An Evaluation of Transcutaneous Carbon Dioxide Partial Pressure Monitoring during Apnea Testing in Brain-dead Patients

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Background: Diagnosis of brain death usually requires an arterial carbon dioxide partial pressure (PaCO2) of 60 mmHg during the apnea test, but the increase in PaCO2 is unpredictable. The authors evaluated whether transcutaneous carbon dioxide partial pressure (PtcCO2) monitoring during apnea test can predict that a PaCO2 of 60 mmHg has been reached.

Methods: The authors compared PtcCO2 measured with a transcutaneous ear sensor (V-Sign® Sensor, Sentec Digital Monitoring System; SENTEC-AG, Therwil, Switzerland) and PaCO2 obtained from arterial blood gas measurements in 32 clinically brain-dead patients.

Results: In the first 20 patients, the mean PaCO2–PtcCO2 gradient was 0.7 ± 3.6 mmHg at baseline and 8.7 ± 7.1 mmHg after 20 min of apnea. Using receiver operating characteristic curve analysis (area under the curve: 0.983 ± 0.013), the best threshold value of PtcCO2 to predict that a PaCO2 of 60 mmHg had been reached was 60 mmHg (positive predictive value: 1.00 [0.93–1.00]). In the following 12 patients investigated with use of this PtcCO2 target value of 60 mmHg, the mean duration of the apnea test (11 ± 4 vs. 20 ± 0 min; P < 0.001), hypercapnia (74.0 ± 4.9 vs. 98.3 ± 20.0 mmHg; P < 0.001), acidosis (pH: 7.18 ± 0.06 vs. 7.11 ± 0.08; P < 0.001), and decrease in arterial oxygen partial pressure (–47 ± 44 vs. –95 ± 89; P < 0.05) at the end of the test were reduced as compared with the 20-min apnea test group.

Conclusion: During the apnea test in brain-dead patients, a PtcCO2 of 60 mmHg accurately predicts that a PaCO2 of 60 mmHg has been reached. This may allow a reduction in the duration of the apnea test and consecutively limit occurrence of complications.

BRAIN death is defined by the irreversible cessation of all cortical functions, including the brainstem reflexes, motor responses, and respiratory drive, in a normothermic, unsedated, comatose patient with an irreversible major brain injury and a noncontributing metabolic disorder. When brain death is clinically suspected, an important component of the clinical diagnosis is the apnea test, although this is not always required by guidelines and/or law throughout the world. An arterial carbon dioxide partial pressure (PaCO2) target value of 60 mmHg at the end of the apnea test is usually recommended. However, during the apnea test in brain-dead patients, the estimated PaCO2 increase is slow, from 1.7 to 3.7 ± 2.3 mmHg/min, and biphasic with a decline in the increase rate throughout the duration of the apnea test. In addition, the increase in PaCO2 has been reported as unpredictable, from 0.5 to 10.5 mmHg/min, because of carbon dioxide washout, atelectasis, cardiac-induced ventilations, and other potentially unknown factors, which explains the failure of attempts to estimate the required duration of the apnea test to reach the threshold of a PaCO2 of 60 mmHg.

Transcutaneous carbon dioxide partial pressure monitoring (PtcCO2), which has been used for several decades in infants, is now a valid technique in adults and provides noninvasive, accurate, and real-time monitoring of PaCO2 and allows a significant reduction in, but does not replace, arterial samples for blood gas analysis. Although PtcCO2 monitoring has been reported to be in good agreement with PaCO2 during stable ventilatory and circulatory conditions both in volunteers and in anesthetized patients, it had been reported that the accuracy of this monitoring became more imprecise during major increases in PaCO2, such as the apnea test in brain-dead patients. Indeed, Lang et al. had previously studied PtcCO2 monitoring during an apnea test in brain-dead patients, but because they induced an increase in PaCO2 either by hyperventilation or by artificial carbon dioxide augmentation, both followed by a real apnea time of only 0.5–1 min, they overlooked the dynamic component of the PaCO2 increase during the apnea. Moreover, this apnea test procedure performed in their two studies was not the one commonly recommended throughout the world, which usually requires a starting arterial PaCO2 of 40 mmHg before disconnection from the ventilator.

