Problems in Cerebral Blood Flow Calculation Using Xenon-133 in Patients With Pulmonary Diseases

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We used the end-tidal concentration of xenon-133 (air curve) to estimate the profile of its arterial concentration in calculating cerebral blood flow. We examined the effects of pulmonary disease and artificial ventilation on the air curve and the calculated cerebral blood flow. We studied the relation between arterial and end-tidal xenon activities in 19 subjects, of whom 15 had pulmonary dysfunction. The $t_{1/2}$ of the declining phases of the arterial and air curves were used to express their shapes. The mean±SD reference $t_{1/2}$ from 15 normal volunteers was 26.8±8.4 seconds. The mean±SD $t_{1/2}$s of the air and arterial curves from the 15 patients with pulmonary dysfunction were 10.4±2.9 and 33.8±10.9 seconds. The degree of pulmonary dysfunction (expressed as the pulmonary shunt percentage) correlated with distortion of the air curve. Substituting the arterial for the air curve, mean calculated cerebral blood flow (as the initial slope index) increased from 40 to 61 for the 12 patients with chronic obstructive pulmonary disease. The degree of underestimation of cerebral blood flow using the air curve correlated with the pulmonary shunt percentage. Our work confirms the problems of estimating cerebral blood flow in subjects with pulmonary dysfunction. (Stroke 1990;21:745-750)

Cerebral blood flow (CBF) can be estimated using the xenon-133 clearance method, administering xenon by either intra-arterial or intravenous injection or by inhalation. The latter technique is widely used, inexpensive, and atraumatic. However, xenon is carried to the brain not as a bolus, but in increasing amounts as its concentration in the blood rises during inhalation. Knowledge of the time profile of xenon input to the brain is essential to correctly calculate CBF. The time profile is usually determined from the end-tidal xenon concentration, assuming equilibrium between gas tensions in the pulmonary blood and the alveolar space. This equilibrium is disturbed in persons with pulmonary dysfunction.

The purpose of our study was to examine the effects of pulmonary disease and artificial ventilation on the xenon-133 input function by comparing the end-tidal xenon concentration (air curve) with the xenon concentration in blood samples (arterial curve). We also studied the consequences on calculated CBF of substituting the arterial for the air curve as the input function.

Subjects and Methods

We studied 19 subjects. Group 1 included 12 patients (mean age 60.4, range 46–71 years) with chronic obstructive pulmonary disease (COPD). Group 2 comprised three neurosurgical patients (aged 37, 53, and 63 years) artificially ventilated for 7–17 days. Groups 1 and 2 represent patients with pulmonary dysfunction. Group 3 consisted of three neurosurgical patients (aged 18, 52, and 63 years) artificially ventilated for <48 hours. One healthy subject (aged 24 years) was also studied. Reference air curves from 15 normal volunteers (mean age 32.3, range 20–43 years) were also examined.

CBF was measured in all 19 subjects using the xenon-133 inhalation technique and a Novo Cerebrograph 32A with Novo Diagnostic System software (Novo Diagnostic System, Hadsund, Denmark). Recordings were made from 32 collimated NaI crystals during 1 minute of xenon inhalation and 10 minutes of isotope washout. CBF was calculated as both the unitless initial slope index (ISI) from 0.5 to 1.5 minute and as the CBF in milliliters blood per minute.

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100 g brain per minute. IS1 mainly determines the fast-flow component because the first part of the curve is dominated by cortical blood flow. CBF15, calculated as height divided by area, represents an average of the fast- and slow-flow components. End-tidal xenon activity was used to compute the air curve. To describe its shape, the half-time \( t_{1/2} \) (time to 50% activity) values for the declining part of the air curve were measured.

For determining the arterial curve, blood samples were drawn from a radial artery catheter using syringes impervious to xenon. Five arterial samples (3 ml each) were drawn from the six patients in groups 2 and 3, 30, 60, 90, 120, and 180 seconds after the start of xenon inhalation. From the 12 patients in group 1 and the one healthy subject, six samples were drawn 20, 40, 60, 90, 120, and 180 seconds after the start of xenon inhalation. Within 10 minutes the xenon activity during 100 seconds was determined with a Scaler-Timer SHA-11 (Meditronic, Lyngby, Denmark). To construct the arterial curve, arterial xenon activity at 60 seconds was superimposed on the corresponding value of the air curve. The remaining arterial values were calculated as fractions of the value at 60 seconds and positioned relative to the 60-second value at the appropriate times. The points were connected by a smooth curve, and a new CBF was calculated.

