Simplified quantitative determination of cerebral perfusion reserve with $H_2{}^{15}O$ PET and acetazolamide

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Abstract. The measurement of regional cerebral blood flow (rCBF) and perfusion reserve (PR) with $H_2{}^{15}O$ positron emission tomography (PET) and acetazolamide challenge is of importance in evaluating patients with cerebrovascular disease and is thought to be useful in selecting patients for possible vascular surgery. Full quantitative assessment of rCBF with PET requires arterial blood sampling, which is inconvenient in a clinical setting. In this work, we present a simple non-invasive method with which to quantitatively evaluate PR in one PET session lasting no more than 30 min. In ten patients with cerebrovascular disease, rCBF was measured with $H_2{}^{15}O$ PET under the baseline condition and after administration of 1 g acetazolamide using a standard technique involving arterial blood sampling. The activity accumulated over 60 s was normalized to injected activity per kilogram body weight (nAA) and compared with rCBF in eight different brain regions. A high linear correlation was found for PR based on nAA (PR_{nAA}) and rCBF (PR_{rCBF}) (PR_{nAA}=0.843 PR_{rCBF} + 0.092, r=0.83, Pearson's correlation coefficient). Bland-Altman analyses further confirmed that PR_{nAA} reflects PR in a quantitative manner. These results demonstrate that the method based on normalized counts allows the quantitative assessment of PR without blood sampling.

Key words: Positron emission tomography – Cerebral perfusion – Cerebrovascular disease

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Introduction

The evaluation of regional cerebral blood flow (rCBF) and perfusion reserve (PR) is important in the investigation of patients with cerebrovascular disease (CVD). Knowledge of perfusion and in particular of vasoreactivity measured with acetazolamide challenge is useful in selecting patients for a surgical procedure such as endarterectomy or extra-intracranial (EC-IC) bypass surgery [1, 2, 3, 4, 5]. Results with respect to the benefit of surgical treatment of occlusive CVD per se are still inconclusive. One large international trial failed to demonstrate the effectiveness of EC-IC bypass surgery in preventing cerebral ischaemia in patients with arteriosclerotic CVD [6]. However, one criticism of that study is that the patients' preoperative haemodynamic status was not fully assessed. It is feasible that a quantitative evaluation of the haemodynamic situation may better select patients who can potentially benefit from bypass surgery. A recent study in 12 patients demonstrated haemodynamic improvement following bypass surgery using quantitative $H_2{}^{15}O$ positron emission tomography (PET) [5]. A Japanese trial involving patients with low rCBF demonstrated no benefit of EC-IC bypass surgery with regard to stroke prevention, although a significant improvement in rCBF was found in the surgical group [7]. The effect of endarterectomy on the outcome in patients with symptomatic carotid stenoses has been investigated in two multicentre trials [8, 9]. In both trials it was concluded that endarterectomy is especially beneficial for patients with stenoses of 80% or more. Since no comprehensive evaluation of rCBF was performed in these trials, they do not shed new light on the usefulness of a thorough assessment of rCBF in the preoperative evaluation of CVD patients. In principle, several techniques are available for the assessment of cerebral perfusion. For semiquantitative assessment of rCBF and PR, single-photon emission tomography (SPET) is an established method. If quantitative information on rCBF is required, PET is the method of choice. A more widely available option is xenon-enhanced computed tomography (CT). However, this technique has the disadvantage of only delivering images of predetermined slices of the brain [10]. Another quantitative method is based on measuring the washout rate of intravenously administered radioactive xenon using an array of detectors. In one study this method was used to

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investigate the effect of endarterectomy on rCBF in patients with unilateral internal carotid stenosis [11]. A drawback of the method is the relatively low spatial resolution.

Fully quantitative perfusion PET has some disadvantages in a clinical setting. The required arterial blood sampling is associated with discomfort for the patient. Furthermore, the data processing, involving some form of tracer kinetic modelling, contains considerable sources of error. It would therefore be desirable to use a simpler method without losing the potential benefit of quantitation. In this study we assessed such a method. It is based on normalized brain activity accumulated over 1 min following the arrival of the bolus in the brain. The method was evaluated by comparing its results with an established fully quantitative method involving arterial blood sampling.

Materials and methods

Patients

The study was performed using the data of ten patients (seven males and three females) suffering from CVD with a mean age of 51.6 years (range 15–78). Three subjects had a complete occlusion and four had a high-grade stenosis of either the right or the left internal carotid artery, one patient had an aneurysm of the posterior communicating artery and two suffered from Moya-Moya disease. All patients were sent for PET scanning through the neurosurgical clinic for preoperative assessment.