Therefore, the aim of this prospective clinical study was first to evaluate the accuracy of PtcCO2 monitoring as a real-time estimate of PaCO2 during the apnea test in brain-dead patients and second to determine whether PtcCO2 monitoring could accurately predict that the PaCO2 target value of 60 mmHg has been reached, therefore enabling shortening of the duration of the apnea test.

Materials and Methods

Study Population
The study was approved by our local ethics committee (Comité de Protection des Personnes se Prêtant à la
bral angiography is mandatory, we usually perform the
sensor. The PtcCO2 measurement by the V-Sign® Sensor
Switzerland), which also combines a pulse oximetry
skin at the monitoring site for the PtcCO2 measurement.
warmed up to 42°C to achieve local arterialization of the
dioxide tension sensor. The sensor temperature is
is based on a Severinghaus-type electrochemical carbon
dioxide tension sensor. The sensor temperature is
warmed up to 42°C to achieve local arterialization of the
dioxide tension sensor. The sensor temperature is
warmed up to 42°C to achieve local arterialization of the

cardiac death. Care of the patients conformed to standard
procedures in our ICU for severely comatose patients.
The patients were monitored with an arterial pressure
catheter, enabling samples to be taken for arterial blood
gas measurements. PtcCO2 was continuously measured
with a heated transcutaneous ear sensor (V-Sign® Sensor,
Sentec Digital Monitoring System; SENTEC-AG, Therwil,
Switzerland), which also combines a pulse oximetry
sensor. The PtcCO2 measurement by the V-Sign® Sensor
is based on a Severinghaus-type electrochemical carbon
dioxide tension sensor. The sensor temperature is
warmed up to 42°C to achieve local arterialization of the

Because of hypothermia
alogram is unhelpful in confirming brain death (mainly
plification. On the other hand, when the electroenceph-
ence on one electroencephalogram with maximal am-
phases, and usually showed vasoplegia and diabetes
insipidus. All these findings strongly indicate brain
death.19 Because the apnea test has been shown to be
deleterious in some patients and may therefore limit
organ procurement for transplantation,9,20–22 we have
decided in our ICU to perform the apnea test only after
brain death has been confirmed by electrocortical si-
ence on one electroencephalogram with maximal am-
plification. On the other hand, when the electroenceph-
alogism is unhelpful in confirming brain death (mainly
because of hypothermia < 35°C or because of a signifi-
cant residual blood concentration of sedative drugs), we
usually require the absence of intracerebral blood flow on
four-vessel cerebral angiography. However, angiograp-
hy is not only potentially deleterious, but also risky
because of transportation of the patient to the radiology
department, especially when there is major hemody-
namic instability.23,24 Therefore, when four-vessel cere-
bral angiography is mandatory, we usually perform the
apnea test before angiography. In such cases, before the
apnea test, we always verify the absence of intracerebral
blood flow by transcranial Doppler ultrasonography.5

The Apnea Test

The apnea test was performed after a 20-min preoxy-
genation period with an inspired oxygen fraction of
100%. After the ventilator was disconnected, a 94/min
oxygen flow was delivered through the endotracheal
tube via an oxygen cannula (12-French catheter). The
patient was then closely observed for respiratory efforts.
If spontaneously respiratory efforts or complications
(major hemodynamic instability despite increase in the
dose of catecholamine and/or severe hypoxemia) oc-
curred, the apnea was discontinued and the patient was
immediately reconnected to the ventilator. Otherwise,
the apnea was continued, and afterward, the patient was
reconnected to the ventilator at the end of the test. The
apnea test was considered positive if there was no respira-

the apnea test was performed according to our
standard guideline, i.e., over a 20-min fixed period. Using
the receiver operating characteristic (ROC) curve, this
enabled us to calculate the best PtcCO2 target value
which estimates that the PaCO2 threshold of 60 mmHg
has been reached. Thereafter, for the following 12 brain-
dead patients (PtcCO2 targeted apnea test group), the
apnea test was performed until this previously calculated
PtcCO2 target had been reached.

