Imaging of Cerebral Blood Flow-to-Volume Distribution Using SPECT

Wolfram H. Knapp*, Rüdiger von Kummer, and Wolfgang Kübler

Institute for Nuclear Medicine, German Cancer Research Center; and Neurologic Department, University of Heidelberg, FRG

The ratio between cerebral blood flow (CBF) and cerebral blood volume (CBV) has been proposed as an adequate parameter for the evaluation of cerebrovascular disease (CVD), but to date it has not been assessed with SPECT. We have chosen [^{123}I]IMP for CBF and [^{99m}Tc] erythrocytes for CBV imaging. The distribution of both nuclides was investigated in succession using corrections for the contamination of the ^{99m}Tc tomograms by ^{123}I. The ratio between ^{123}I and ^{99m}Tc tomograms yielded the CBF/CBV distribution. Quantitation was obtained by side-to-side comparison of both hemispheres and of segments containing the territories affected by CVD. In 16 patients with CVD, CBF of the affected territories was 85 ± 19% (s.d.) when related to the nonsymptomatic contralateral side (100%). When the regions of interest defined within one slice encompassed the entire affected hemisphere, the average CBF was 95 ± 9%, again related to the nonsymptomatic side. The corresponding CBF/CBV data in 15 of these 16 patients were 60 ± 32% and 81 ± 16%. In unilateral internal carotid artery stenoses >50% (N = 10), segmental CBF averaged 81.1 ± 10.1% and CBF/CBV 49.6 ± 15.5% relative to the contralateral side. The figures for the hemispheres were 92.8 ± 5.8 and 75.8 ± 12.6, respectively. These clinical findings mirror the characteristics of CBF autoregulation, namely the vasodilation of small vessels in decreased arterial perfusion pressure. They, therefore, substantiate SPECT imaging of CBF/CBV for the assessment of cerebral perfusion reserve in CVD.

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Stenoses or occlusions of the internal carotid artery may result in embolism or in a reduction of cerebral perfusion pressure. Since the latter—though often clinically mute—is a risk factor for tissue integrity of the brain (*1*), the diagnostic evaluation has to consider the early autoregulation response to decreased perfusion pressure. This response consists of cerebral vasodilation that may occur before a drop of regional blood flow becomes evident (*2,3*). Therefore it is important to assess the intravascular volume together with the blood flow. To date, combined measurements of cerebral blood flow (CBF) and cerebral blood volume (CBV) have been the domain of positron emission tomography (PET). Investigations with this technique suggest that the ratio CBF/CBV was most sensitive in the detection of hemodynamic risks to the brain (*4*).

The purpose of this study was to describe a procedure for semiquantitative CBF/CBV imaging with single photon emission computed tomography (SPECT), and to investigate the consistency of data under different clinical circumstances.

MATERIAL AND METHODS

SPECT was carried out in 16 patients (3 F, 13 M) ranging in age from 37–73 yr and having had transient ischemic attacks (TIA) or remote cerebral infarctions. The delay (range 9–80 days) between the last respective event and the investigation averaged 32 days. All patients underwent computed tomographic (CT) scanning and angiography of one or both internal carotid arteries.

Four to five millicuries of *N*-isopropyl-(^{123}I)-*p*-iodoamphetamine ([^{123}I]IMP)† was injected intravenously, immediately followed by the injection of a pyrophosphate kit‡ for subsequent in vivo labeling of

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For reprints contact: W. H. Knapp, MD, Herzzentrum Nordrhein-Westfalen D-4970 Bad Oeynhausen 1, FRG.

