Cerebral Blood Flow Measurement with Iodine-123-IMP SPECT, Calibrated Standard Input Function and Venous Blood Sampling

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We previously reported simple methods for measuring cerebral blood flow (CBF) with ^{123}I-labeled N-isopropyl-p-iodoamphetamine (IMP) and SPECT: table look-up method and autoradiography. With these methods, the arterial input function is obtained by calibrating the standard input function using one-point arterial blood sampling 10 min after IMP infusion. In this study, we sought to determine if these approaches can be as successful when used with venous blood sampling. **Methods:** After IMP infusion, simultaneous arterial and venous blood samples were drawn from 30 subjects without heart or lung disease. **Results:** The activity ratios of venous whole blood from the cubital vein to arterial blood were 0.75 ± 0.09, 0.77 ± 0.10, 0.78 ± 0.03 and 0.83 ± 0.11, respectively, at 10, 20, 30 and 50 min after IMP infusion. Venous blood activities were always 20% lower than the artery values over 50 min. When blood was sampled from the dorsal hand vein, however, the respective ratios were 0.92 ± 0.03, 0.93 ± 0.05, 0.97 ± 0.04 and 0.98 ± 0.08 after 10, 20, 30 and 50 min. Furthermore, when the palm was exposed to heat during the sampling period, blood activity levels increased to 0.92 ± 0.04, 0.96 ± 0.04, 0.99 ± 0.05 and 0.98 ± 0.03. Thus, venous blood activities were consistent with arterial activity, presumably because of the numerous arteriovenous anastomoses in the palm. Optimal times for venous blood sampling, with and without palm heating, were determined by error analysis to be 15 and 20 min, respectively, after IMP infusion. **Conclusion:** Venous blood sampling from the dorsal hand can be substituted for arterial blood sampling in IMP-CBF studies.

Key Words: iodoamphetamine; single-photon emission computed tomography; cerebral blood flow; input function; venous blood sampling

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Iodine-123-labeled N-isopropyl-p-iodoamphetamine (IMP) is used as a cerebral blood flow (CBF) tracer in SPECT because of its large extraction fraction and high affinity for the brain (*1,2*). Significant clearance, however, causes a change in IMP distribution in the brain with time (*3,4*) and leads to an underestimation of CBF when conventional microsphere model analysis (*5*) is applied with prolonged data acquisition (*6–9*). Previously, we described simple methods for CBF measurement with IMP that take into account the clearance effect: the table look-up method (*10–12*) and autoradiography (*13,14*). For these methods, one or two SPECT scans (one in the autoradiography method, two in the table look-up approach) and a one-point arterial blood sample 10 min after IMP infusion are required. The arterial input function is obtained from calibrating the standard input function. If, however, venous blood sampling could be used instead of invasive arterial blood sampling, application of these methods would be simplified. The aim of this study was to determine the validity of calibrating the standard input function using one-point venous blood sampling as a substitute for one-point arterial blood sampling.

MATERIALS AND METHODS

Patients

SPECT studies were performed on 30 subjects: 13 patients with cerebral contusions, 11 patients with cerebrovascular disease and 6 normal volunteers. No subject had heart or lung disease. Informed consent was obtained from each subject after thorough explanation.

SPECT

SPECT scans were obtained at a midscan time of 40 min after a 1-min intravenous infusion of 222 MBq IMP. We used two types of SPECT scanners in this study: for a four-head rotating gamma camera with in-plane and axial resolutions of 8 mm FWHM (*15*) and a three-head rotating gamma camera with an in-plane resolution of 9 mm FWHM and an axial resolution of 10 mm FWHM (*16*). For the four-head camera, scan protocol acquired 64 projections at 62.5 sec/projection with 360° camera rotation. The protocol for the second camera acquired 64 projections at 50 sec/projection with 120° camera rotation. With both SPECT scanners, reconstruction was performed by filtered backprojection using a Butterworth filter (*17*), and attenuation correction was made numerically by assuming the object shape to be an ellipse and the

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TABLE 1
Radioactivity Ratios of Venous to Arterial Whole Blood*

Time (min)	Cubitus† (n = 7)	Forearm† (n = 6)	Dorsal hand†	
			Without heating (n = 7)	With heating (n = 10)
10	0.75 ± 0.09	0.85 ± 0.08	0.92 ± 0.03	0.92 ± 0.04
15	0.77 ± 0.10	0.88 ± 0.09	0.94 ± 0.05	0.96 ± 0.03
20	0.77 ± 0.10	0.92 ± 0.06	0.93 ± 0.05	0.96 ± 0.04
25	0.76 ± 0.08	0.95 ± 0.04	0.95 ± 0.04	0.96 ± 0.03
30	0.78 ± 0.08	0.93 ± 0.04	0.97 ± 0.04	0.99 ± 0.05
40	0.79 ± 0.04	0.95 ± 0.05	0.99 ± 0.04	0.99 ± 0.04
50	0.83 ± 0.11	0.97 ± 0.04	0.98 ± 0.08	0.98 ± 0.03

