The ratio between arterio-venous PCO$_2$ difference and arterio-jugular oxygen difference as estimator of critical cerebral hypoperfusion

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Aim. The aim of this study was to evaluate the arterio-venous difference in carbon dioxide tension (DPCO$_2$) and the ratio between DPCO$_2$ and arterio-jugular oxygen difference (AJDO$_2$) as indicators of compensated or uncompensated cerebral hypoperfusion.

Methods. Cerebral blood flow (CBF) was reduced stepwise in 6 pigs by inducing intracranial hypertension with consequently cerebral perfusion pressure (CPP) reduction: CBF 100%, 50-60 % of baseline, 20-30% of baseline. Intracranial pressure (ICP), mean arterial pressure (MAP), CPP and CBF (laser-Doppler method) were continuously recorded. Superior sagittal sinus was punctured for the determination of AJDO$_2$ and DPCO$_2$.

Results. CBF impairment was accompanied by changes in AJDO$_2$ from 6.03±1.21 vol% to 7.32±1.30 vol%, up to 8.07±1.32 vol% (P<0.01), in DPCO$_2$ from 12.17±3.25 mmHg to 16±4.12 mmHg, up to 26.5±6.41 mmHg (P<0.01), and DPCO$_2$/AJDO$_2$ ratio from 2.05±0.59 to 2.06±0.72 up to 3.41±1.09 in the 3 phases (P<0.05).

Conclusion. When CBF declines AJDO$_2$ increases, indicating greater extraction of O$_2$ to satisfy aerobic metabolism. However, this mechanism can no longer compensate once a critical CBF threshold is reached. DPCO$_2$ rises slowly during moderate CBF reduction because of defective washout; the rise is steeper during marked CBF impairment when anaerobic metabolism takes place. During cerebral hypoperfusion the venous blood gases and acid base variables mirror the degree of cerebral perfusion. In particular the DPCO$_2$, and the DPCO$_2$/AJDO$_2$ ratio may be useful markers of critical brain hypoperfusion.

Key words: Arterio-venous difference - Oxygen - Cerebral hypoperfusion.
threshold, this decrease cannot be compensated by a further increase in \( O_2 \) extraction: it follows that, when the shift from aerobic to anaerobic metabolism takes place, \( AJDO_2 \) is not a reliable indicator for metabolic derangement. This was suggested by Robertson et al., in 100 severely head injured patients. In that study most patients with an extremely low CBF (less than 20 mL/100 g/min) had normal or low \( AJDO_2 \) values.\(^3\)

In experimental models and in clinical setting, in cases of sepsis, hypovolemic shock and cardio-circulatory arrest, an increase of arterio-venous difference of \( PCO_2 \) has been suggested as a reliable indicator of hypoperfusion and subsequent ischemia. During compensated hypoperfusion \( DPCO_2 \) would increase because of decreased carbon dioxide wash out from the tissue. During uncompensated hypoperfusion \( DPCO_2 \) would increase further because of tissue metabolic acidosis.\(^4-11\)

The aims of this paper are:

1) To clarify whether \( PCO_2 \) gradients (\( DPCO_2 \)) are good indicators of cerebral perfusion failure in a model of progressive cerebral ischemia in pigs.

2) To investigate whether the simultaneous evaluation of both \( DPCO_2 \) and \( AJDO_2 \), by mean of their ratio, may identify situations of compensated or uncompensated cerebral hypoperfusion.

**Materials and methods**

The experiments were conducted in accordance with the guidelines for animal research published by the European Union and acknowledged by Italian Law n. 116/92.

Six 8-week-old domestic pigs, weighting 18-22 kg, were used for this study. They had free access to food and water until the night before the experiment. Thirty minutes before the induction of anesthesia a bolus of 100 mg of ketamine was given by intramuscular injection. This ensured an adequate sedation before general anesthesia, which was induced by propofol (2 mg/kg) and succinylcholine (1 mg/kg) and maintained with isoflurane 1%; myorelaxation during the experiment was maintained by 0.3 mg/kg/h pancuronium bromide. An orotracheal tube was positioned and ventilation was administered with a controlled volume modality to achieve \( PaCO_2 \) 30-35 mmHg. Inspiratory oxygen fraction (\( FiO_2 \)) was kept at 25% and 30% to obtain a \( PaO_2 \) of 100-120 mmHg.