Data Collection

Clinical characteristics, etiology of brain death, and
hemodynamic variables (heart rate, systolic arterial
blood pressure, and oxygen peripheral saturation) were
recorded. PtcCO2 was continuously monitored before,
during, and after the apnea test, and data were stored on a
computer for off-line analysis. Complications during
the apnea test were recorded as hypotension (defined as
a decrease in systolic arterial blood pressure of more
than 20% of baseline value and/or the need for an in-
crease in the dose of catecholamine administered), hy-
pertension (defined as an increase in arterial blood pres-
sure of more than 20% of baseline value and/or the need
for a decrease in the dose of catecholamine adminis-
tered), and severe hypoxemia (defined as a decrease of
oxygen peripheral saturation < 90%). For PaCO2 mea-
surements (Blood Gas Analyzer ABL725; Radiometer,
Copenhagen, Denmark), arterial blood gases were ob-
tained through an indwelling radial arterial line and were
compared with the simultaneous PtCO2. In the 20-min
apnea test group, arterial blood gases were sampled
before the apnea test (baseline) and thereafter at 5, 10,
15, and 20 min of apnea. In the PtcCO2 targeted apnea
test group, arterial blood gases were sampled before the

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The apnea test (baseline) and thereafter at the end of the apnea test when the PtcCO2 had reached the calculated target value. In addition, after reconnection of the patient to the ventilator at the end of the apnea test, arterial blood gases were sampled at 5-min intervals for 30 min in 10 patients of the 20-min apnea test group.

Statistical Analysis

Data are expressed as mean ± SD. Comparison of two means was performed using the Student t test. The ROC curve was used to determine the best threshold value for PtcCO2 to predict that PaCO2 has reached the mandatory threshold of 60 mmHg. The area under the ROC curve was also calculated. Sensitivity, specificity, positive and negative predictive values, accuracy (defined as the sum of concordant cells divided by the sum of all cells in the two-by-two table), and their 95% confidence intervals were calculated. The best threshold value was defined as the one that simultaneously minimizes the distance to the ideal point (sensitivity = specificity = 1) and that provides a positive predictive value as close as possible to 1. All P values were two tailed, and a P value of less than 0.05 was considered significant. The NCSS 2001 statistical program (Statistical Solutions Ltd., Cork, Ireland) was used for all statistical analyses.

Results

The apnea test was performed 32 times in 32 patients, 24 men and 8 women (mean age, 48 ± 14 yr). Causes of brain death were cerebral hemorrhage (n = 20), blunt head trauma (n = 5), cerebral anoxia (n = 4), and cerebral gunshot injury (n = 3). At the time of investigation, 31 patients required catecholamine administration, and 23 patients exhibited diabetes insipidus. The confirmatory test of brain death was electroencephalogram in 19 patients, whereas the 13 other patients required cerebral angiography because of significant residual blood concentration of sedative drugs. The apnea test was completely performed in the 20 patients of the 20-min apnea test group, and none of them showed any spontaneous respiratory movement during the 20-min apnea period. Similarly, in the 12 patients of the PtcCO2 targeted apnea test group, the apnea test was performed until PtcCO2 had reached the calculated target value, and none of them showed any spontaneous respiratory movement during apnea. Fourteen patients in the 20-min apnea test group and 4 patients in the PtcCO2 targeted apnea test group showed a significant hypotension requiring an increase in the dose of catecholamine administered (P < 0.05). Finally, whatever the apnea test group, none of the 32 investigated patients showed significant hypoxemia during the apnea test.