PET scanning

The PET studies were performed on a whole-body scanner (Advance, GE Medical Systems, Waukesha, Wis., USA). This is a scanner with an axial field of view of 14.6 cm and a reconstructed in-plane resolution of 7 mm. Prior to positioning of the patients in the scanner, catheters were placed in an antecubital vein for tracer injection and the radial artery for blood sampling. Two studies were performed within half an hour, a baseline study and a second study 13 min following the intravenous injection of 1 g of acetazolamide. This interval was chosen based on the data of various studies which showed that the maximum vasodilatatory effect of acetazolamide is reached between 10 and 20 min following administration [5, 12, 13, 14]. Between the perfusion studies a 10-min transmission scan was acquired for the correction of photon attenuation. For each perfusion study 600–800 MBq $H_2{}^{15}O$ was injected using an automatic injection device which delivers a predefined amount of activity over 20 s. With the arrival of the bolus in the brain, a series of 18 scans of 10 s each was initiated in three-dimensional mode. The time course of the arterial radioactivity was assessed by continuous sampling of arterial blood drawn from the radial artery.

Data analysis

Transaxial images of the brain were reconstructed using filtered backprojection (128×128 matrix, 35 slices, 2.34×2.34×4.25 mm voxel size).

Fully quantitative reference method. Quantitative parametric maps representing rCBF were calculated using the integration method described by Alpert et al. [15]. This method relies on knowledge of the arterial input curve. Compared with the true input curve in the brain, the measured time course of arterial activity in the radial artery is time-shifted and distorted due to dispersion. Both time shift and dispersion were corrected for by the method described by Meyer [16]. The rCBF maps were calculated using the dedicated software PMOD [17]. This JAVA-based software allows the easy implementation of the models needed to calculate rCBF, including the corrections of the input curve.

Method based on normalized brain activity. The radioactivity accumulated over 60 s following the arrival of the bolus in the brain was calculated by adding the first six scans. This summed scan was normalized by dividing each voxel by the injected activity per kilogram bodyweight, yielding maps of nAA (i.e. normalized accumulated activity).

Both methods were compared using the mean values of rCBF and nAA in nine different volumes of interest (VOIs) defined over the left and right cerebellum, thalamus, anterior and posterior cortex and whole brain. In order to facilitate and standardize the placement of the VOIs, the rCBF and nAA maps were transformed into a stereotactic space using the software SPM96 [18]. The regional PR in the VOIs was calculated by dividing rCBF and nAA following acetazolamide ($rCBF_{ac}$, nAA_{ac}) by the respective values at baseline ($PR_{rCBF} = rCBF_{ac}/rCBF_{base}$; $PR_{nAA} = nAA_{ac}/nAA_{base}$).

The further question of the optimal duration of the interval over which the brain activity should be accumulated for the calculation of PR was addressed by using intervals of 90, 120 and 150 s in addition to the 60-s interval used above. The ratio of PR based on nAA and the different accumulation intervals and PR calculated with rCBF was analysed using univariate analysis of variance (ANOVA). The usefulness of nAA maps as a marker for rCBF and PR was further evaluated by linear regression analysis and evaluation of residuals. Pearson's correlation coefficient was used to characterize the correlations. The validity of PR values based on nAA was further assessed by using the statistics suggested by Bland and Altman [19]. All statistical evaluations were performed using the software package SAS (SAS Institute Inc, Cary, N.C. USA).

Results

A typical example of arterial input curves and tissue time-activity curves (TACs) at baseline and following administration of acetazolamide is illustrated in Fig. 1. The two input curves seem practically identical. After acetazolamide administration, the ascending phase of the TAC is steeper, the peak is higher and is reached earlier, and the washout rate is faster than at baseline.

The correlation of nAA and rCBF in the pooled VOIs of all subjects at baseline and following acetazolamide is demonstrated in the top left panel of Fig. 2. The rCBF values were in the range 16–102 ml/min/100 g. In order to investigate whether the correlation line could be used to estimate rCBF from nAA, the inverse correlation was calculated and the residuals were expressed as percentage deviation from rCBF (rCBF=1.82 nAA + 8.44,