**Placement of the probes and monitoring**

Deep branches of the carotid artery and the jugular vein were surgically exposed and cannulated for arterial pressure, arterial blood gasses, arterial hemoglobin oxygen saturation \( (SaO_2) \) monitoring and infusion of fluids. Saline was infused at the rate of 3 mL/kg/h. Rectal temperature was monitored and kept between 37.5 and 38.5 °C by using heating pads.

The animals were placed in the prone position and a linear incision was made along the midline from the inion to the nasion. The scalp was exposed and 3 burr holes were placed 1.5 cm from the midline on the right side through and across the coronal suture. Two more burr holes were done, one through the sagittal suture and the other through the left coronal suture (1.5 cm from the midline). Through a dural incision, in the cerebral parenchyma (from the front to the rear and on the right side), we placed the tips of the CBF probe, the \( PtiO_2 \) probe and the intracranial pressure (ICP) transducer. Through the burr hole on the left side a ventricular catheter was placed and connected to an infusion pump. The burr hole through the sagittal suture gave access to the superior sagittal sinus and was punctured for monitoring venous blood gases and venous hemoglobin oxygen saturation (\( SsO_2 \)).

ICP was measured by a parenchymal fiberoptic device (Camino Lab). \( PtiO_2 \) was measured by a polarographic Clark-type microcatheter (Licox, GMS). \( PtiO_2 \) was allowed to stabilize for 2 h after insertion of the catheter and was corrected for rectal temperature during the experiment. After the \( PtiO_2 \) probe was removed, the sensitivity drift was checked, as suggested by the manufacturer. CBF estimation was obtained continuously by laser Doppler flowmetry (Peri-flux,
Perimed) and was calculated as percentual changes of the baseline signal.

Cerebral electrical activity was monitored by a three-point EEG (Cerebro-trac, SDR Medical). Mean arterial pressure (MAP), ICP, cerebral perfusion pressure (CPP), PtO2, end-tidal CO2, CBF and temperature signals were filtered by an analog digital converter (Mac Lab) and stored in a Macintosh computer for off-line analysis.

Intermittent samples were drawn simultaneously from superior sagittal sinus and from the artery and processed for blood gases, pH, hemoglobin and oxyhemoglobin concentration by a gas-analyzer (ABL 30 Radiometer) and a CO-oximeter (OSM 2 Radiometer).

**Calculations**

The AJDO2 was calculated as follows: 
\[ Hb \times 1.34 \times (SaO2\% - SsO2\%) + 0.003 \times (PaO2 - PsO2) \]

The oxygen delivery to the brain (DO2) was calculated by multiplying arterial oxygen content (Hb \* 1.34 \* SaO2\% + 0.03 \* PaO2) by estimated CBF, assuming that the intact CBF amounted to 50 mL/100 g/min.

The cerebral metabolic rate for oxygen (CMRO2) was calculated by multiplying AJDO2 by estimated CBF.

The cerebral CO2 production (V.CO2) was calculated as the product of estimated CBF and the arterio-venous CO2 content difference.

Total CO2 content (venous or arterial) was calculated as: 
\[ PCO2 \times 10^{(0.91 \times pH - 6.99)} \times 2.26 \]

The difference between superior sagittal sinus PCO2 (psCO2) and arterial PCO2 (PaCO2) was calculated and named DPCO2.

The ratio indicates: DPCO2/AJDO2.

The difference between arterial pH (pHa) and superior sagittal sinus pH (pHS) was calculated and named DpH.

**Induction of progressive ischemia**

The model was developed to achieve progressive CBF reduction in 3 stable steps: baseline (CBF 100%), CBF 50-60% of baseline, CBF 20-30% of baseline. CBF was reduced by inducing intracranial hypertension. That was obtained by infusing saline (warmed to 38°C), into the left lateral ventricle through a catheter connected with an infusion pump. ICP was raised stepwise by a bolus of saline. Once the end-point was reached (in terms of reduction of CPP and CBF), the velocity of fluid infusion into the ventricles was titrated to keep ICP, CPP and CBF stable during each step. During each staircase CBF reduction arterial and venous blood were sampled twice, when the end-point was reached and at the end of the phase.

Cushing response elicited by the ICP increase was inhibited by the infusion of \( \alpha-\beta \) blockers (repeated bolus of labetalol 0.5-1 mg/kg).

At the end of the experiment the animals were euthanized by increasing the isoflurane concentration to 4% and by infusing 60 mEq of KCl.