* Present address: Herzzentrum Nordrhein-Westfalen, Georgstr. 11, D-4970 Bad Oeynhausen, FRG.

red blood cells. Iodine-123 IMP was free of ^{124}I contamination. Imaging was begun 25 min after injection; 1-min images were obtained from 2 × 30 equally spaced projections rotating about the patient's head in a 180° arc, using a dual head rotating camera. Approximately 20,000 counts were obtained for each projection. The procedure was repeated after i.v. injection of 10 mCi technetium-99m (^{99m}Tc) pertechnetate, resulting in ~50,000 counts for each projection. During the whole period, the patient's head was fixed with the orbitameatus (OM) line perpendicular to the axis of rotation. The position of the OM line was marked with a point source. Prior to the ^{99m}Tc injection, the count rate in the ^{99m}Tc channel was measured in anterior and posterior projection in order to estimate the ^{123}I contamination fraction to the ^{99m}Tc images. Transaxial tomographic slices (1.2 cm thick) were reconstructed using filtered back-projection algorithms.[§]

The distribution of ^{99m}Tc-labeled red cells (and thus CBV) was assessed by determining for each voxel:

$$C_{Tc} = C_{Tc}^* - \lambda \cdot C_I,$$

with C_{Tc} = true ^{99m}Tc counts, C_{Tc}^* = total counts measured in the ^{99m}Tc channel, C_I = ^{123}I counts measured in the ^{123}I channel, λ = contamination fraction of ^{123}I to the ^{99m}Tc channel as shown above. λ Averaged 0.38 ± 0.02 (s.d.).

CBF/CBV images were obtained by calculating the ratio $C_I/(C_{Tc} + n)$ for each voxel with n = 5% of the maximum counts C_{Tc} per voxel. This constant was introduced to prevent image distortion in case of random low values of the denominator. Each slice representing CBF or CBV contained about 200,000–300,000 impulses.

For quantitation of radionuclide distribution abnormalities, the most relevant tomogram of each patient (range 1.2–4.8 cm above the OM line) underwent further display processing. The activity contents of both hemispheres and of corresponding segments of each side perpendicular to the interhemisphere axis with a sagittal extension of 1.6 cm were determined. The abnormality was expressed as the ratio between the count number of the side of stenosis or occlusion and that of the contralateral, nonsymptomatic side. This quantitation was carried out in all three parametric images (CBF, CBV, and CBF/CBV) using identical regions of interest (ROIs).

In three patients, activity over brain, lung, liver, and muscle was recorded during the investigation using small proportional counters fixed over the respective organs. Sampling rate was 1 min^{-1}.

RESULTS

In 12 of 16 patients investigated, focal reduction of ^{123}I activity by at least 10% was found ipsilateral with the predominantly affected internal carotid artery. Fifteen patients of the total group had ^{99m}Tc tomograms. In 11 individuals, a focal decrease of ^{123}I activity was accompanied by a >10% increase of ^{99m}Tc activity at the same site (Fig. 1). Thus, in the majority of patients, a discordant pattern of both radioagents was found. The residual individuals (N = 4) in whom no focal augmentation of ^{99m}Tc was observed, had extended cerebral infarction prior to the investigation (three patients, Fig. 2) or bilateral stenoses (one patient). Table 1 shows the activity of segments involved and that of the global cross-sectional area of the affected hemisphere as related to the contralateral side in each subpopulation according to angiography, clinical, and CT findings. One patient with an 80% stenosis and absence of cerebral infarction was re-examined after thromboendarterectomy. The distribution pattern of CBF, CBV, and the ratio CBF/CBV appeared to be fairly symmetric (Fig. 3).

The tomographic abnormalities of the ratio $^{123}I/^{99m}Tc$ generally exceeded those of the ^{123}I activity distribution itself. This was due to the contrary side-to-side distribution of ^{123}I and ^{99m}Tc activity in the majority of patients. An example is given in Fig. 4. Only two out of 15 patients with $^{123}I/^{99m}Tc$ tomograms did not have

