The wash-in/washout protocol in stable xenon CT cerebral blood flow studies.

S Kashiwagi, T Yamashita, S Nakano, W Kalender, A Polacin, T Takasago, Y Eguchi and H Ito

AJNR Am J Neuroradiol 1992, 13 (1) 49-53
http://www.ajnr.org/content/13/1/49

The Wash-in/Washout Protocol in Stable Xenon CT Cerebral Blood Flow Studies

Shiro Kashiwagi,[1] Tetsuo Yamashita,[1] Shigeki Nakano,[1] Willi Kalender,[2] Arkadiusz Polacin,[2] Teiichi Takasago,[1] Yuuki Eguchi,[1] and Haruhide Ito[1]

Purpose: We conducted a comparative study to optimize the scanning and inhalation protocols for xenon CT cerebral blood flow (CBF) examination (Xe CT), with the aim of improving the practical performance of Xe CT as a routine clinical examination. **Materials and Methods:** Four different inhalation protocols, including 3-min, 6-min, and 8-min wash-in protocols, and a 3-min wash-in/5-min washout protocol, were compared in five healthy volunteers. Each subject underwent two serial Xe CT examinations with an interval of 30 min between the first one (wash-in) and the second one (wash-in/washout). A computer simulation was also performed to support the results of the clinical study. The rate of success was calculated from our experience of 110 clinical cases examined with the wash-in/washout protocol over the last 9 months. **Results:** The mean CBF values with 6-min and 8-min wash-in protocols were 59.0 and 59.5 mL/100-g brain per min in the thalamus, and 19.5 and 19.0 mL/100-g brain per min in the frontal white matter, respectively. The mean CBF values with 3-min wash-in/5-min washout protocol were 60.0 mL/100-g brain per min in the thalamus and 18.5 mL/100-g brain per min in the frontal white matter, respectively. Computer simulation showed improved signal-to-noise ratio by employing the 3-min wash-in/5-min washout protocol instead of 8-min wash-in protol for the same number of data points. The rate of success improved to 99.1% due to the significant decrease in head motion with the shorter period of inhalation. **Conclusion:** A wash-in/washout protocol is a useful alternative in Xe CT CBF measurement and more useful than the wash-in method for clinical purposes.

Index terms: Cerebral blood flow; Blood, computed tomography; Xenon

AJNR 13:49–53, January/February 1992

Cerebral blood flow (CBF) studies using stable xenon inhalation and computed tomography (Xe CT) have been recognized to be an important diagnostic tool in a variety of clinical situations (1–6). There are, however, two major problems with this technique that remain to be solved before it will receive wide acceptance as a routine clinical examination. One is head motion during the study, which adversely affects data acquisition, and the other is CBF activation due to the direct effect of xenon.

Head motion is a major practical problem caused by the subanesthetic effect of xenon (7–9), resulting in a rate of failure of 14% to 6% with a 4-min 20-sec wash-in protocol (9). Even with minor head motion, the accuracy of CBF values is severely affected. CBF activation, that is, a CBF increase with inhalation of xenon, has been reported in both animals and humans (10, 11). This phenomenon may have serious implications as to the interpretation of flow values.

The magnitudes of head motion and flow activation are both related to the time period of xenon inhalation (12, 13). Therefore, optimization of the inhalation and scanning protocols is necessary to improve practical performance of Xe CT.

The purpose of this paper is to compare four different xenon inhalation protocols, including three wash-in protocols with different inhalation times and a wash-in/washout protocol, to improve the practical performance of Xe CT. The relevance of the application of a wash-in/washout protocol is discussed based on the results of a comparative study on volunteers and clinical experience in 110 cases.

Received November 5, 1990; revision requested January 28, 1991; revision received May 30; final acceptance June 6.

[1] Department of Neurosurgery, Yamaguchi University School of Medicine, 1144 Kogushi Ube Yamaguchi, 755 Japan. Address reprint requests to S. Kashiwagi.

[2] Siemens Medical Systems, Henkestrasse 127, D-8520 Erlangen, Germany.