**Statistical analysis**

Data were summarized as mean±standard deviation. Intracranial and extracranial parameters at different CBF values were compared using repeated-measures analysis of variance. Post-hoc analysis was performed when indicated by using Tukey adjustment. A paired t-test was used to compare differences between 2 groups. A P<0.05 was considered as statistically significant.

**Results**

The 3 phases of the experiment (baseline and 2 stepwise reductions of the CBF) lasted respectively 47.2±14.2, 47.3±10.9 and 43.5±11.6 min.

**Intracranial hemodynamics and brain tissue oxygenation**

Details of intracranial hemodynamic changes during the experiment have been previously published.12, 13 The reductions in CPP (from 96.17±9.98 mmHg to 49.17±7.49 mmHg and to 25.33±4.2 mmHg) were reached step-wise and reflected both the increase in ICP (from 7.25±3 mmHg to 37.92±6.41 mmHg and to 47.92±11.14 mmHg) and the slight reduction of MAP (from 103.17±9.17 to
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87.08±11.35 and to 73.25±14.7) due to the use of α-β blockers to blunt the Cushing reflex. CBF reduction was associated with a parallel decrease in O₂ delivery (DO₂: from 5.9±0.55 mL/min/m² to 3.03±0.84 mL/min/m² and to 1.19±0.25 mL/min/m²) and in PtiO₂. PtiO₂ averaged 25.05±4.3 mmHg with intact CBF, declining to 12.92±3.02 mmHg during 50-60% baseline CBF and to 2.41±2.34 mmHg during the last step. Progressive CBF impairment was associated with a sustained reduction in EEG amplitude when CBF was 50-60% of baseline, and by a flat EEG when CBF was 20-30% of baseline.

Arterial and venous blood gases

Hemoglobin dropped slightly (from 9.6±1 to 7.9±1.1 g/dL. P=0.03) probably due to blood sampling and infusions, accounting for the decrease of arterial O₂ content. The temperature remained constant at 37.7±0.4 °C throughout the experiment. The reduction of CBF from baseline to 50% was characterized by a slight AJDO₂ increase from 6.05±1.21 vol% to 7.52±1.3 vol% (n.s.) and a DPCO₂ increase from 12.17±3.25 mmHg to 16±4.12 mmHg (n.s.) with no changes in their ratio from 2.05±0.39 to 2.06±0.72. The further CBF reduction to 20-30% from baseline (equal to an estimated CBF of 11.5±4 mL/100 g/min) was characterized by a slight AJDO₂ increase to 8.07±1.31 vol% (P=0.02 compared to baseline) with a more pronounced DPCO₂ increase to 26.5±6.41 mmHg (P<0.001 compared to CBF 50% and to baseline) leading to a significant ratio increase 3.41±1.08 (P<0.05 compared to CBF 50% and to baseline).

Markers of brain tissue oxygenation

The relationship between AJDO₂, DPCO₂, ratio, DpH and PtiO₂ across the 3 steps of the experiment are depicted in Figure 1. In the progression to severe brain tissue hypoxia AJDO₂ slightly increased (the best fitting between AJDO₂ and PtiO₂ was a linear model r²=0.23). On the contrary DPCO₂ increased slightly until PtiO₂ levels of 10 mmHg but rose steeply for PtiO₂ levels < 10 mmHg, corresponding in any case to severe hypoperfusion: CBF=20-30% from baseline (the best fitting for DPCO₂ and PtiO₂ was obtained by polynomial model, r²=0.70). Similarly the ratio remained unchanged until the threshold of 10 mmHg PtiO₂, then rose significantly (the best fitting for ratio and PtiO₂ was obtained by polynomial model, r²=0.65). DpH linearly increased in the progression to severe brain tissue hypoxia (r²=0.82).

O₂ consumption and CO₂ production

Despite the significant increase in DPCO₂ and in the ratio, the calculated total venous CO₂ content (CBF 100%: 55.9±0.58 mL/100 mL blood, CBF 50%: 52.6±1.75 mL/100 mL blood, and CBF 20-30%: 57.7±1.08 mL/100 mL blood) did not significantly change during the phases of the experiment. CMRO₂ declined from 2.88±0.56 mL/100 g/min at baseline to 2.05±0.62 mL/100 g/min during moderate hypoperfusion, down to 0.92±0.24 mL/100 g/min during severe hypoperfusion (P<0.001). CO₂ production paralleled these changes, falling from 3.49±1.06 mL/100 g/min at baseline to 2.16±0.97 mL/100 g/min during moderate hypoperfusion and 1.26±0.71 mL/100 g/min during severe hypoperfusion (P=0.002) (Figure 2).
Discussion and conclusions

The development of ischemia is a crucial step in the natural history of cerebral pathologies, both traumatic and vascular.\textsuperscript{14, 15} Nevertheless, there is still no marker usable at the bedside, to help understand the degree and reversibility of ischemia.

