably because of the intermittent sampling.

Time Course

Normal and compensated hypoperfusion patterns occurred close to each other, 34.6 ± 13.3 and 29.9 ± 14.6 h before brain death, respectively. Uncompensated hypoperfusion and the death pattern occurred 14.57 ± 8.27 and 2.07 ± 2.94 h before brain death. The different patterns progressed sequentially over time from compensated hypoperfusion to uncompensated hypoperfusion and ultimately brain death.

Progression to Uncompensated Hypoperfusion

Arteriojugular oxygen difference showed no significant changes across the various patterns. DPco₂ showed a significant increase from normal to compensated ($P = 0.03$) and uncompensated ($P < 0.01$) hypoperfusion. The ratio increased steeply in the uncompensated phase, with a significant difference from both the normal state ($P < 0.01$) and compensated hypoperfusion ($P < 0.01$). CPP showed no significant changes between the normal and compensated hypoperfused states, but all patients in

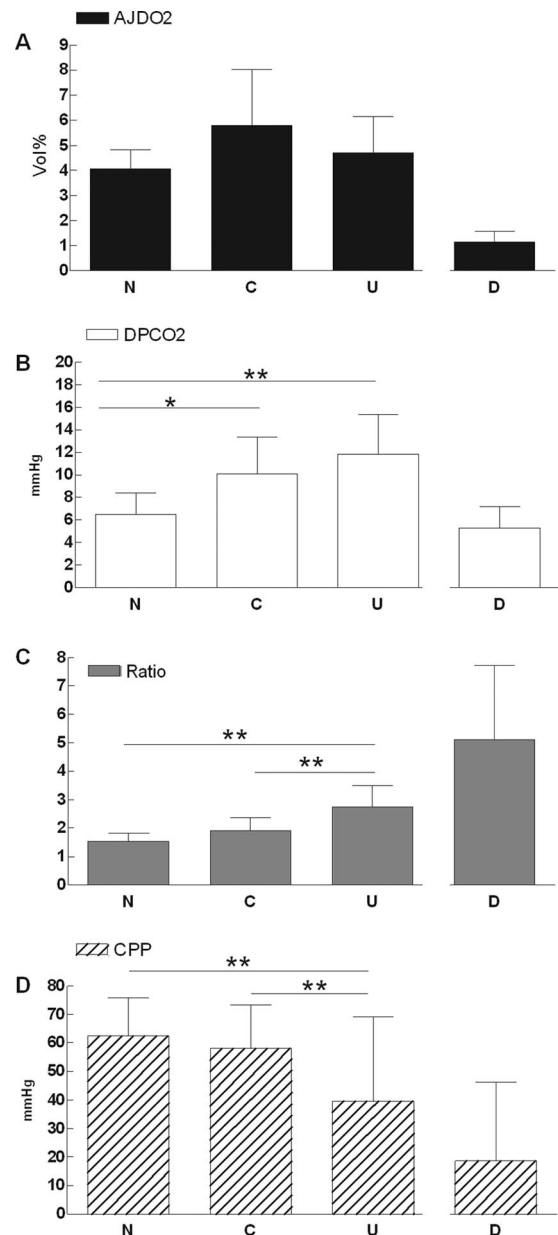


Fig. 1. Mean (\pm SD) arteriojugular oxygen difference (AJDO₂) (A), venoarterial difference in carbon dioxide tension (DPco₂) (B), DPco₂/AJDO₂ ratio (ratio) (C), and cerebral perfusion pressure (CPP) (D) across the different patterns: normal (N), compensated hypoperfusion (C), uncompensated hypoperfusion (U), death (D). * $P < 0.05$, ** $P < 0.01$.

the uncompensated state had a critical CPP ($P < 0.05$; fig. 1).

Brain Death

Arteriojugular oxygen difference, DPco₂, and ratios during brain death were no different from those measured in the external jugular vein of a separate group of brain-injured patients (fig. 2). In this group, AeJDO₂ was 1.33 ± 0.33 vol%, DPejco₂ was 5.72 ± 2.27 mmHg, and the ej ratio was 4.9 ± 1.7 . The high ratio is the effect of an extremely low AJDO₂ despite DPco₂ in the normal range.