The mean PaCO2–PtcCO2 gradient was 0.7 ± 3.6 mmHg for baseline measurement before the apnea test in the 32 investigated patients. Figure 1 presents the typical recording of PaCO2 and PtcCO2 during the apnea test in one patient of the 20-min apnea test group. The increases in PaCO2 and PtcCO2 during the apnea test in the 20-min apnea test group are shown on figure 2. During the apnea test, the mean PaCO2–PtcCO2 gradient was fairly stable, approximately 8.7 ± 7.1. The box plot representation of the PaCO2–PtcCO2 gradient clearly shows that the gradient observed during the apnea test could not be analyzed in the same manner as the baseline gradient.
The Bland-Altman analysis for comparison of $\text{PtcCO}_2$ versus $\text{PaCO}_2$ during the 20-min apnea test (i.e., excluding baseline measurements) revealed a mean bias of 8.6 mmHg, with limits of agreement ($\pm 1.96 \times \text{SD}$) of 22.4 and −5.3 mmHg (fig. 3B). There was no significant correlation between the $\text{PaCO}_2$–$\text{PtcCO}_2$ gradient and the rate of increase in $\text{PaCO}_2$ during the apnea ($R = 0.19$). At the end of the 20-min apnea test, we observed major hypercapnia, acidosis, and decrease in $\text{PaO}_2$ as compared with baseline measurement (table 1). During the first 30 min after reconnection of the patient to the ventilator, the mean $\text{PaCO}_2$–$\text{PtcCO}_2$ gradient progressively increased from $1.8 \pm 11.5$ mmHg to $8.5 \pm 6.0$ mmHg (fig. 2).

The capacity of $\text{PtcCO}_2$ to predict that the targeted $\text{PaCO}_2$ 60 mmHg had been reached was assessed with a ROC curve analysis (fig. 4). The area under the ROC curve was $0.983 \pm 0.013$, indicating a very high accuracy of $\text{PtcCO}_2$ monitoring. The best threshold value on receiver operating characteristic curve analysis is the one that simultaneously minimizes the distance to the ideal point (sensitivity = specificity = 1) and that provides a positive predictive value as close as possible to 1.

![Fig. 3](image)

Fig. 3. (A) Box plot representation of the arterial carbon dioxide partial pressure ($\text{PaCO}_2$)–transcutaneous carbon dioxide partial pressure ($\text{PtcCO}_2$) gradient for baseline and during the apnea test in the 20-min apnea test group. The $\text{PtcCO}_2$–$\text{PaCO}_2$ gradient is clearly increased during the apnea test as compared with baseline measurement. (B) Bland-Altman representation of the $\text{PaCO}_2$–$\text{PtcCO}_2$ gradient (y-axis) versus ($\text{PaCO}_2$–$\text{PtcCO}_2$)/2 (x-axis) during the apnea test in the 20-min apnea test group. The bias and the limits of agreement ($\pm 1.96 \times \text{SD}$) are shown as dashed and dotted lines, respectively.

![Fig. 4](image)

Fig. 4. Receiver operating characteristic curve showing the relation between sensitivity and 1-specificity in determining the best threshold value of transcutaneous carbon dioxide partial pressure ($\text{PtcCO}_2$) to predict that the target value of arterial carbon dioxide partial pressure of 60 mmHg has been reached. The area under the receiver operating characteristic curve was $0.983 \pm 0.013$, indicating a very high accuracy of $\text{PtcCO}_2$ monitoring. The best threshold value on receiver operating characteristic curve analysis is the one that simultaneously minimizes the distance to the ideal point (sensitivity = specificity = 1) and that provides a positive predictive value as close as possible to 1.