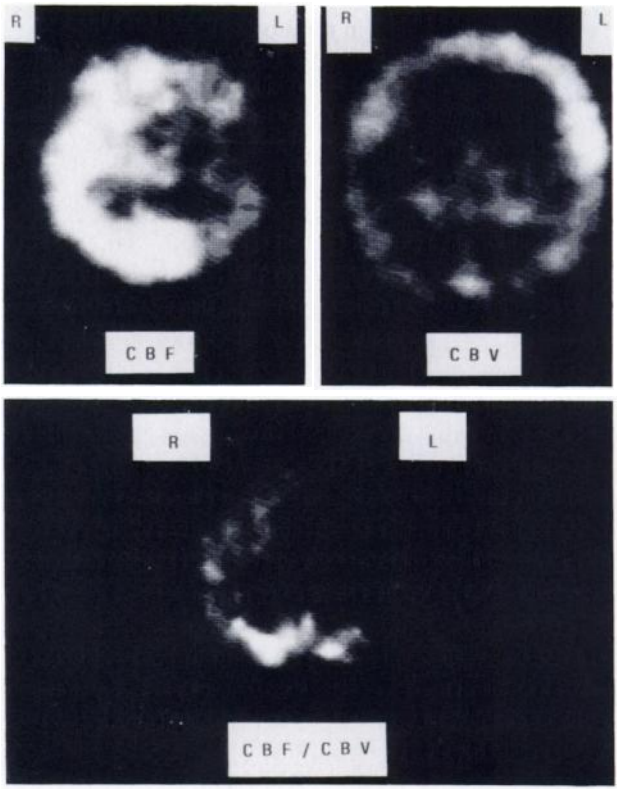

FIGURE 1
Occlusion of left internal carotid artery without infarcted territories. Images were taken at OM + 2.4 cm. Reduced CBF in affected area of left hemisphere is accompanied with increased CBV

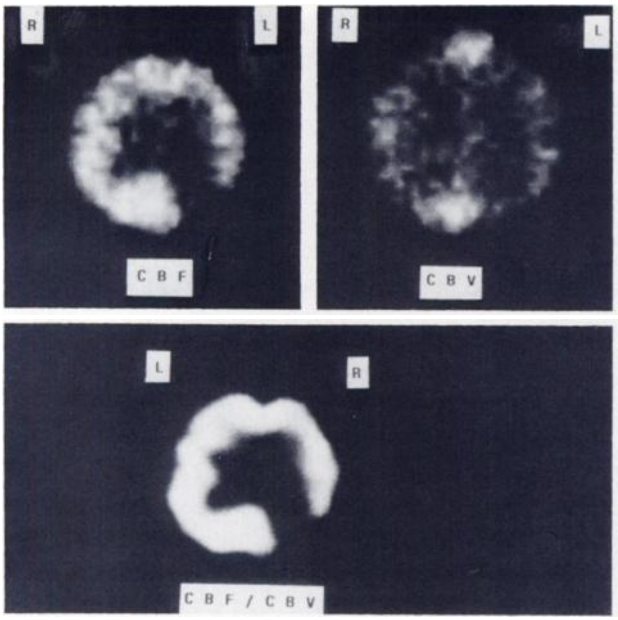

FIGURE 2
Occlusion of left internal carotid artery with infarcted territory. Images were taken at OM + 4.8 cm. CBF deficit occipito-parietal, no focal increase in CBV