The main purpose of our model, which has been described in detail elsewhere,\textsuperscript{12} was to achieve a reduction in CBF in reproducible steps, stable enough to allow the study of brain oxygenation and metabolism in a steady state. Two levels of CBF impairment were selected so as to reproduce the states of either compensated or decompensated cerebral hypoperfusion. There is reliable evidence that in animals and humans half-normal CBF (23-25 mL/100 g/min) leads to metabolic changes compatible with compensated hypoperfusion: increased extraction of O$_2$ and a slight reduction of CMRO$_2$, but no rise in lactate. If CBF drops to about 20-30% of the physiological values (8-15 mL/100 g/min) the glucose metabolism becomes almost totally anaerobic, as indicated by an increase in lactate and a drop in parenchymal pH levels. If this situation persists, it leads to ATP depletion and membrane failure.\textsuperscript{16-19}

In our experiment the end-points of reduced CPP and CBF were obtained in all the animals studied, with small variance.

O$_2$ delivery and AJDO$_2$

The AJDO$_2$ increased during the various stages of the experiment, confirming that CBF becomes progressively less able to meet the tissue’s metabolic demand, in agreement with the thresholds widely reported elsewhere.\textsuperscript{3, 20} The change in AJDO$_2$ from moderate to severe CBF impairment was less pronounced than from intact to moderately impaired CBF, suggesting that, when CBF and O$_2$ supply are greatly reduced, the possibility of increasing O$_2$ extraction from hemoglobin is close to its limit. This leads to the marked tissue hypoxia revealed by the polarographic O$_2$ sensor.

Carbon dioxide

Mean DPCO$_2$ during the first stage of the experiment (which should reflect normal CBF), was 11±4 mmHg. This is higher than the value reported in the systemic circulation: 6.5-7 mmHg, probably because of the high metabolic activity of the brain compared to other organs.\textsuperscript{4, 7, 10} The literature provides some references regarding CO$_2$ tension and pH in the brain parenchyma and the changes during complete ischemia, but data on DPCO$_2$ are sparse.

In humans following brain injury mean PCO$_2$ in the tissue was between 47 and 64 mmHg; values of 90-150 mmHg were detected in cases of brain death.\textsuperscript{21} In a study conducted on 12 patients with acute cerebral damage that evolved to brain death DPCO$_2$ increased form 6.5±1.9 mmHg with a CPP of 62.5±13.4 mmHg to a DPCO$_2$ of 10.1±1 mmHg with a CPP of 57.9±5.8 mmHg up to a DPCO$_2$ of 11.8±1 mmHg with a CPP of 39.7±10.5 mmHg suggesting uncompensated hypoperfusion.\textsuperscript{22}

In our animal model DPCO$_2$ rose slowly during moderate CBF reduction because of the decreased removal of CO$_2$ during hypoperfusion, but more steeply during the last CBF reduction step because, in addition to impaired CO$_2$ clearance there was a shift from aerobiosis to anaerobiosis.

During ischemia hydrogen ions are generated as a by-product of lactic acid and from

![Figure 2.—Cerebral metabolic rate of oxygen (CMRO$_2$) and carbon dioxide production (VCO$_2$), during the 3 stages of the experiment. (*P<0.05 vs CBF 100%, °P<0.05 vs CBF 50-60% baseline).](image-url)
the hydrolysis of ATP and ADP. These ions are buffered by bicarbonate from which CO₂ is generated. The first mechanism is mainly responsible for the rise in DPCO₂ during the slight reduction of CBF, and the second accounts for most of the PCO₂ that is produced anaerobically.

The venous CO₂ content, expressed as mL/100 mL blood, did not significantly change during the 3 stages of the experiment. CO₂ content is in fact mainly determined by the sum of dissolved CO₂ and bicarbonate. Therefore, if an acid load is added to the venous blood, the acid will be titrated by the HCO₃⁻/CO₂ buffer system and the total CO₂ content does not change. What changes is the form in which CO₂ is present in the solution (gaseous CO₂ instead of HCO₃⁻). In the rat, the total brain CO₂ content, measured by a microdiffusion technique, did not change after complete cerebral ischemia, confirming our findings.