AJNR 13:49–53, Jan/Feb 1992 0195-6108/92/1301-0049

Materials and Methods

Stable Xe CT CBF studies were performed with a Somatom DR 3 CT scanner with software for CBF imaging (Siemens Medical Systems, Erlangen, Germany). A Xetron III (Anzai Sogyo Ltd., Tokyo, Japan) closed-circuit inhalator was used to deliver xenon gas. The theoretical background, validity, and clinical applications of the stable Xe/CT CBF method have been reported previously (1–3). In our case, after two baseline CT scans, the patient inhaled a 30% xenon/30% oxygen/40% nitrogen gas mixture with a face mask, while a series of CT scans was obtained according to the inhalation protocol described below. The scan parameters were 96 kV, 680 mAs, 7 sec scan time, and 8 mm slice thickness. The end-tidal Xe concentration was measured with an AZ-723-SX xenon monitor (Anzai Sogyo) and converted to reflect the arterial xenon enhancement. For calculating parameter images of flow and the xenon partition coefficient (lambda), a modified fitting algorithm was used which performs a series of linear least-squares calculations instead of a single iterative nonlinear least-squares calculation (3, 14).

Five healthy volunteers were subjected to a comparative study (four men and one woman; age range, from 26 to 54 years of age, with an average of 33.6 years of age). They underwent two serial Xe CT examinations with an interval of 30 min between the two examinations for the clearance of xenon inhaled in the first one.

In the first Xe CT examination, the gas mixture was inhaled for 8 min. Xenon-enhanced CT scans were obtained at one min intervals for the 8 min. In the second Xe CT examination, the gas mixture was inhaled for 3 min. Xenon-enhanced CT scans were obtained at 1, 2, and 3 min after the initiation of xenon inhalation in the wash-in phase and then at 1, 2, 3, 4, and 5 min after the termination of xenon inhalation in the washout phase.

The parameter (flow and lambda) values for the thalamus and frontal white matter in both hemispheres were selected as representatives of those of a fast flow compartment and a slow flow compartment, respectively. The parameter values were calculated and imaged as follows: in groups 1, 2, and 3 (wash-in), the parameters were calculated and imaged using the data obtained in the first 3, 6, and 8 min of the wash-in phase of the first Xe CT examination, respectively. In group 4 (wash-in/washout), the parameter values were calculated and imaged using 3-min wash-in and 5-min washout data obtained in the second Xe CT examination.

Computer simulation studies were carried out to support the findings of the clinical studies on volunteers. The simulation system used variation of all the parameters that were relevant for blood flow studies. In the present study, we selected scan parameters according to the clinical protocol, as defined above. In the simulations, we assumed a flow of 80 mL/100 g per min and a lambda of 0.8 for gray matter, and a flow of 20 mL/100 g per min and a lambda of 1.4 for white matter. Arterial data were assumed to have the basic form:

$$Ca(t) = C_{sat} (1 - \exp(-t/\tau))$$

where $C_{sat} = 8$ HU and $\tau = 30$ sec.

Using these parameters, tissue enhancement was calculated according to the Kety-Schmidt equation as a function of time; the respective values were stored as synthetic 512 × 512 image matrices. Pixel noise was added to these images, assuming a normal noise distribution with a mean of zero. A reference image with zero enhancement and noise added to it was also obtained. Such series of images were submitted to the standard blood flow calculation routines in exactly the same way as for the clinical studies.

Results

The parameter values obtained with the four different inhalation protocols are shown in Figure 1A, for lambda, and Figure 1B, for flow. The mean lambda value in group 1 (3-min wash-in) was higher in the thalamus (1.71) than that in the frontal white matter (1.20). This indicated an unsatisfactory estimate of the lambda with the 3-min wash-in protocol due to poor signal to noise ratio. The mean flow values in groups 2 (6-min wash-in) and 3 (8-min wash-in) were 59.0 and 59.5 mL/100-g brain per min in the thalamus, and 19.5 and 19.0 mL/100-g brain per min in the frontal white matter, respectively. The mean flow values in group 4 (wash-in/washout) were 60.0 mL/100-g brain per min in the thalamus and 18.5 mL/100-g brain per min in the frontal white matter, which were 0.9% higher and 2.6% lower than those in group 3 (8-min wash-in), respectively.

The parameter images obtained with the four different inhalation protocols are shown in Figure 2 (Figs 2A, 2B, and 2C: lambda; Figs 2D, 2E, and 2F: flow). The quality of the lambda and flow

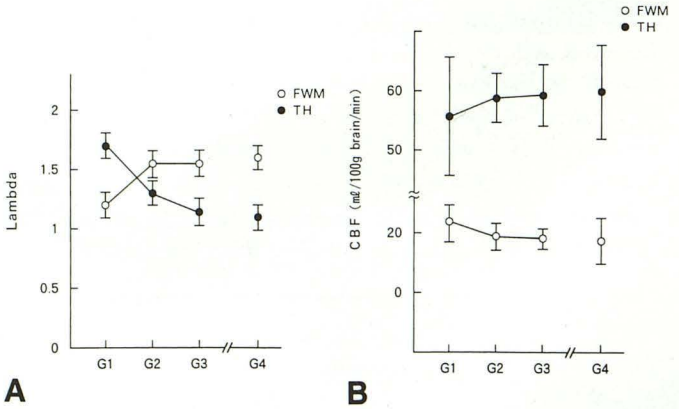

Fig. 1. Lambda (*A*) and flow values (*B*) for four different inhalation protocols in the frontal white matter (*open circle*) and thalamus (*closed circle*) measured in 10 hemispheres of five healthy adults. G1, G2, G3, and G4 represent 3-min wash-in, 6-min wash-in, 8-min wash-in, and 3-min wash-in/5-min washout protocols, respectively.