Pulmonary dysfunction can be characterized by either the pulmonary shunt percentage or the forced expiratory volume in 1 second (FEV1). The pulmonary shunt percentage, reflecting the disproportion between overall ventilation and perfusion of the lungs, was determined in 17 patients from the relation between \( Fio_2 \) and \( Pao_2 \). Paco2 was measured using an automatic blood gas analyzer (ABL-2, Radiometer, Copenhagen, Denmark). FEV1, representing the obstructive component of lung disease, was measured in the 12 group 1 patients using a Vitalograph Spirometer 20600 S-model (Spiropharma, Klampenborg, Denmark).

In three group 1 patients with COPD but no history of cerebrovascular disease, the cerebral arteriovenous difference for oxygen (AVDO2) was measured. A polyethylene catheter was inserted into the right internal jugular vein using a low cervical puncture. AVDO2 was calculated as milliliters oxygen per 100 ml blood using the formula 1.39 \( \times \) 1.61 \( \times \) Hgb \( \times \) (SAT - SAT'), where Hgb is the concentration of hemoglobin in millimoles per liter, SAT' is the arterial blood oxygen saturation, and SAT is the venous blood oxygen saturation. Oxygen saturation was determined by an automatic blood gas analyzer (Oxyhemometer OSM-2, Radiometer). The cerebral metabolic rate for oxygen (CMRO2) was calculated as mean CBF15 multiplied by AVDO2 and divided by 100, expressed as milliliters oxygen per 100 g brain per minute. The average of the 32 regional CBF15 values was considered to be a good approximation of global CBF.

Results are expressed as mean \( \pm \) SD. The \( t_{1/2} \) values of groups 1, 2, and 3 were compared with the reference \( t_{1/2} \) value using the two-tailed \( t \) test.

Results

A typical air curve from the healthy subject is shown in Figure 1, top. This curve should be compared with that in Figure 1, bottom, which shows a typical air curve and the estimated arterial curve from a patient with severe pulmonary dysfunction (Group 2). The reference \( t_{1/2} \) was 26.8 \( \pm \) 8.4 seconds.

Air curves from the 15 patients in groups 1 and 2 showed reduced \( t_{1/2} \) values (mean \( \pm \) SD 10.4 \( \pm \) 2.9 seconds), that is, a steep curve, significantly different \((p=0.0001)\) from the reference \( t_{1/2} \) (Figure 2). Controlled ventilation for \( >7 \) days in the group 2 patients resulted in increased pulmonary shunt percentages (to 10%, 18%, and 20%) and reduced \( t_{1/2} \) values (to 7.1, 8.8, and 11.5 seconds), much the same as in the group 1 patients with COPD.

In groups 1 and 2, the arterial curve had a \( t_{1/2} \) significantly longer (33.8 \( \pm \) 10.9 seconds, Figure 2) than either the air curve \( t_{1/2} \) \((p=0.0001)\) or the reference \( t_{1/2} \) \((p=0.027)\). In the healthy subject, the air and arterial curves were identical. In the group 3 patients, only minor differences between the air and arterial curves were found. These three patients all had pulmonary shunt percentages of \(<5\%\).

In Figure 3, the \( t_{1/2} \) value for 17 of the patients are given as a function of their pulmonary shunt percentage. The 15 reference \( t_{1/2} \) values are also included. The seven patients with pulmonary dysfunction and a shunt percentage of \( >10\% \) had \( t_{1/2} \) values of \(<13 \) seconds. In contrast to the \( t_{1/2} \) values from the air curves, those from the arterial curves were not correlated with the pulmonary shunt percentage (Figure 3). No correlation was found between FEV1 and \( t_{1/2} \) of the air curves for group 1 patients \((r=0.349)\) (data not shown).

