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Local cerebral blood flow measured by stable xenon CT during fentanyl-diazepam anesthesia

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Abstract: We assessed the local cerebral blood flow (LCBF) in 40 patients under fentanyl-diazepam anesthesia. The measurement of LCBF was made using 50%–70% stable xenon with 20 min of inhalation interval and a shuttle method for computed tomography imaging. All patients were anesthetized with 5.95 ± 1.76 $\mu g \cdot kg^{-1}$ fentanyl and 0.22 ± 0.07 $mg \cdot kg^{-1}$ diazepam under mechanical ventilation during CBF measurement. The values and distribution of LCBF on non-affected hemisphere appeared to be unaltered by fentanyl-diazepam anesthesia. We also assessed the cerebral carbon dioxide reactivity in 6 patients. The cerebral carbon dioxide reactivity, expressed as percentage change in LCBF per unit change in arterial carbon dioxide partial pressure, was 5.39 ± 1.07, and there were no significant differences of reactivity among regions studied. In conclusion, we showed reference values of LCBF and carbon dioxide reactivity, measured by stable xenon-enhanced computed tomography, in patients under fentanyl-diazepam anesthesia. Carbon dioxide reactivity was preserved in all regions including gray matter, white matter, and basal ganglia.

Key words: Anesthesia, Cerebral blood flow, Carbon dioxide

Introduction

The measurement of local cerebral blood flow (LCBF) by the stable xenon (Xe) computed tomography (CT) method has become an important diagnostic tool in a variety of clinical situations. This technique provides optimal resolution and correct estimates of both the local brain: blood partition coefficient and LCBF values, even in disease states [1–5].

There are various challenges associated with the use of the xenon CT CBF method, but immobilization is still one of the most limiting aspects [1,4]. With a relatively high degree of resolution, significant misregistration can occur with movement as small as a few millimeters in any plane of motion. The pharmacologic properties of xenon are associated with a number of theoretical and real problems. At high concentrations, xenon itself has anesthetic or sedating effects. Even at 30%–40% concentration, xenon alters the sensorium and may induce patient motion [1,4]. General anesthesia may be occasionally conducted to improve the accuracy of the measurement. Johnson et al. [1] demonstrated that intubated patients are easily studied with xenon CT/CBF, and nearly 100% of the studies yielded diagnostic information. However, there are few reports about the LCBF of anesthetized human [6]. It is clinically important to determine reference values of LCBF under general anesthesia.

The present study was undertaken to assess the LCBF and cerebral carbon dioxide reactivity of patients anesthetized with fentanyl and diazepam.

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Materials and methods

Between March, 1983, and March, 1989, 216 patients underwent Xe/CT CBF measurements at the National Cardiovascular Center. Of these, 40 patients were selected for this study based on the following criteria: (1) patients do not have bilateral hemispheric lesions, diagnosed by CT and angiography; (2) the unilateral hemispheric lesion is small or mild; and (3) patients are not in the acute stage. The age range of these patients was 19–72 years with a mean of 50 years. There were 31 men and 9 women in this series. The study included patients with ischemic cerebrovascular disease ($n = 25$), arteriovenous malformation ($n = 10$), brain tumor ($n = 2$), epilepsy ($n = 2$), and cervical spondylosis ($n = 1$).

After institutional approval and informed consent were obtained, Xe/CT CBF measurement was performed. Premedication was accomplished intramuscu-