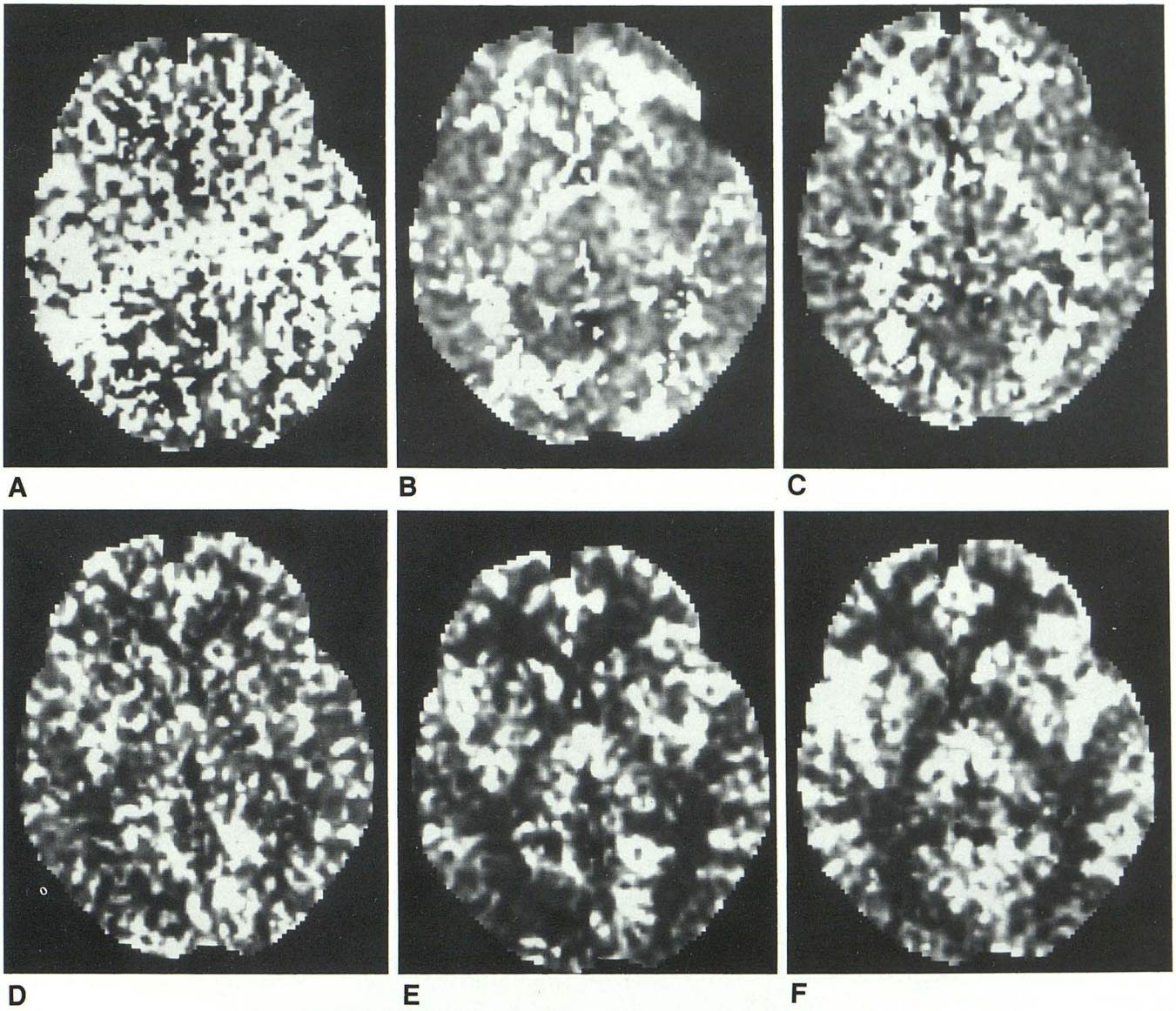

Fig. 2. *A*, *B*, and *C*: Lambda images of a 23-year-old healthy man with 3-min wash-in (*A*), 8-min wash-in (*B*), and 3-min wash-in/5-min washout (*C*) protocols.