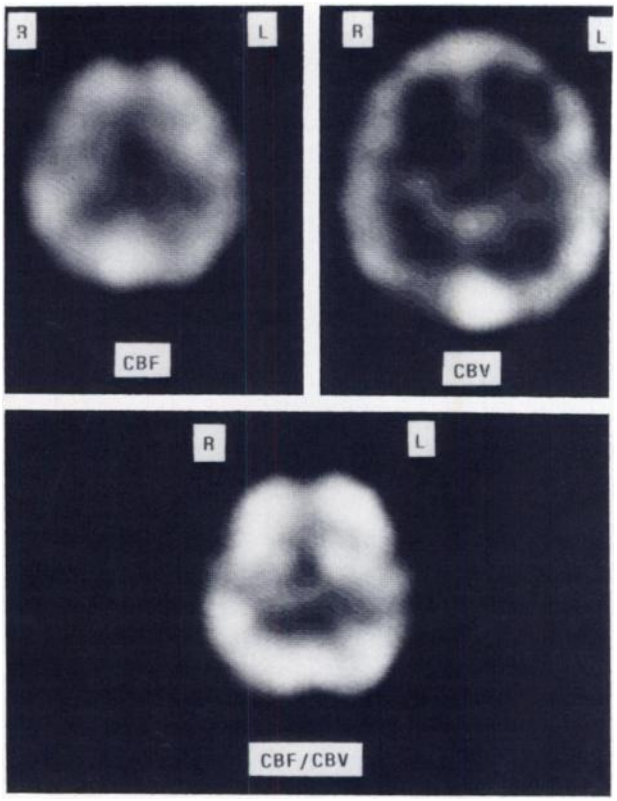

FIGURE 3
ACI Revascularization: thromboendarterectomy in patient having had 80% stenosis of left internal carotid artery without cerebral infarction. No important activity differences between left and right hemispheres (OM + 3.6 cm)

reduced activity ratios at the affected site when compared with the contralateral hemisphere. One of these two patients had a stenosis of <50%; the other had left and right stenoses within the siphon section. Individual data of patients with unilateral stenoses >50% or obliterations are listed in Table 2. In each of these patients, CBF/CBV shows greater deviations from symmetry than CBF alone, regarding both segmental and hemispheric analysis.

In three patients, continuous activity monitoring over the brain showed somewhat constant ^{123}I activity (+2% on average) during the period of tomographic imaging, while the count rates over the lungs and the liver decreased by 22% and increased by 40%, respectively. Muscle activity remained constant. Technetium-

TABLE 1
Cerebral Hemodynamics in Cerebrovascular Disease Related to Clinical Findings and Diagnostic Results

	Clinical findings		CT		Angiography				
	0 or TIA*	Infarction	0	Infarction	Unilateral stenosis	Unilateral occlusion	Bilateral stenosis or occlusion	Sum	
CBF†	N = 9	N = 7	N = 6	N = 10	N = 6	N = 6	N = 4	N = 16	
Segment	89 ± 16‡	79 ± 23	92 ± 16	80 ± 20	91 ± 18	80 ± 10	82 ± 31	85 ± 19	
Hemisphere	97 ± 10	94 ± 7	101 ± 9	92 ± 8	98 ± 9	94 ± 9	94 ± 9	95 ± 9	
CBV†	(N = 8)		(N = 5)			(N = 5)		(N = 15)	
Segment	136 ± 48	128 ± 54	122 ± 47	137 ± 47	143 ± 62	118 ± 18	133 ± 50	132 ± 46§	
Hemisphere	103 ± 6	114 ± 14	106 ± 5	109 ± 14	108 ± 16	108 ± 9	111 ± 7	108 ± 12	$p < 0.001$§
CBF/CBV†									
Segment	65 ± 32	54 ± 33	78 ± 35	51 ± 27	64 ± 40§	50 ± 13	66 ± 40	60 ± 32	$p < 0.001$§
Hemisphere	85 ± 18	76 ± 14	95 ± 13	74 ± 13	84 ± 20	74 ± 13	85 ± 16	81 ± 16	$p < 0.001$§

* Transient ischemic attacks.
† The territory of affected internal carotid artery was compared with contralateral territory (= 100%). Identical ROIs were used for determining CBF and CBV.
‡ Standard deviation.
§ Significant difference compared with CBF using Student's t-test for paired values $p < 0.01$.