*Mean ± s.d.
†Venous blood was obtained from cutaneous veins of the cubitus, forearm and dorsal hand, the latter with and without palm heating.

attenuation coefficient to be uniform, using Chang's method (*18,19*) for the four-detector camera, 0.08 cm^{-1}; and Sorenson's method 0.12 cm^{-1} (*20*) for the second camera. Image slices were set parallel to the orbito-meatal (OM) line and obtained for 8-mm intervals through the whole brain.

Blood Sampling

Arterial and venous blood samples were simultaneously performed 10, 15, 20, 25, 30, 40 and 50 min after intravenous infusion of IMP. Venous blood also was sampled 5 min postinjection. Arterial blood was taken from the brachial artery and venous blood from the cutaneous vein of the cubitus, forearm or dorsal hand on the side opposite to the IMP infusion (cubitus, seven subjects; forearm, six subjects; dorsal hand, seventeen subjects). Ten of the 17 subjects who underwent blood sampling from the dorsal hand vein had the palm of the blood sampling side heated to 41°–42°C by an electric heater from 10 min before IMP infusion to the end of the study. Whole blood radioactivity concentrations were measured for each pair of samples.

Image Analysis

Regions of interest (ROIs) in the cerebellum, pons, thalamus, putamen, semioval center and cerebral cortex, including the frontal, temporal, parietal and occipital lobes, were outlined on the SPECT image. ROIs were defined by a circle with a 28-mm diameter for the cerebellum and an ellipsis with a short-axis of 16–20 mm and a long-axis of 20–40 mm for the other regions.

Optimization of Venous Blood Sampling Time

Error analysis was performed to optimize venous blood sampling. The mean difference rates (percent difference) between the integrated input function for the time period (0–40 min) obtained from calibrating the standard input function using 10-min arterial blood data and the venous blood data sampled at each time point were calculated as follows:

$$\%\text{difference}\ (t_m) = \frac{1}{n}\sum_{i=1}^{n} \frac{\left|\int_0^{40} Cv_i(t_m)dt - \int_0^{40} Ca_i(t_{10})dt\right|}{\int_0^{40} Ca_i(t_{10})dt},$$

where $\int_0^{40} Ca_i(t_{10})dt$ = the integrated input function for the time period (0–40 min) obtained from calibrating the standard input function using 10-min arterial blood data, $\int_0^{40} Cv_i(t_m)dt$ = the integrated input function for the time period (0–40 min) obtained from calibrating the standard input function using venous blood data for each sampling point, t_m = venous blood sampling time (5, 10, 15, 20, 25, 30, 40 and 50 min) and n = number of subjects.

The optimized venous blood sampling time was determined as that with the minimum percent difference.

RESULTS

Table 1 and Figure 1 show the radioactivity ratios of venous whole blood to arterial whole blood. Values obtained from the cutaneous cubital vein were 0.75 ± 0.09, 0.77 ± 0.10, 0.78 ± 0.08, 0.79 ± 0.04 and 0.83 ± 0.11, respectively, at 10, 20, 30, 40 and 50 min after IMP infusion. The venous blood activities were thus always 20% lower than those from artery samples over the 50-min period. The ratios, however, for cutaneous dorsal hand vein without palm heating were 0.92 ± 0.03, 0.93 ± 0.05, 0.97 ± 0.04, 0.99 ± 0.04 and 0.98 ± 0.08 at the same time points; with palm heating, they were 0.92 ± 0.04, 0.96 ± 0.04, 0.99 ±