larly with 0.5 mg atropine and 35 mg pethizine. Anesthesia was induced with 3–5 mg·kg^{-1} thiopental, and 1–2 mg·kg^{-1} succinylcholine or 0.1–0.2 mg·kg^{-1} vecuronium or pancuronium, and maintained with 5.95 ± 1.76 μg·kg^{-1} fentanyl and 0.22 ± 0.07 mg·kg^{-1} diazepam under mechanical ventilation. The Xe/CT CBF measurement was started 45 min after the induction of anesthesia. The Xe/CT CBF measurement was performed using the GE-8800CT/T (Milwaukee, Wisc.) and stable xenon, which has been described as the "shuttle method" [7]. In brief, body nitrogen was displaced by inhalation of 100% oxygen for 10 min prior to measurement. Inhalation of 50%–70% xenon gas mixed in oxygen was then instituted for 20 min. A semi-closed partial rebreathing system was utilized to administer the gas mixture. Scannings were performed at the cervix and the brain alternately by use of table incrementation. We obtained the time-dependent CT images of the common carotid artery at the cervical level as well as that of brain tissue at three to five brain levels. The baseline scans were averaged to reduce noise levels. Four to six enhanced images were then obtained at each level during xenon inhalation. The averaged baseline images were subtracted from the enhanced images, and each voxel was subsequently defined by a series of enhanced values as a function of time [ΔCT(t)]. This series was used to solve the Kety-Schmidt equation in which ΔCa(u) and ΔCT(t) were used as input data;

$$\Delta CT(t) = \lambda k \int_0^t \Delta Ca(u) e^{-k(t-u)} du \quad (1)$$

and $f = \lambda k$

where ΔCT(t) = time-dependent brain xenon concentration,
λ = brain:blood partition coefficient,
k = brain uptake flow rate constant,
ΔCa(u) = time-dependent arterial xenon concentration, and f = CBF.

A weighted least square fit routine was used to derive the estimates of two parameters, f (blood flow) and λ. The derivation of the various independent and dependent parameters for each voxel resulted in a set of images that was used to generate the final flow image. Preanalysis smoothing routines (5 × 5 pixels) were used to reduce pixel-to-pixel noise.

The LCBF values on the non-lesion side were determined. We also assessed the cerebral vascular carbon dioxide reactivity during fentanyl-diazepam anesthesia in six patients. Following the measurement of LCBF during normoventilation, hyperventilation was induced. After 15 min, $Paco_2$ was measured, and the LCBF values during hyperventilation were determined in the same fashion. Carbon dioxide reactivity was defined as the percentage change in LCBF per unit change in arterial carbon dioxide partial pressure and differences among the regions were compared.

Statistical comparisons were made using one-way analysis of variance, and $P < 0.05$ was considered significant. Data are expressed as mean ± SD.

Results

The LCBF values on the non-lesion side during fentanyl-diazepam anesthesia are shown in Table 1. Mean arterial pressure was 96.2 ± 13.7 mmHg and $Paco_2$ was 40.8 ± 1.7 mmHg during measurements of LCBF. Table 2 shows the LCBF values during normoventilation and hyperventilation, and cerebral vascular carbon dioxide reactivity. Xenon/CT CBF images in one case under fentanyl and diazepam anesthesia are shown in Fig. 1. Hyperventilation induced a reduction of $Paco_2$ from 41.5 ± 1.4 mmHg to 31.7 ±

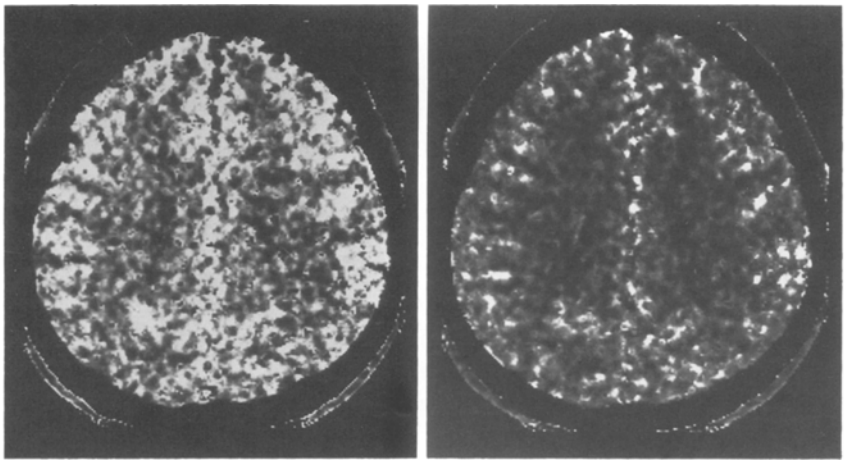
Table 1. Local cerebral blood flow (LCBF) during fentanyl-diazepam anesthesia