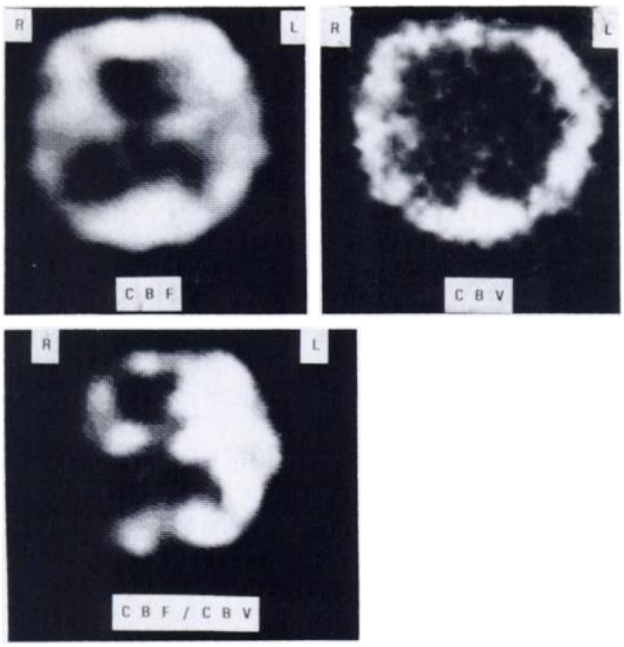

FIGURE 4
Stenosis >90% of right internal carotid artery, no significant CT alterations. 4.8 cm above OM-line, parietal CBF reduction <10% while CBF/CBV is reduced by ~60%

99m activity as recorded over the brain, varied an average of −5% during the imaging procedure.

DISCUSSION

Iodine-123 IMP has been synthesized and proposed for use as a tracer of CBF based upon its high brain uptake index (*5*). The validity of the method for regional CBF mapping was demonstrated by various investigators (*6–8*). Kuhl et al. (*6*) have shown that [^{123}I]IMP—after being almost completely removed on first pass through the brain—does not undergo relevant distribution changes within a period of 1 hr. The constancy of activity between 25 min and 1 hr was confirmed by our recordings. It is apparently because slow washout of activity from the brain is compensated by new [^{123}I]IMP delivered from the pulmonary reservoir where [^{123}I]IMP is trapped immediately after i.v. injection (*6*).

Since CBF is regulated by a number of important physiologic and pathophysiologic factors (*9*), the possibility of investigating CBF noninvasively with standard nuclear medicine equipment has generated considerable enthusiasm among neurologists. The diagnostic use of the [^{123}I]IMP method, however, depends on whether, and to what extent, the autoregulation of CBF is involved in the suspected disease. The most frequent cerebrovascular disorders at an early stage, without extended remote cerebral infarctions, may involve a reduction of the arterial perfusion pressure as the primary pathophysiologic consequence.

CBF fails to undergo significant changes over a wide range of arterial perfusion pressures (*2,3*) because of a compensatory drop of vascular resistance elicited by reduced oxygen supply and the release of vasodilator metabolites. Thus, the parameter CBF is significantly changed in CVD as late as exhaustion of the autoregulatory capacity. This may explain why [^{123}I]IMP uptake was abnormal almost exclusively in severe cerebral disease and, in particular, in infarctions (*10,11*). Patients who had transient ischemic attacks generally did

TABLE 2
CBF and Flow-to-Volume Ratios (CBF/CBV) in Patients with Unilateral Internal Carotid Artery Stenoses >50%

No	Pertinent findings		CBF (%)*		CBF/CBV (%)*	
			Segment	Hemisphere	Segment	Hemisphere
1	Obliteration	No infarction	87	95	72	82
2	Obliteration	No infarction	84	91	41	70
3	80% Stenosis	No infarction	90	96	71	94
4	Obliteration	Infarction	69	100	54	85
5	Siphon stenosis	Infarction	86	98	33	58
6	90% Stenosis	No infarction	100	95	46	75
7	80% Stenosis	No infarction	78	93	66	87
8	Obliteration	Infarction	77	79	41	54
9	Obliteration	Infarction	70	92	43	79
10	90% Stenosis	Infarction	70	89	29	74
	Mean		81.1	92.8	49.6	75.8
	s.d.		±10.1	±5.8	±15.5	±12.6
					$p < 0.001$†	$p < 0.001$†
					$p < 0.05$‡	

* Territory of affected internal carotid artery was compared with contralateral territory (100%). Identical ROIs were used for determining CBF and CBF/CBV.

† Significant difference compared with CBF using Student's t-test for paired values.

