Xenon-Enhanced CT of the Brain:
Effect of Flow Activation on Derived Cerebral Blood Flow Measurements

Walter F. Good[1]
David Gur

The errors associated with derivation of cerebral blood flow values by the xenon-enhanced CT method have been evaluated through computer simulations as a function of flow-activation patterns and different scanning protocols. The results of this study indicate that actual flow activation during inhalation increases the derived flow values in a systematic way. Compared with the errors introduced by CT noise and/or variations in scanning protocols, flow activation introduces relatively small errors in the derived flow value when the washin technique is used.

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A noninvasive technique for measuring local cerebral blood flow by xenon-enhanced X-ray transmission CT was developed and reported on extensively in recent years [1–6]. In this method, nonradioactive xenon gas is inhaled, and the temporal changes in radiographic enhancement produced by the inhalation are measured by sequential-scanning CT. Time-dependent xenon concentration within various tissue segments in the brain is used to derive both the local partition coefficient (λ) and cerebral blood flow in each tissue volume (voxel) of the CT image. Although technical issues associated with this methodology have been addressed in detail in recent years, several questions regarding the quantitative nature of derived flow values remain [7].

A major concern that has been repeatedly raised about this technology is the possibility that xenon-induced flow activation during the procedure may preclude its use as a reproducible quantitative flow-measurement technique [7]. A recent report [8] indicates that simulations of the protocol in a changing flow environment may result in significant errors in the estimated flow values obtained with this technique. In this article, we describe the results of simulations of various Xe/CT protocols under changing flow environments and assess the potential errors in flow estimates that are introduced by flow activation during these studies.

Materials and Methods

We implemented a comprehensive computer simulation of the Xe/CT blood flow technique based on a generalization of the Kety-Schmidt equation to the case of variable flow. Software was written to calculate tissue enhancement C(t) given a flow function F(t), a partition coefficient λ, and an arbitrary arterial curve $C_a(t)$; and inversely given $C_a(t)$ and an estimate of C(t) to find values for the rate constant k and for λ, which correspond to the least-squares fit of the Kety-Schmidt equation to the estimate of C(t).

A data collection protocol consisting of two baseline scans and five enhanced scans, taken at 1-min intervals, was used throughout the study. This choice was intended only to be representative of typical protocols currently used for Xe/CT blood flow studies, and it was used here to maintain consistency throughout the simulation. Its use does not imply that we consider it to be an optimal protocol.

Calculations were performed over a range of blood flow values (0.20–1.0 ml/cm^3/min). Similarly, the range 0.5–1.7 was chosen for partition coefficients. These values were assumed

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[1] Both authors: Departments of Diagnostic Radiology and Radiation Health, RC403B, Scaife Hall, University of Pittsburgh, 3550 Terrace St., Pittsburgh, PA 15261. Address reprint requests to W. F. Good.

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to encompass those expected to occur in the bulk of cerebral tissue. Two particular pairs of values that were given disproportionate attention were G (flow = 0.8, partition coefficient = 0.8), representing predominantly gray matter, and W (flow = 0.2, partition coefficient = 1.6), representing predominantly white matter.

All synthetic arterial data had the following basic form:

$$Ca(t) = C_{max}[1 - \exp(-bt)] \quad (1)$$

for the washin (inhalation portion) and

$$Ca(t) = C_T[\exp(-bt)] \quad (2)$$

for the washout (exhalation portion), with C_T being the enhancement in arterial blood at the termination of xenon inhalation. C_{max} = 10 H was assumed to be the blood saturation level if inhalation was continued indefinitely. An arterial rate constant value b = 2.5 min^{-1}, which is a typical washin or washout rate constant for humans with normal pulmonary function, was used throughout the calculations.

The basic paradigm used to study the effects of flow activation on the derived estimates of flow and partition coefficient is shown in the following steps:

1. On the basis of an assumed prestudy flow (F_{pre}), a flow function F(t) was constructed that incorporated the effects of flow activation.
2. Given F(t) and λ, and assuming our standard arterial curve and data collection protocol described above, a sequence of "noise-free" enhancements was calculated for each activation pattern.
3. Estimates of flow (F′) and partition coefficient (λ') were calculated from the enhancement values by using the standard arterial curve and an unconstrained least-squares fit of equation 3:

$$C(t) = F' \int_0^t Ca(u)\exp[-k'(t-u)]du \quad (3)$$

4. The derived flow (F′) was compared with the prestudy flow (F_{pre}). In several simulations, we followed recent recommendations to include both the washin and washout in the protocol. However, to preserve the total radiation exposure in each protocol, the number of scans was kept at two baselines and five enhancements. In these simulations, a 3-min inhalation (washin) of xenon gas followed by a 5-min washout was assumed (Nakano et al. and Toshima et al. Papers presented at the International Conference on Stable Xenon/CT CBF, Orlando, February 1990).