Changes in both measures of CBF after substituting the arterial for the air curve are shown for 14 of the groups 1 and 2 patients in Figure 4. Calculated CBF increased in these patients with pulmonary dysfunction. Using the air curve for the 12 group 1 patients with COPD, mean \( \pm \) SD ISI was 40.0 \( \pm \) 7.4; using the arterial curve, it was 60.9 \( \pm \) 8.25. The corresponding values of CBF15 were 32.4 \( \pm \) 4.5 and 48.3 \( \pm \) 9.1 ml/100 g/min. PaCO2 in these 12 patients was 39.3 \( \pm \) 4.5 torr.

The relation between pulmonary shunt percentage and percentage change in ISI for 17 of the patients is plotted in Figure 5, which shows increasing underestimation of CBF with increasing pulmonary shunt percentage. Shunt percentages of 10% and 20% are associated with mean underestimations of approximately 27% and 46%.

Table 1 lists the AVDO2 and CBF15 and CMRO2 calculated first with the air curve and then with the arterial curve as input functions for three patients with COPD. Assuming a normal mean AVDO2 of 6.3 (range 3.9-8.7, 2 SD) ml/100 ml11 and a normal mean CBF15 of 45.4 ml/100 g/min,12 the calculated mean CMRO2 should be 2.86 ml/100 g/min. The AVDO2 values were within the normal range.
range, as expected in these patients without a history of cerebrovascular disease. Using the air curve, mean CMRO$_2$ was 1.7, clearly below the normal mean. Using the arterial curve, CMRO$_2$ was almost normal in one patient and above normal in the other two.

**Discussion**

We studied the relation between end-tidal xenon concentration and arterial blood xenon concentration in patients with pulmonary dysfunction. A crucial point is whether our constructed arterial curve reflects the true time profile of the arterial blood xenon concentration. In one healthy subject without pulmonary dysfunction, we found the air curve and estimated arterial curve to be equivalent. Furthermore, in three patients artificially ventilated for $<48$ hours and with only minor increases in pulmonary shunt percentages, good agreement was found between the air curve and the estimated arterial curve. Obrist et al$^2$ have reported a similar good agreement between air and arterial curves in healthy young subjects.

Elevated pulmonary shunt percentages were found in patients with COPD and patients artificially ventilated for $>7$ days. Patients treated for $<48$ hours did not show increased pulmonary shunt percentages. Prolonged artificial ventilation may thus lead to a state of pulmonary dysfunction that should be taken into account when measuring CBF using the xenon-133 inhalation method.

A crucial point in using the xenon-133 inhalation method for measuring CBF is the time profile of the xenon input to the brain. The input function is usually computed from the end-tidal xenon activity, assuming that it reflects the arterial blood concentrations, but this is not the case in patients with pulmonary disease.

With increasing degrees of pulmonary dysfunction the input function obtained from the air curve changes, with a steeper increase during xenon administration and a steeper decrease during isotope washout (Figure 1). The shift in the air curve profile in patients with pulmonary disease has been described.$^{12}$ We used the $t_{1/2}$ values during the decrease to characterize the shape of the air curve. As shown in Figure 2, all patients with pulmonary disease or artificially ventilated for $>7$ days had very low air curve $t_{1/2}$ values compared with the reference value. The differences in $t_{1/2}$ cannot be accounted for by differences in the mean ages of the groups since Melamed et al$^{13}$ found no significant differences in the rates of pulmonary clearance of xenon-133 in normal subjects of various ages. The abnormally low $t_{1/2}$ obtained from air curves of patients with pulmo-
FIGURE 2. Scatterplot of half-time values ($t_{1/2}$) for washout period of air curve from 15 normal volunteers (reference value, mean±SD 26.8±8.4 seconds) and 15 patients with pulmonary disease (mean±SD 10.4±2.9 seconds). Very low $t_{1/2}$ for patients with pulmonary disease indicate rapid washout of xenon. However, $t_{1/2}$ from arterial curves of these 15 patients (mean±SD 33.8±10.9 seconds) are significantly greater than values from air curves from normal volunteers.

nary dysfunction must be an artifact, not reflecting the actual clearance of xenon from the blood. When measuring xenon clearance on arterial curves, a much higher $t_{1/2}$ was obtained, one significantly longer than the reference value. The degree of lung insufficiency (expressed as the pulmonary shunt percentage) was positively correlated with the decrease in $t_{1/2}$ of the air curve. This correlation indicates that the degree of air curve distortion is determined by the severity of pulmonary disease and reflected in the shunt percentage. The same correlation could not be obtained comparing $t_{1/2}$ with FEV-1, indicating that the distortion of the air curve in patients with COPD is not caused by obstruction of the airways but by disproportionate perfusion of the lungs during ventilation. The steep decline of the air curve is due to a lack of equilibrium between the blood and the airways and could be explained by perfusion of poorly ventilated areas, which delays the removal of xenon from the blood. In accordance with this, a slight but significant increase in true (arterial curve) $t_{1/2}$ values was found in the 12 patients with pulmonary dysfunction compared with the 15 normal volunteers.