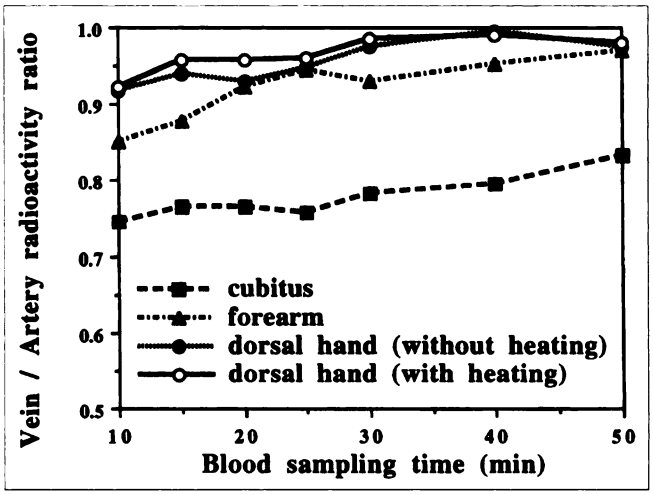

FIGURE 1. Time course of activity ratios of venous to arterial whole blood (mean values). Venous blood was obtained from cutaneous veins of the cubitus, forearm and dorsal hand, the latter with or without palm heating. Of the three routes, the activities obtained from dorsal hand were most consistent with those of arterial blood, especially with the palm heated.

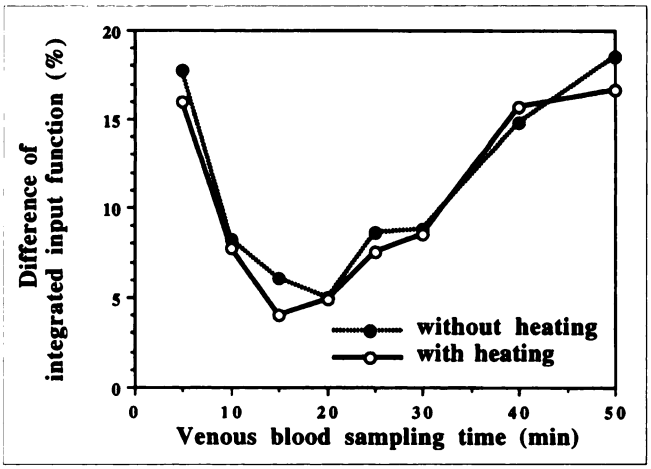

FIGURE 2. Mean rates of integrated input function difference (%) between the calibrated standard input functions with 10-min arterial and venous blood sampling from the dorsal hand at various time points. The minimum values were 15 and 20 min after IMP infusion, with and without palm heating, respectively.

0.05, 0.99 ± 0.04 and 0.98 ± 0.03. The venous blood activities in these subjects, especially with palm heating, were therefore essentially consistent with arterial values.

Figure 2 shows the mean difference rates (percent difference) between the integrated input function estimated from 10-min arterial blood data and from venous blood data for dorsal hand samples. The percent differences without palm heating were 17.8%, 8.3%, 6.1%, 5.0%, 8.6%, 14.8% and 18.5%, and 16.0%, 7.8%, 4.0%, 5.0%, 7.5%, 15.7% and 16.7% without palm heating at the 5-, 10-, 15-, 20-, 25-, 30-, 40- and 50-min sampling times. The minimum percent difference values were obtained at 15 and 20 min, with and without palm heating, and these were taken as optimal venous sampling times.

Figure 3A shows the correlation between CBF values obtained by the autoradiography method (*13,14*) using arterial blood drawn 10 min after IMP infusion and venous blood drawn 20 min after IMP infusion from the dorsal hand without palm heating. A good correlation was observed ($Y = 1.11X - 1.92$; $r = 0.99$), with only a 5.2% overestimation of CBF values for the 20-min venous blood compared with the 10-min arterial blood.

Figure 3B shows the correlation between CBF values obtained by the autoradiography method (*13,14*) using 10-min arterial blood after IMP infusion and 15-min venous blood from the dorsal hand with palm heating. Again, a good correlation was observed ($Y = 1.11X - 1.85$; $r = 0.98$), with only a 5.4% overestimation of CBF values for the 15-min venous blood compared to the 10-min arterial blood.

DISCUSSION

Results of this study demonstrate that whereas the activity of venous blood sampled from the cutaneous cubital vein was always 20% lower than the artery values over 50 min, the decrease was much lower when blood samples were taken from dorsal hand vein with or without palm heating (Table 1, Fig. 1), thus indicating that the dorsal hand is the best location for venous in place of arterial blood sampling. IMP might be trapped in capillary vessels, which could explain why the venous blood activity values for the cubital vein were not consistent with arterial levels. On