### Table 1. Arterial Blood Gases before and at the End of the Apnea Test for the 20-min Apnea Test Group and the $\text{PtcCO}_2$ Targeted Apnea Test Group

<table>
<thead>
<tr>
<th></th>
<th>20-min Apnea Test (n = 20)</th>
<th>$\text{PtcCO}_2$ Targeted Apnea Test (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End of Apnea</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>End of Apnea</td>
</tr>
<tr>
<td>$\text{Pao}_2$, mmHg</td>
<td>353 ± 98</td>
<td>368 ± 121*</td>
</tr>
<tr>
<td>$\Delta\text{Pao}_2$, mmHg</td>
<td>−95 ± 89</td>
<td>−105 ± 93*</td>
</tr>
<tr>
<td>$\text{SaO}_2$, %</td>
<td>99.7 ± 0.8</td>
<td>99.9 ± 10.8*</td>
</tr>
<tr>
<td>$\text{pH}$</td>
<td>7.40 ± 0.08</td>
<td>7.11 ± 0.08*</td>
</tr>
<tr>
<td>$\text{HCO}_3$, mm</td>
<td>25.0 ± 2.7</td>
<td>28.9 ± 3.8*</td>
</tr>
<tr>
<td>$\text{PaO}_2$, mmHg</td>
<td>41.4 ± 6.3</td>
<td>98.3 ± 20.0*</td>
</tr>
<tr>
<td>$\text{PtcCO}_2$, mmHg</td>
<td>41.1 ± 5.8</td>
<td>88.6 ± 20.0*</td>
</tr>
<tr>
<td>$\text{Pao}_2$ – $\text{PtcCO}_2$, mmHg</td>
<td>0.3 ± 4.2</td>
<td>9.7 ± 9.0*</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

* $P < 0.05$ vs. baseline in the same apnea test group. † $P < 0.05$ vs. end of apnea in the 20-min apnea test group.

$\text{PaCO}_2$ = arterial carbon dioxide partial pressure; $\text{PaO}_2$ = arterial oxygen partial pressure; $\Delta\text{PaO}_2$ = arterial oxygen partial pressure in baseline conditions minus arterial oxygen partial pressure at the end of the apnea test; $\text{PtcCO}_2$ = transcutaneous carbon dioxide partial pressure; $\text{SaO}_2$ = oxygen saturation.
The mean rate of increase in PaCO2 during the 20-min apnea test was 2.9 ± 0.8 mmHg/min in our study, close to those reported by Ropper et al.4 (2.6 ± 0.8 mmHg/min) and Orliaguet et al.7 (2.7 mmHg/min). We did not find a significant correlation between the PaCO2–PtcCO2 gradient and the rate of increase in PaCO2 during the apnea. On one hand, the PaCO2 increase is highly variable among brain-dead patients during the apnea test because of carbon dioxide washout, atelectasis, cardiac-induced
ventilations, and other potentially unknown factors. On the other hand, the instantaneous PaCO₂–PtcCO₂ gradient during such dynamic conditions probably depends on many factors, such as the rate of increase in PaCO₂, but also hemodynamic, temperature, ear lobe vascularization, and skin condition. At last, 5 min after reconnection of the patient to the ventilator, PtcCO₂ was very close to PaCO₂, likely because the rapid decrease in PaCO₂ overtook the delay of PtcCO₂ variations (fig. 2). Afterward, the late increase in the mean PaCO₂–PtcCO₂ gradient is unexpected and could be due to a drift of the transcutaneous sensor because of the extreme and rapid changes in PaCO₂ during the apnea test and reconnection to the ventilator.

The area under the ROC curve was 0.983 ± 0.013, indicating a very high accuracy of PtcCO₂ in predicting that the target PaCO₂ 60 mmHg had been reached (fig. 4). The best threshold value on ROC curve analysis was determined as a PtcCO₂ of 60 mmHg, providing a sensitivity of 0.80, a specificity of 1.00, and a positive predictive value of 1.00 (table 2). Indeed, none of the 12 patients of the PtcCO₂ targeted apnea test group investigated using this threshold of 60 mmHg exhibited a PaCO₂ lower than 60 mmHg at the end of the apnea test. In a previous study investigating PtcCO₂ monitoring for apnea testing in brain-dead patients, Lang17 showed that a PtcCO₂ of 66 mmHg had a predictive value of 82% for PaCO₂ of 60 mmHg or greater and empirically recommended a PtcCO₂ of 60–66 mmHg for the confirmatory arterial blood gas check. This discrepancy as compared with our result may be fully explained, because in their analysis of the PaCO₂–PtcCO₂ gradient, they overlooked the dynamic component of PaCO₂ increase during the apnea. Finally, the apnea test procedures performed in their study were either hypoventilation or artificial carbon dioxide insufflation, with a real apnea time of only 0.5–1 min, i.e., far from the apnea test procedure commonly recommended throughout the world.1,3