The subset of actual flow patterns and scanning protocols reported here include:

1. A 5-min washin protocol with linear-flow activation beginning at 1.5 min after initiation of xenon inhalation and reaching 15, 30, and 45% at 2 min after initiation of xenon inhalation (pattern A).
2. A washout protocol with flow activation as in pattern A and actual flow remaining activated during the washout phase (pattern B).
3. A washout protocol similar to pattern B with linear-flow deactivation beginning 1 min after termination of xenon inhalation and returning to baseline flow at 1.5 min after termination of xenon inhalation (pattern C).
4. A combination washin and washout protocol with flow activation and deactivation as in pattern C (pattern D).

TABLE 1: Derived Flow Values and Percent Error for Different Actual Flow Activation Patterns

Prestudy Flow (ml/cm³/min)	Percent Activation	Derived Flow Values (ml/cm³/min)	Percent Error Compared with Prestudy Flow
Washin Scanning Protocol			
Actual Flow Pattern A			
0.80	15	0.807	0.9
0.20	15	0.202	1.0
0.80	30	0.815	1.8
0.20	30	0.205	2.6
0.80	45	0.823	2.9
0.20	45	0.209	4.5
Washout Scanning Protocol			
Actual Flow Pattern B			
0.80	15	0.894	11.7
0.20	15	0.218	8.8
0.80	30	1.01	26.6
0.20	30	0.235	17.5
0.80	45	0.113	40.8
0.20	45	0.254	26.9
Actual Flow Pattern C			
0.80	15	0.849	6.1
0.20	15	0.213	6.4
0.80	30	0.942	17.7
0.20	30	0.218	8.8
0.80	45	1.03	28.4
0.20	45	0.237	18.5
Washin/Washout Scanning Protocol			
Actual Flow Pattern D			
0.80	15	0.847	5.8
0.20	15	0.207	3.7
0.80	30	0.891	11.4
0.20	30	0.216	7.9
0.80	45	0.934	16.8
0.20	45	0.216	7.9

Results

Table 1 gives a summary of the simulation studies for derived flow values under different activation and deactivation flow patterns. From this table it is clear that derived flow values are affected by the scanning protocol (washin, washout, or washin/washout) and the amount of actual flow activation during xenon inhalation. In the worst-case scenario of a washout only scanning protocol (pattern B) and actual flow activation of 45%, which remains during the washout, the errors in derived flow values are 40.8% and 26.9% for fast (gray) and slow (white) flows, respectively. This result is expected, since the flow is artificially elevated during the study, and the derived values are closer to prewashout actual flow values. On the other hand, the washin protocol shows errors of less than 5%, since the flow activation occurred too late to have a significant impact on tissue enhancement patterns.

Discussion

Although there are large animal and clinical data bases to demonstrate the repeatability of quantitative flow estimates derived by this technique, a recent report [8] indicates that simulated scanning protocols show large variation in computed flow values if activation occurs at 2 min after initiation of xenon inhalation. Despite the fact that flow activation has been documented and discussed in the literature, the stability and robustness of the solution to the Kety-Schmidt relationship can be tested within one study by comparing flow estimates computed from the first three enhanced scans with those obtained when four, five, or six scans are used [9]. In this study, however, a simulation was performed with different scanning protocols and with different flow activation and deactivation patterns. Our results clearly stand in opposition to those reported recently in that, in spite of flow activation, the derived flow values are extremely stable, and the quantitative nature of the technique is affected significantly more by system noise (e.g., CT noise, number of scans, patient motion) than by flow activation (due to xenon inhalation). This has been found to be the case for all reasonable activation and deactivation patterns even when extreme flow activations (45%) were simulated. The effects of system noise on derived flow values have been discussed in detail elsewhere [10].

This study also demonstrated that the washin protocol is less affected by the flow activation than either the washout or the washin/washout protocols if the prestudy flow values are the desired ones for scientific and, more importantly, clinical management purposes. If the average flow during the 4–5 min study is examined rather than the prestudy flow, the errors due to activation would decrease somewhat from those reported here.

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The reader's attention is directed to the commentary on this article, which appears on the following pages.