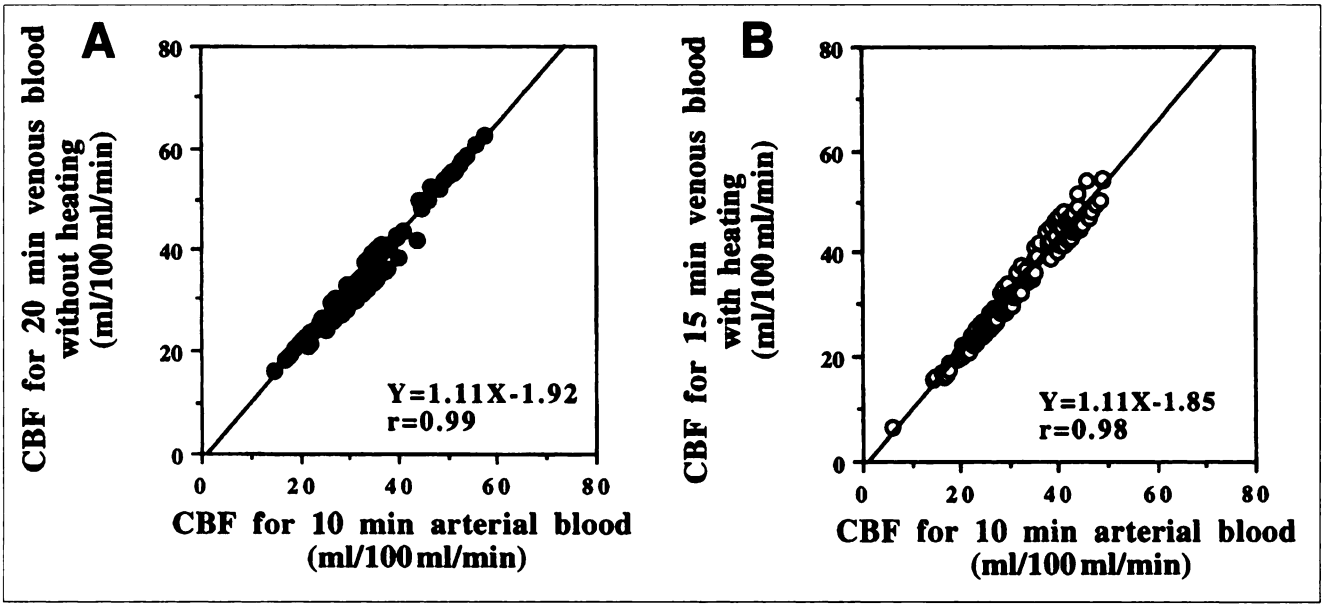

FIGURE 3. (A) Correlation between CBF values obtained by the autoradiography method using 10-min arterial and 20-min venous blood sampled from the dorsal hand without palm heating. Good correlation was observed, with only a 5.2% overestimation of CBF values with venous as compared to arterial blood. (B) Correlation between CBF values obtained by the autoradiography method using 10-min arterial and 15-min venous blood sampled from the dorsal hand with palm heating. Good correlation was observed, with only a 5.4% overestimation of CBF values with venous as compared to arterial blood.

the other hand, the presence of numerous arteriovenous anastomoses in the palm (*21*) suggests that venous blood sampled from the dorsal hand might include an appreciable component passing through such anastomoses, which might account for the higher venous blood radioactivity at this site.

The method of withdrawing blood from the dorsal hand used in this study may be applicable to other radiopharmaceuticals. It has been reported that arterialized venous blood can be obtained by heating the hand and forearm (*22–24*). In the present study we therefore performed venous blood sampling from the dorsal hand while heating the palm, which caused a slight improvement in results (Table 1, Fig. 1). Furthermore, the blood pH, CO_2 and O_2 gaseous pressures were 7.43 ± 0.02, 39.3 ± 3.7 mmHg and 91.9 ± 17.7 mmHg (mean ± s.d.), respectively, in arterial blood, and 7.42 ± 0.02, 40.3 ± 3.4 mmHg and 73.4 ± 15.8 mmHg (mean ± s.d.), respectively, in venous blood from the dorsal hand, with palm heating. The fact that blood pH and CO_2 gaseous pressures were consistent between arterial and venous blood indicates that venous CO_2 gaseous pressure analysis for measuring CBF can be substituted for arterial blood sampling.

In the table look-up method (*10–12*) and the autoradiography method (*13–14*), the optimized arterial blood sampling time is 10 min after IMP infusion. Venous and arterial blood activity, however, became more consistent with a greater passage of time after IMP infusion (Table 1, Fig. 1) and error analysis revealed optimized sampling times of 15 min and 20 min after IMP infusion, with and without palm heating (Fig. 2).

The finding that CBF values obtained for arterial blood correlated well with those from 15- and 20-min venous blood sampled from the dorsal hand with and without palm heating, respectively (Fig. 3) provides evidence that such venous blood can be reliably substituted for arterial blood for CBF measurement by the table look-up and autoradiography methods.

CONCLUSION

One-point venous blood sampling can be used as a substitute for arterial blood sampling in conjunction with the table look-up and autoradiography methods to measure CBF.

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