	LCBF (ml/100 g per min)
Thalamus	96.0 ± 22.3
Caudate nucleus	96.4 ± 24.4
Putamen	96.8 ± 23.3
Frontal gray	73.5 ± 18.9
Frontal white	38.4 ± 12.2
parietal gray	71.7 ± 18.0
Parietal white	37.4 ± 11.6
Occipital gray	69.9 ± 17.8
Occipital white	33.2 ± 10.4
Temporal gray	73.4 ± 19.6

Table 2. LCBF during normoventilation and hyperventilation, and CO_2 reactivity during fentanyl-diazepam anesthesia

	Normoventilation	Hyperventilation	CO_2 reactivity
MAP (mmHg)	87.3 ± 12.0	88.0 ± 11.4	
$Paco_2$ (mmHg)	41.5 ± 1.4	31.7 ± 2.6	
Thalamus	112.9 ± 25.4	50.2 ± 11.5	6.27 ± 2.79
Caudate nucleus	89.1 ± 37.3	59.4 ± 18.1	3.00 ± 4.07
Putamen	117.1 ± 26.1	64.1 ± 18.8	5.17 ± 3.27
Frontal gray	91.1 ± 24.6	41.1 ± 6.1	6.15 ± 3.03
Frontal white	45.8 ± 13.2	18.5 ± 4.5	6.51 ± 2.49
Parietal gray	82.1 ± 25.3	43.1 ± 5.1	4.18 ± 4.60
Parietal white	40.0 ± 15.1	18.2 ± 3.4	5.55 ± 2.75
Occipital gray	78.2 ± 16.4	38.8 ± 4.8	5.63 ± 1.86
Occipital white	39.6 ± 17.7	19.3 ± 9.3	5.93 ± 2.24
Temporal gray	91.9 ± 21.7	48.4 ± 3.8	5.47 ± 2.40
Average			5.39 ± 1.07

CO_2 reactivity was defined as percent changes in cerebral blood flow per unit changes in $Paco_2$. Data are mean ± SD
MAP, mean arterial pressure



a b

Fig. 1a,b. Xenon computed tomography/cerebral blood flow images in a patient anesthetized with fentanyl and diazepam **a** during normoventilation ($Paco_2$ = 40.8 mmHg), and **b** during hyperventilation ($Paco_2$ = 33.4 mmHg)

2.6 mmHg. Mean arterial pressure remained constant during the assessment of carbon dioxide reactivity. Average carbon dioxide reactivity was 5.39 ± 1.07, and there were no significant differences in reactivity among the regions studied.

Discussion

The present study showed the reference values of LCBF during fentanyl-diazepam anesthesia, which were measured using a Shuttle method for CT imaging and 50%–70% stable xenon with an inhalation interval of 20 min. Carbon dioxide reactivity was preserved in all regions during fentanyl-diazepam anesthesia.

A number of approaches have been taken in quantitating LCBF using stable xenon CT/CBF imaging [4], but since each method has both advantages and disadvantages, the best way has not been determined. We have chosen our method for the following reasons. First, the shuttle technique makes possible in vivo measurements of xenon concentration in arterial blood as well as brain tissue [7]. By the use of on-line data acquisition and data assessment system, LCBF study can be performed in a short period of time (50 min in total, including computation time). Second, although 30%–35% xenon inhalation has been widely accepted because it is well tolerated by patients [1,4], we considered that the signal-to-noise ratio was not adequate if GE CT/T 8800 with 3-4 standard deviations were used for the CBF study [7]. Furthermore, all patients were not able to tolerate the inhalation of xenon even at a concentration of about 30%. The study was terminated in several cases because of agitation, and slowing and irregularity of the respiratory pattern. While 50%–70% xenon provides a high signal-to-noise ratio, it may have a sedating or anesthetic effect at that concentration [1]. Since even the patient receiving 30%–35% xenon is not considered to be in the normal physiologic state, we performed CBF study using 50%–70% xenon under general anesthesia. Third, short inhalation intervals of xenon may be insufficient to evaluate true λ, as considerable error in the estimation of LCBF may result [3]. The time course for tissue saturation of xenon was found to be different by region and to be altered by brain edema, infarction, and tumor [1,2,4]. In our experience, to obtain plateau level of CT numbers after xenon inhalation, it takes 15 min for gray matter and more than 30 min for white matter. Therefore, we used a xenon inhalation interval of 20 min for more accurate measurement of λ and LCBF.