For the 12 patients of the PtcCO₂ targeted apnea test group, the mean duration of the apnea test, hypercapnia, acidosis, and decrease in PaO₂ at the end of the apnea test were significantly reduced as compared with the 20-min apnea test group. This result is important, because performing an apnea test in brain-dead patients may lead to complications, such as hypotension and hypoxia, especially in patients with hemodynamic instability. In the worst possible situation, the apnea test may exceptionally induce a sudden and irreversible cardiac arrest, which prevents any organ donation.9,27,28 Limitation of the duration of the apnea test reduces the importance of hypercapnia, acidosis, and decrease in PaO₂ at the end of the apnea and therefore probably reduces the occurrence of complications related to the test. Indeed, we observed significantly less hypotension in the PtcCO₂ targeted apnea test group than in the 20-min apnea test group. On the other hand, whatever the apnea test group, none of our 32 patients exhibited severe hypoxemia during the apnea test. Indeed, the 20-min preoxygenation period with an inspired oxygen fraction of 100% and the 9-l/min oxygen insufflation inside the endotracheal tube during the apnea test, both performed in our study, probably limited the occurrence of significant hypoxemia during the apnea test.1,9,29 Nevertheless, further studies are mandatory to determine whether reduction of the duration of the apnea test in brain-dead patients may lead to a significant improvement in the prognosis of transplanted organs.

Finally, one could argue that the 20-min apnea test period we have chosen for the first 20 investigated patients was dramatically too long, because the mean PaCO₂ at 5 min of the apnea test (63.8 ± 10.1 mmHg, fig. 2) in the 20-min apnea test group was already higher than the threshold of 60 mmHg and because the mean duration of the apnea test in the PtcCO₂ targeted apnea test group was reduced to 11 ± 4 min. However, the PaCO₂ increase during the apnea test in brain-dead patients is unpredictable from one patient to another, and shorter apnea test times, such as 10 min, have been previously reported as insufficient in some patients to reach the PaCO₂ threshold value of 60 mmHg.6,9,30 Similarly, estimation of the required apnea test duration to reach the threshold of 60 mmHg has also been reported as inefficient because of the unpredictability of PaCO₂ increase during the apnea test.4,10 This explains why some investigators, who had reported an apnea test lasting from 1 min to more than 1 h, strongly discourage a time-locked approach for the apnea test and conversely insist on arterial blood gas determinations.31 On the other hand, keeping in mind the dynamic PaCO₂–PtcCO₂ gradient during the apnea test, PtcCO₂ monitoring offers an on-line estimation of PaCO₂, whereas PaCO₂ analysis from a blood gas sample requires a minimum delay of several minutes to get the result, and eventually a longer time depending on the distance between the laboratory and the ICU.32 Nevertheless, one should keep in mind that the high predictive value of PtcCO₂ reported in our study with the VSign® sensor may not be found with other transcutaneous carbon dioxide sensors, according to technology and time–response differences between devices.

In conclusion, PtcCO₂ monitoring during the apnea test in brain-dead patients may permit a significant reduction in the duration of the apnea test. We found that a PtcCO₂ of 60 mmHg has a predictive positive value of 100% in predicting that the target threshold of PaCO₂ of 60 mmHg has been reached. Reducing the duration of the apnea test may limit hypercapnia, acidosis, and decrease in PaO₂ at the end of the apnea test and eventually occurrence of complications such as hypoxemia and hypotension.

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