‡ Significant difference from null hypothesis (no difference between affected territory and contralateral side) using significance test for single means and t distribution.

not show marked [^{123}I]IMP deficits. For this reason, the detection of the causative hemodynamic alterations requires left-right quantitative analysis (*12*).

We made an attempt to detect the autoregulatory vasodilation in cerebrovascular diseases, resulting in an increase of the CBV, simultaneously with CBF mapping. The degree of CBV increase depends on whether all small blood vessels or only arteriolar resistance vessels are involved in vasodilation. There is some experimental and clinical evidence for concomitant vasodilation of small cerebral veins with arteriolar vessels in reduced perfusion pressure and for response of CBV to arterial blood pressure (*13,14*). For this reason, carbon-11 (^{11}C)carboxyhemoglobin has been employed as a CBV indicator in assessing cerebral perfusion reserve using positron emission tomography (PET) (*4*).

In contrast to approaches using PET, combined CBF and CBV analysis using SPECT is hampered by the relatively long effective half-lives of both radiotracers used. In order to subtract the ^{123}I contamination from the ^{99m}Tc image, our protocol required the measurement of ^{123}I impulses in the ^{99m}Tc channel for each voxel. These data were obtained by multiplying the photopeak tomograms with the correction factor λ. Certainly, they might differ slightly from those obtained at 140 keV, where ^{123}I contaminates the ^{99m}Tc signals; however, the approximation appears reasonable for the following reasons.

1. The doses of ^{99m}Tc greatly exceeded the ^{123}I doses. Even considering that the relative brain content of ^{99m}Tc is smaller than that of [^{123}I]IMP, it is understood that the signals for which the images were corrected represent a minor fraction of the total count rate in the ^{99m}Tc channel.

2. The quantitative analysis (side-to-side ratios) is based on relatively rough anatomic structures.

Another difficulty in determining CBF/CBV with SPECT arises when the data are converted into absolute figures (e.g., in sec^{-1} for a total slice). This is certainly a limiting factor for some physiologic studies and for the investigation of global brain diseases. Cerebrovascular disease, however, appears to be particularly distinguished by regional or focal abnormalities (*15*) that can find expression in abnormal distributions of even relative parameters obtained with SPECT.

Our preliminary clinical data substantiate the concept of CBF/CBV imaging to detect hemodynamic alterations in CVD. In all patients with unilateral ACI stenoses >50%, CBF and CBV show a contrary distribution resulting in clearly decreased CBF/CBV ratios, even when CBF is symmetrically distributed. In the latter case, it must be assumed that the perfusion reserve is still sufficient. In fact, the majority of these patients had no permanent neurologic deficit.

Five patients of the group mentioned had remote infarctions; four of them were clinically evident. In three instances more than 6 wk had elapsed from the acute episode. Though infarction-positive [^{99m}Tc]pertechnetate scans usually return to normal by this delay (*16*), a potential accumulation of the unbound ^{99m}Tc fraction must be considered. Therefore, it may be preferable to use in vitro labeling of red cells in order to avoid an overestimation of CBV in infarcted areas.

Nevertheless, decreased CBV and therefore no contrary side-to-side distribution pattern in CBF and CBV imaging, appeared in some patients with extended cerebral infarctions. A reduction of active tissue mass in infarcted areas may account for this finding. This reduction would affect the amount of trapped ^{123}I as well as the blood volume.

Our clinical data are consistent with the pathophysiologic considerations, particularly with the assumption that CBF/CBV is altered in autoregulatory vasodilation and mirrors perfusion reserve. The results demonstrate the adequacy of the technical procedure chosen for CBF/CBV imaging with SPECT. Future work should be dedicated to evaluating the sensitivity of the method in the detection of CVD.

FOOTNOTES

† Fa. Squibb-von Heyden, Munich, FRG.
‡ Byk-Mallinkrodt, Dietzenbach, FRG.
§ SPETS-S, Fa. Nuclear Diagnostics, Stockholm, Sweden.

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