The effect of xenon itself must be considered at first. The xenon induced changes in CBF have been reported in both animals and humans [8–12]. It depends on the concentration of inhaled xenon, the duration of inhalation, and the particular animal model. Giller et al. [12] summarized the previous findings. They documented that although administration of xenon at high concentrations or for prolonged periods resulted in a fall in CBF, the inhalation of 35%–40% xenon for 4–5 min led to a 15%–40% rise in CBF. However, there has been no data about the effect of 50%–70% xenon with an inhalation interval of 20 min on CBF during neuroleptanesthesia in humans.

There have been no reports about the influence of anesthetics on LCBF measured by the three-dimensional technique such as stable xenon CT, positron emission tomography, or photon emission CT. Several authors have reported the effects of fentanyl and/or diazepam on CBF and carbon dioxide reactivity in both animals and humans [13–17]. However, they used a global CBF measurement technique or a two-dimensional CBF measurement tequnique using ^{133}Xe intracarotid injection or inhalation method. In animal studies, both an increase and a decrease in CBF have been reported following the administration of fentanyl [13–15]. The discrepancy in results was explained by the fact that fentanyl in some species induced epileptic

electroencephalogram (EEG) changes and metabolic activation. In human studies, it has been reported that CBF was decreased during neuroleptanesthesia by fentanyl supplemented with nitrous oxide, and droperidol or midazolam [6,16,17]. Vernhiet et al. [6] reported that following the administration of fentanyl 10 $\mu g \cdot kg^{-1}$ and diazepam 10 mg, the gray matter flow decreased by 54%, but white matter flow did not change significantly.

In the present study, we cannot determine the effects of fentanyl and diazepam on LCBF because control values are not available. However, the LCBF values in the present study seem not to be reduced and to be similarly distributed compared with previous reports which measured LCBF using stable xenon in awake subjects [5,18]. This is not consistent with the results of previous reports about CBF during neuroleptanesthesia. The reason for this discrepancy is unknown, but it may be due to differences in methodology or light anesthesia.

The present study showed the preservation of carbon dioxide reactivity during fentanyl-diazepam anesthesia. This is compatible with the previous reports [6,19,20]. McPherson and Traystman reported that fentanyl did not alter cerebral vascular reactivity to changes in $Paco_2$ in dogs [19]. Several authors reported that the cerebral carbon dioxide reactivity was preserved during fentanyl-diazepam anesthesia in human subjects [19,20]. However, the values of carbon dioxide reactivity obtained in the present study are somewhat greater than those of the previous reports. A 3%–5% change in CBF per unit change in $Paco_2$ within the range of 20–60 mmHg in normal individuals has been reported [21]. Further study is needed to clarify these differences. To our knowledge, this is the first report to assess carbon dioxide reactivity during fentanyl-diazepam anesthesia using the three-dimensional CBF measurement tequnique. Several regions including gray matter, white matter, and basal ganglia had similar reactivity to changes in $Paco_2$.

It was the aim to provide comprehensive data indicating reference values of LCBF and cerebral carbon dioxide reactivity during neuroleptanesthesia. Although the effects of fentanyl and diazepam on CBF were not actually determined in the present study, these data can be of clinical use. However, the use of these reference values may be limited to conditions similar to those in the present study.

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