A mean ISI of 40 and a mean CBF$_{15}$ of 32.4 ml/100 g/min were found in the 12 patients with COPD using the air curve as the input function. When using the arterial curve, a mean ISI of 60.9 and a mean CBF$_{15}$ of 48.3 ml/100 g/min were obtained. To examine the validity of the calculated CBF$_{15}$ values, cere-

bral AVD0$_2$ was measured in three patients with COPD. As shown in Table 1, mean CMRO$_2$ calculated from CBF$_{15}$ using the air curve is less than normal.$^{11}$ As the AVD0$_2$ values were within normal limits, the low calculated CMRO$_2$ indicates underestimation of CBF$_{15}$. An underestimation of CBF in patients with pulmonary disease has also been described by Jaggi and Obrist$^5$ and Obrist et al.$^{12}$ This underestimation of CBF can be explained by the observed profile of the input function, which overestimates the area under the curve during xenon inhalation and underestimates it during xenon washout.$^{12}$

The percentage underestimation of CBF using the air curve was correlated with the degree of pulmonary dysfunction (Figure 5), whether the dysfunction was due to COPD or to prolonged artificial ventilation. As seen in Figure 5, patients with none or low shunt percentages have essentially no underestimation of CBF using the air curve as the input function. It is important to emphasize that the end-tidal (air) curve can be used as the input function in subjects with normal or only slightly impaired pulmonary function. Problems arise only when dealing with patients showing pronounced pulmonary dysfunction. With a pulmonary shunt percentage of >10%, a CBF was underestimated by 20–50% compared with
FIGURE 4. Graph of changes in two measures of calculated cerebral blood flow (CBF) using air curve (A) and arterial curve (B) as input function in 15 patients with pulmonary dysfunction. For initial slope index (ISI), mean ± SD CBF increased from 40.0 ± 7.4 to 60.9 ± 8.25. For CBF15, mean ± SD CBF increased from 32.4 ± 4.4 to 48.3 ± 9.1 ml/100 g/min. All but one patient revealed increase in CBF after substituting arterial for air curve.

CBF calculated using the arterial curve as the input function.

The mean ISI of 60.9 as well as the mean CBF15 of 48.3 ml/100 g/min calculated using the arterial curves are above the normal range in young, healthy volunteers. Therefore, it seems likely that CBF is overcorrected when using the constructed arterial curve. The data from Table 1 support this since in two of the three patients the calculated CMRO2 using CBF15 was greater than the normal mean value. Assuming correct measurement of AVDO2, the high CMRO2 must be caused by an overestimation of CBF, probably due to difficulties in the detailed construction of the arterial curve. The limited number of samples reduce the accuracy in estimating the shape of the arterial curve, particularly during the rapid increase and decrease. CBF could be overcorrected due to underestimation of the area under the first part of the arterial input curve and overestimation of that under the second part. A better estimate of the shape, and consequently a more accurate estimate of CBF, would require more frequent sampling, for example, every 5–10 seconds.2

To summarize, the input function estimated from end-tidal xenon measurements does not reflect the arterial concentration in patients with pulmonary dysfunction, whether due to COPD or to prolonged artificial ventilation. When we used the air curve as the input function, we underestimated CBF, proportional to the degree of pulmonary dysfunction.

References

TABLE 1. AVDO2, CBF15, and CMRO2 in Three Patients With Chronic Obstructive Pulmonary Disease but No History of Cerebrovascular Disease

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<tr>
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AVDO2, cerebral arteriovenous difference for oxygen (ml O2/100 ml blood); CBF15, cerebral blood flow (ml/100 g brain/min); CMRO2, cerebral metabolic rate for oxygen (ml O2/100 g brain/min).

**KEY WORDS** • pulmonary disease • xenon • cerebral blood flow
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