The ratio of DPCO₂ to AJDO₂

Our data indicate that in the brain, low flow states involve abnormalities not only in O₂ availability and extraction, but also in CO₂ production and in acid base equilibrium. The ratio between these 2 parameters, coupling AJDO₂ and DPCO₂, should reflect the metabolic state of the brain, particularly the efficiency or inefficiency of Krebs cycle.

The ratio in fact doubled during severe CBF impairment indicating that when the brain’s ability to compensate for low blood flow is exceeded, DPCO₂ outweighs AJDO₂ and the ratio increases. Our human data are in agreement with this finding in that no changes in the ratio were observed moving from a preserved perfusion state to compensated hypoperfusion (1.55±0.3 to 1.92±0.14), moreover for further cerebral perfusion reduction there was a steep ratio increase up to values of 2.7±0.2.22

Markers of brain tissue oxygenation

PtiO₂ values when CBF was intact were greater than 20 mmHg; these declined parallel to the flow reduction, confirming extensive reports about the PtiO₂ thresholds for hypoperfusion and subsequent ischemia. CBF in this study was measured semi-quantitatively with laser Doppler, while the PtiO₂ was measured directly. To explore the value of the different markers we used PtiO₂ as independent variable since, although it only explores a limited region of the brain tissue, in our model of global ischemia it should reflect the whole brain tissue oxygenation.

From these data it appears that the best indicators of critical brain ischemia appear to be the variables which do not follow the process of hypoperfusion linearly, but increase steeply at critical levels as DPCO₂.

This study, however, has several limitations. Brain ischemia was global, the physiological Cushing response was blunted, the estimate of CBF was semiquantitative and the computation of CO₂ content may be inaccurate.

Nevertheless we believe the bulk of data fits with the known underlying physiopathology of blood gas acid-base changes during ischemia. Moreover the recent translation to the clinical setting of the above described experimental evidences increase the importance of DPCO₂ and the ratio monitoring to detect conditions of inadequate brain perfusion at the bedside.

Riassunto

Il rapporto tra la differenza veno-arteriosa di PCO₂ e
la differenza in contenuto di ossigeno come indicatore
di ipoperfusione cerebrale

Obiettivo. Lo scopo di questo lavoro era valutare
differenza veno-arteriosa in anidride carbonica
(DPCO₂) e il rapporto fra DPCO₂ e la differenza arte-
ro-venosa in contenuto di ossigeno (AJDO₂) come indicatori di ipo-
perfusione cerebrale compensata e scompensata.

Metodi. Mediante l'induzione di ipertensione intra-
cranica e conseguente riduzione della pressione di
perfusion cerebrale (cerebral perfusion pressure,
CPP) abbiamo ottenuto in un gruppo di maialini (n=6)
a una riduzione per gradi del flusso ematico cerebrale
cerebral blood flow, CBF 100%, a 50-60% e fino a 20-
30% del valore basale). La pressione intracranica
(intracranial pressure, ICP), la pressione arteriosa
media (mean arterial pressure, MAP), la CPP e il CBF
(methodo di laser-Laser-Doppler) sono stati registrati
in continuo. La AJDO₂ e della DPCO₂ sono state
determinate con campioni di sangue prelevati dal seno sagittale e dall’arteria.

Risultati. In corrispondenza della riduzione del CBF si è osservato un aumento dell’AJDO2 da 6,0±0,5, 9, a 2,0±0,5, 9, fino a a 5,4±1,09 durante le 3 fasi (P<0,05).

Conclusioni. Quando il CBF si riduce, l’AJDO2 aumenta, perché, per mantenere il metabolismo aero- blo, aumenta l’estrazione di ossigeno. Questo meccanismo tuttavia diventa insufficente, una volta raggiunta una riduzione critica di CBF. La DPCO2 aumenta durante la riduzione di CBF per il ristagno di CO2 e metaboliti; aumenta in maggior misura durante la fase di riduzione del CBF al 20-30% del valore basale, quando si innesca il metabolismo anaerobio. Durante le diverse fasi di ipoperfusione cerebrale, le tensioni dei gas nel distretto venoso e le variabili acido-base rispecchiano il grado di ipoperfusione cerebrale. In particolare la DPCO2 e il rapporto DPCO2/AJDO2 potrebbero essere utili indicatori di ipoperfusione cerebrale.

Parole chiave: Differenza artero-venosa - Ossigeno - Ipoperfusione cerebrale.

References