D, *E*, and *F*: Flow images of the same subject with 3-min wash-in (*D*), 8-min wash-in (*E*), and 3-min wash-in/5-min washout (*F*) protocols. The image quality in terms of resolution of the white and gray matters was equivalent between the 8-min wash-in (*B* and *E*) and the 3-min wash-in/5-min washout (*C* and *F*) protocols.

TABLE 1: Mean values and standard deviations for CBF and lambda in simulation studies of different measurement methods

Method In/Out	Frontal White Matter		Thalamus	
	Flow[a]	Lambda	Flow[a]	Lambda
3/5	20.1 ± 4.3	1.47 ± 0.36	80.1 ± 11.5	0.81 ± 0.117
3/0	27.3 ± 14.1	1.28 ± 0.72	77.6 ± 22.2	0.93 ± 0.310
6/0	21.4 ± 6.8	1.46 ± 0.47	79.3 ± 17.9	0.81 ± 0.072
8/0	20.5 ± 5.1	1.50 ± 0.37	80.6 ± 17.7	0.81 ± 0.061

Note.—White matter was assumed to have CBF = 20 and lambda = 1.4, gray matter with CBF = 80 and lambda = 0.8.

[a] mL/100-g brain per min.

images in group 4 (Figs. 2C and 2F) was as good as that in group 3 (Figs. 2B and 2E) in terms of contrast resolution of the gray and white matter.

The computer simulations yielded results that were principally in agreement with the clinical findings (Table 1). The standard deviation of the estimated flow values was reduced by a factor of 1.2 for white matter and 1.6 for gray matter, respectively, by employing a 3-min wash-in/5-min washout protocol instead of the 8-min wash-in protocol. This confirms that more stable estimates of CBF with the same number of scans and radiation dose can be obtained with the 3-

min wash-in/5-min washout protocol, in spite of the lower brain tissue enhancement.

The rate of success with the wash-in/washout protocol was 99.1% for the 110 Xe CT examinations performed in our institute over the last 9 months. One unsuccessful examination resulted from head motion near the end of the wash-in phase. We have not experienced any respiratory problem during the 3-min wash-in phase of the wash-in/washout protocol.

Discussion

The results of our clinical studies on volunteers indicated that the 3-min wash-in/5-min washout protocol could replace the 8-min wash-in protocol. The rate of success improved to 99.1%, due to a significant reduction in head motion, as compared with 96% reported by an experienced institute using a 4-min 20-sec wash-in protocol (9). The quality of images was satisfactory in terms of contrast resolution of the gray and white matter. The difference in the estimated flow values was 0.9% in the thalamus and 2.6% in the white matter between the 3-min wash-in/5-min washout and 8-min wash-in protocols.

The maximal contrast enhancement was lowered from approximately 6.5 to 5.5 HU for gray matter and from 7.5 to 3 HU for white matter by reducing the inhalation time from 8 to 3 min. However, the signal to noise ratio did not decrease, but slightly increased with the wash-in/washout data due to the optimal combination of data points, which was demonstrated by a computer simulation comparing the two protocols. We did not simulate the effect of flow activation, which would be of value if the exact time course and magnitude of flow activation in humans were elucidated.

The magnitude of the change in CBF with inhalation of 30%–35% xenon for 3 to 5 min was reported to be approximately 30% (10, 11), but the real time course of the change in flow is difficult to determine in humans. Good and Gur used a computer simulation to study the effect of flow activation on derived CBF measurement (15). In their simulation, it was presumed that a linear increase in CBF began at 1.5 min after xenon inhalation, a maximum level being reached at 2 min after initiation of xenon inhalation and maintained thereafter in the wash-in phase. In the washout phase, linear deactivation began at 1 min after termination of xenon inhalation, CBF returning to the baseline at 1.5 min after termination of xenon inhalation. In the case of this particular time course of flow activation, the computer simulation showed that the maximal errors in the calculated flow were 2.9% for gray matter and 4.5% for white matter with the 5-min wash-in protocol, and 16.8% for gray matter and 7.9% for white matter with the 3-min wash-in/2-min washout protocol (they restricted the number of scans to five to preserve the total radiation exposure in each protocol). However, studies using transcranial Doppler sonography in humans indicated a more gradual, continuous increase in flow velocity, which began at 1 to 2 min after xenon inhalation started and continued to rise for the next several minutes, the maximum being reached in 5 to 10 min after the xenon inhalation started (12). These observations on transcranial Doppler Sonography suggest the possibility that the real time course of flow activation in humans may be somewhat different from that assumed in the model of simulation study and estimated errors may differ according to different activation patterns.