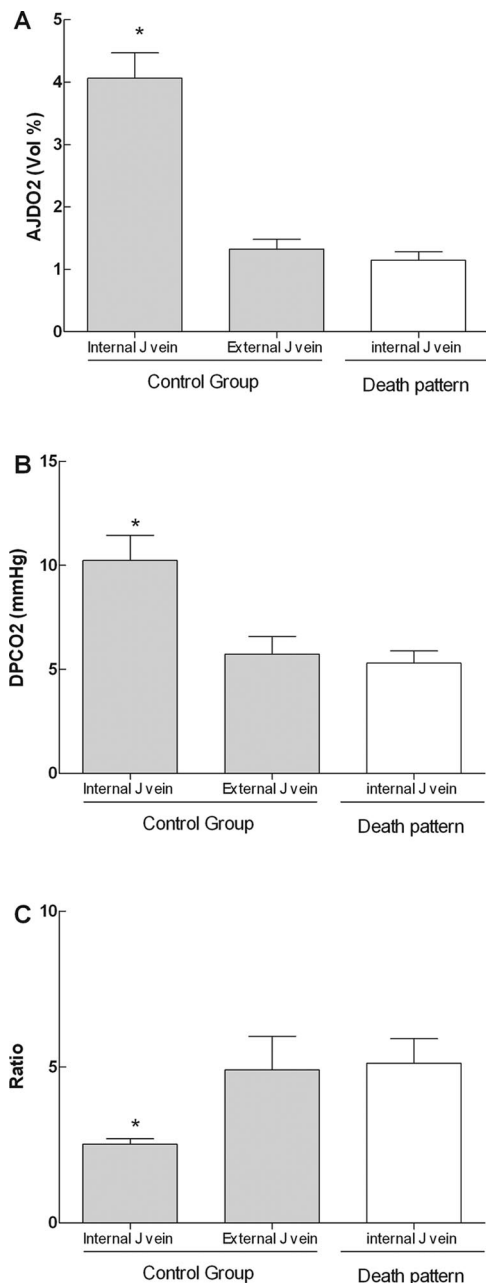


Fig. 2. Mean (\pm SD) arteriojugular oxygen difference (AJDO₂) (A), venoarterial difference in carbon dioxide tension (DPco₂) (B), and DPco₂/AJDO₂ ratio (ratio) (C) of the internal jugular vein (left gray column) and external jugular vein (central gray column) of the control patients and internal jugular vein of brain-death patients (white column). * $P < 0.05$.

Discussion

The main finding of this study is that the progression to brain death is marked by distinct patterns of AJDO₂, DPco₂, and their ratio. When cerebral perfusion initially decreases, there is a coupled increase of AJDO₂ and DPco₂, with no change in the ratio. A further, critical decrease of cerebral perfusion, however, is indicated by an increase in the ratio. These findings are consistent with the transition from compensated to uncompen-

sated hypoperfusion leading to changes in the redox state of the cell and anaerobic metabolism. At this stage, changes in pH, reflecting changes in buffer base, account for most of the increase in jugular Pco₂ and DPco₂.^{12,13} Therefore, although AJDO₂ may indicate the adequacy of CBF relative to oxidative cerebral metabolic requirements as long as oxygen delivery reductions can be compensated by increases in cerebral oxygen extraction, the ratio between DPco₂ and AJDO₂ may detect uncompensated hypoperfusion.

Studies in the systemic circulation have already highlighted the importance of the venoarterial carbon dioxide difference during ischemia.^{5,14} In addition, the ratio of venoarterial Pco₂ difference over arteriovenous oxygen content has been widely used to assess the severity of systemic organ hypoxia and hypoperfusion. In 89 critically ill patients with a pulmonary artery catheter, the ratio, compared with DPco₂, AJDO₂, and SVO₂, was the best predictor of hyperlactatemia (arterial lactate > 2 mM), with 79% sensitivity and 84% specificity.

In the experimental animal setting, our group first described AJDO₂ and DPco₂ in the progression of global cerebral ischemia in a swine model of stepwise CBF reduction, where a small reduction of CBF (50–60% of baseline) was associated with increases of both AJDO₂ (from 5.9 to 7.01 vol%) and DPco₂ (from 10 to 14.5 mmHg). When CBF was further reduced (20–30% of baseline), there was only a slight increase in AJDO₂ (from 7.01 to 8.17 vol%) but a steep increase in DPco₂. Although the ratio was not calculated in that article, the numbers point to a slight increase in the ratio (22%) during mild CBF impairment, and a definite increase (85%) when CBF was severely reduced.^{15,16} In humans, a DPco₂ increase indicative of global cerebral ischemia was described in a case report by Chierigato *et al.*¹⁷ Similar results (Pco₂ increases) in the cerebral tissue during progressive brain ischemia have been shown with focal gas tissue measurement techniques.¹⁸

To our knowledge, however, this is the first study combining AJDO₂, DPco₂, and their ratio. A weakness of this study is that we did not measure CBF, so most of our interpretation is speculative. We purposely selected a group of patients in whom a “normal” baseline could be identified, with data suggesting adequacy of CBF, and who deteriorated, through progressive CPP reduction, to a state of no CBF, as documented by the instrumental and clinical signs of brain death. Therefore, even without CBF measurement, there was presumably a progression from preserved flow to no flow in these patients.

Death Pattern

In 1973, Minami *et al.*¹⁹ studied 40 patients with severe head trauma. The 19 who survived had higher AJDO₂ (4.41%) than patients in a state of brain death (1.86 vol%). In addition, the average DPco₂ was 7.9 mmHg in the survivors and 4.8 mmHg in the brain death group. Our data

confirm these findings: Average $AJDO_2$ in the brain death state was never higher than 1.78 vol%, and DP_{CO_2} was significantly lower than in the uncompensated state. When the brain dies, jugular sampling becomes representative of extracerebral venous drainage, with an extremely low $AJDO_2$ but DP_{CO_2} in the normal range, giving a ratio above the physiologic range for brain tissue. Interestingly, the ratio calculated in the external jugular vein was above 2.1, which is usually considered as the upper physiologic limit. A high ratio can be explained by either a high DP_{CO_2} or a very low $AJDO_2$. It follows that physiologic ranges should be characterized depending on the metabolic rate of the tissue explored.

Conclusions

The adequacy of cerebral perfusion is better disclosed combining CPP with $AJDO_2$, DP_{CO_2} , and their ratio. Until compensatory mechanisms come into effect, $AJDO_2$ and DP_{CO_2} remain coupled, but when the brain's ability to compensate for reduced oxygen delivery is exceeded, the ratio between DP_{CO_2} and $AJDO_2$ starts to increase. These two "new" indicators of decompensated ischemia could be useful for early bedside monitoring of patients with severe cerebral damage.

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