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 ± 1.1 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. 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, 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. 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 anesthesiologist.

Patient characteristics are shown in table 1.

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of the patients were given sedatives. Monitored in all except two patients. During the study, none of the follow-
ing parameters were continuously monitored: mean arterial pressure, and CPP were continuously monitored.

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.

Cerebral venous blood was obtained through a catheter inserted into the superior jugular bulb, usually on the side of the main brain lesion.

In patients with diffuse injury, the right side was preferred. 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 ± 9 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 (PaO2/PjO2), (3) carbon dioxide tension (PaCO2/PjCO2), and (4) oxygen saturation (SaO2/SjO2). The following parameters were calculated: AJDO2 = [(SaO2 – SjO2) × hemoglobin / 1.34 + (PaO2 – PjO2) × 0.003], DPCO2 = PjCO2 – PaCO2, ratio = DPCO2/AJDO2.

We established four patterns. Based on previous data, we classified as “normal pattern” the concurrent presence of AJDO2 of 4.56 ± 0.20 vol%, and DPCO2 of 8.05 ± 0.29 mmHg. 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 AJDO2 and DPCO2 above these values was classified as compensated hypoperfusion. A DPCO2 increase not accompanied by a corresponding increase in AJDO2 was classified as uncompensated hypoperfusion. The death pattern involved a decrease of both AJDO2 and DPCO2.

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 viability 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 AJDO2 of 4.56 ± 0.20 vol%, and DPCO2 of 8.05 ± 0.29 mmHg. 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 AJDO2 and DPCO2 above these values was classified as compensated hypoperfusion. A DPCO2 increase not accompanied by a corresponding increase in AJDO2 was classified as uncompensated hypoperfusion. The death pattern involved a decrease of both AJDO2 and DPCO2.

Statistical Analysis

Continuous variables are expressed as mean ± SD. Changes in AJDO2, DPCO2, 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.

Clinical Management

All patients were treated according to a predefined protocol. 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 μg · kg−1 · min−1 and dopamine up to 10 μg · kg−1 · min−1) were used in euvolemic patients to avoid hypotension. Anemia (hemoglobin < 9 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. In patients with diffuse injury, the right side was preferred. 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 ± 9 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 (PaO2/PjO2), (3) carbon dioxide tension (PaCO2/PjCO2),
Results

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

\[ \text{AJDO}_2, \text{DP}_{\text{CO}_2}, \text{and Their Ratio} \]

We observed four common patterns of \( \text{AJDO}_2, \text{DP}_{\text{CO}_2}, \) and their ratio: (1) \( \text{AJDO}_2 \) of \( 4.1 \pm 0.7 \text{ vol\%} \), \( \text{DP}_{\text{CO}_2} \) of \( 6.5 \pm 1.9 \text{ mmHg} \), and a ratio of \( 1.55 \pm 0.3 \), with CPP of \( 62.5 \pm 13.4 \text{ mmHg} \), corresponding to the normal pattern; (2) a coupled increase of \( \text{AJDo}_2 \) (5.8 \pm 2.2 \text{ vol\%}) and \( \text{DP}_{\text{CO}_2} \) (10.1 \pm 3.5 \text{ mmHg}) with no change in the ratio (1.92 \pm 0.4), obtained with CPP of 57.9 \pm 15.4 \text{ mmHg}, corresponding to the compensated hypoperfusion pattern; (3) \( \text{AJDo}_2 \) 4.7 \pm 1.5 \text{ vol\%} with an increase in \( \text{DP}_{\text{CO}_2} \) (11.8 \pm 3.5 \text{ mmHg}) and a subsequently higher ratio (2.7 \pm 0.8) obtained with CPP of 34.7 \pm 29.5 \text{ mmHg}, corresponding to the uncompensated hypoperfusion pattern; (4) immediately before brain death was diagnosed, there was a decrease of \( \text{AJDO}_2 \) (1.1 \pm 0.4 \text{ vol\%}) and (to a lesser degree) \( \text{DP}_{\text{CO}_2} \) (5.3 \pm 1.9 \text{ mmHg}), with a further increase in the ratio (5.1 \pm 2.6). In this phase (brain death pattern), CPP was 17 \pm 27.6 \text{ mmHg}.

\[ \text{Distribution of Patterns} \]

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.

\[ \text{Time Course} \]

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

\[ \text{Progression to Uncompensated Hypoperfusion} \]

Arteriojugular oxygen difference showed no significant changes across the various patterns. \( \text{DP}_{\text{CO}_2} \) 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 the uncompensated state had a critical CPP \( (P < 0.05) \).

\[ \text{Brain Death} \]

Arteriojugular oxygen difference, \( \text{DPCO}_2 \), and ratios during brain death were no different from those measured in the external jugular vein of a separate group of brain-injured patients. In this group, \( \text{AejDO}_2 \) was 1.33 \pm 0.33 \text{ vol\%}, \( \text{DPejCO}_2 \) was 5.72 \pm 2.27 \text{ mmHg}, and the ej ratio was 4.9 \pm 1.7. The high ratio is the effect of an extremely low \( \text{AJDO}_2 \) despite \( \text{DP}_{\text{CO}_2} \) in the normal range.
Discussion

The main finding of this study is that the progression to brain death is marked by distinct patterns of ΔADO₂, ΔPCO₂, and their ratio. When cerebral perfusion initially decreases, there is a coupled increase of ΔADO₂ and ΔPCO₂, 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 uncompensated 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. Therefore, although ΔADO₂ 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 ΔADO₂ may detect uncompensated hypoperfusion.

Studies in the systemic circulation have already highlighted the importance of the venoarterial carbon dioxide difference during ischemia. 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, ΔADO₂, and SVO₂, was the best predictor of hyperlactatemia (arterial lactate > 2 mEq/L), with 79% sensitivity and 84% specificity.

In the experimental animal setting, our group first described ΔADO₂ and ΔPCO₂ 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 ΔADO₂ (from 5.9 to 7.01 vol%) and ΔPCO₂ (from 10 to 14.5 mmHg). When CBF was further reduced (20–30% of baseline), there was only a slight increase in ΔADO₂ (from 7.01 to 8.17 vol%) but a steep increase in ΔPCO₂. 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. In humans, a ΔPCO₂ increase indicative of global cerebral ischemia was described in a case report by Chieregato et al. Similar results (PCO₂ increases) in the cerebral tissue during progressive brain ischemia have been shown with focal gas tissue measurement techniques.

To our knowledge, however, this is the first study combining ΔADO₂, ΔPCO₂, 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. studied 40 patients with severe head trauma. The 19 who survived had higher ΔADO₂ (4.41%) than patients in a state of brain death (1.86 vol%). In addition, the average ΔPCO₂ was 7.9 mmHg in the survivors and 4.8 mmHg in the brain death group. Our data...
confirm these findings: Average AJDo₂ in the brain death state was never higher than 1.78 vol%, and DPcO₂ was significantly lower than in the uncompensated state. When the brain dies, jugular sampling becomes representative of extracerebral venous drainage, with an extremely low AJDo₂ but DPcO₂ 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 DPcO₂ or a very low AJDo₂. 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 AJDo₂, DPcO₂, and their ratio. Until compensatory mechanisms come into effect, AJDo₂ and DPcO₂ remain coupled, but when the brain’s ability to compensate for reduced oxygen delivery is exceeded, the ratio between DPcO₂ and AJDo₂ 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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References


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