It is difficult to compare the results of the computer simulation by Good and Gur (15) with those of our clinical study on volunteers directly, because of the different methodology and protocol used, but our results showed a less than 3% difference in the calculated flow between the 8-min wash-in and 3-min wash-in/5-min washout protocols. We do not know the exact deviation of CBF from baseline before the xenon inhalation in each protocol, but the CBF values obtained were reasonable for human volunteers of a mean age of 36 years of age, as compared to those obtained by positoron emission tomography (16).

The management of patients was much easier when a wash-in/washout protocol was applied. One can almost completely eliminate problems, such as head motion or respiratory slowing, with 3-min inhalation in the wash-in/washout protocol, and still have comparable values and image quality. Although a 5-min wash-in protocol seemed to be accepted as a standard and its validity clarified, its success rate is not near 100% even in very experienced institutes (9), which should be required for an accepted routine clinical examination. We consider that a wash-in/washout protocol is a useful alternative in the Xe CT CBF examination that improves its practical performance and will make it more widely acceptable as a routine clinical examination for CBF.

References

1. Meyer JS, Hayman LA, Amano T, et al. Mapping local blood flow of human brain by Ct scanning during stable xenon inhalation. *Stroke* 1981;12:426–436
2. Yonas H, Wolfson SK, Gur D, et al. Clinical experience with the use of xenon-enhanced CT blood flow mapping in cerebral vascular disease. *Stroke* 1984;15:443–450
3. Kashiwagi S, Yamashita T, Abiko S, et al. Measurement and imaging of cerebral blood flow with stable xenon and computed tomography (Xe-CT). *Electromedica* 1986;54:136–144
4. Yonas H, Gur D, Claassen D, Wolfson SK, Mossy J. Stable xenon enhanced computed tomography in the study of clinical and pathologic correlates of focal ischemia in baboons. *Stroke* 1988;19:228–238
5. Yonas H, Sekhar L, Johnson DW, Gur D. Determination of irreversible ischemia by xenon-enhanced computed tomographic monitoring of cerebral blood flow in patients with symptomatic vasospasm. *Neurosurgery* 1989;24:368–372
6. Yamashita T, Kashiwagi S, Nakano S, et al. The effect of EC-IC bypass surgery on resting cerebral blood flow and cerebrovascular reserve capacity with stable Xe-CT method and acetazolamide test. *Neuroradiology* 1991;33:217–222
7. Cullen SC, Gross EG. The anesthetic properties of xenon in animals and human beings, with additional observation on krypton. *Science* 1951;113:580–582
8. Latchaw RE, Yonas H, Pentheny SL, et al. Adverse reactions to xenon-enhanced CT cerebral blood flow determination. *Radiology* 1987;163:251–254
9. Winkler S, Turski P. Potential hazards of xenon inhalation. *AJNR* 1985;6:974–975
10. Obrist WD, Jaggi JL, Smith DS. Effect of stable xenon inhalation on human CBF. *J Cereb Blood Flow Metab* 1985;5(suppl 1):S557–S558
11. Dettmers C, Hartman A, Tsuda Y, et al. Stable xenon effects on regional cerebral blood flow and electroencephalography in normal baboons and volunteers. In: Wullenweber R, Klinger M, Brock M, eds. *Advances in neurosurgery*, Vol 15, Berlin: Springer-Verlag, 1987:67–71
12. Giller CA, Purdy P, Lindstrom WW. Effects of inhaled stable xenon on cerebral blood flow velocity. *AJNR* 1990;11:177–182
13. Takasago T, Yamashita T, Nakano S, et al. *Complications and problems of stable Xe/CT CBF study*. Presented at the International Conference on Stable Xenon/CT CBF, Orlando, FL, February 1990
14. Koeppe RA, Holden JE, Ip WR. Performance comparison of parameter estimation techniques for the quantitation of local cerebral blood flow by dynamic positron computed tomography. *J Cereb Blood Flow Metab* 1985;5:224–234
15. Good WF, Gur D. Xenon-enhanced CT of the brain: effect of flow activation on derived cerebral blood flow measurements. *AJNR* 1991;12:83–85
16. Frackowiak RS, Lenzi GL, Jones T, et al. Quantitative measurement of cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography: theory, procedure and normal values. *J Comput Assist Tomogr* 1980;4:727–736