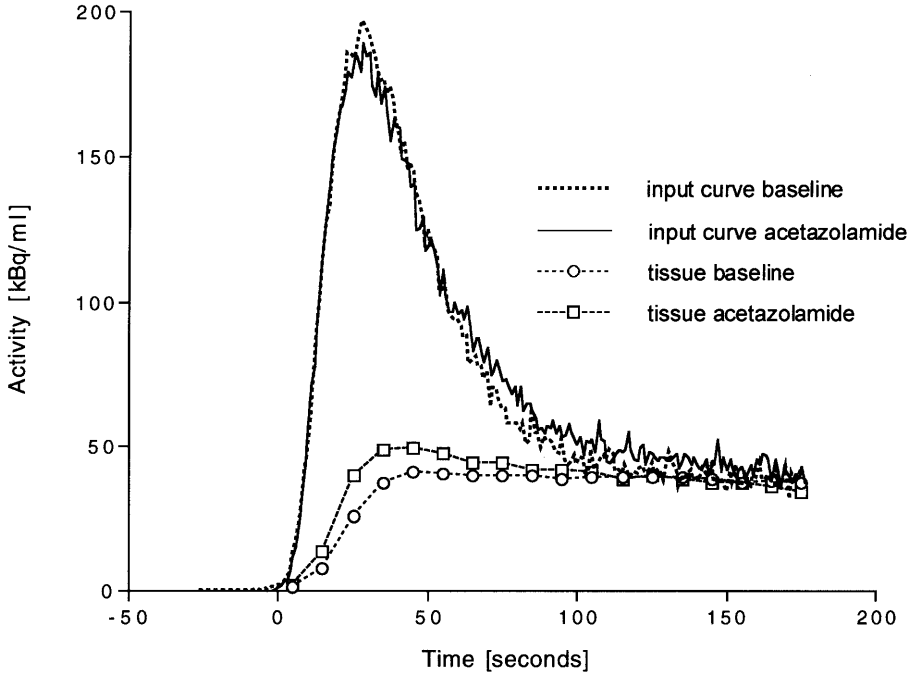

Fig. 1. Arterial input curves and time course of tissue activity in a normal parietal region of one patient at baseline and 14 min following the administration of 1 g acetazolamide. All curves were normalized to injected activity per kilogram body weight

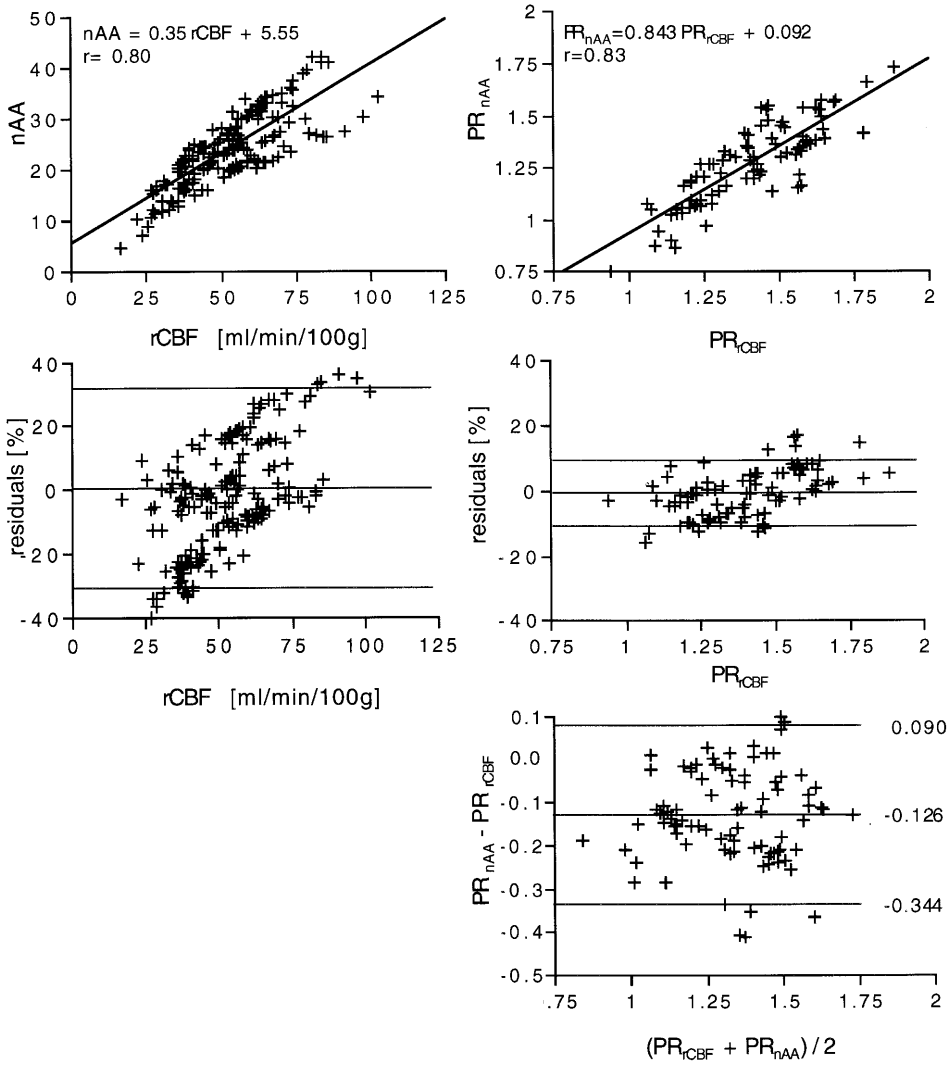

Fig. 2. The *top row* demonstrates the correlation of the normalized accumulated $H_2{}^{15}O$ activity (*nAA*) with rCBF on the *left* and the correlation of the perfusion reserve based on nAA (PR_{nAA}) and that based on rCBF on the *right*. Shown are the mean values in the eight VOIs of all subjects at baseline and following acetazolamide. The *second row* displays the residuals of the inverse correlations (rCBF = *a* nAA + *b*, $PR_{rCBF} = a\ PR_{nAA} + b$), expressed in percent deviation from rCBF and Pr_{CBF} respectively. The *horizontal solid lines* indicate mean ± 2 STD of the residuals. The Bland-Altman plot of PR_{rCBF} vs PR_{nAA} is included in the *bottom right-hand corner*

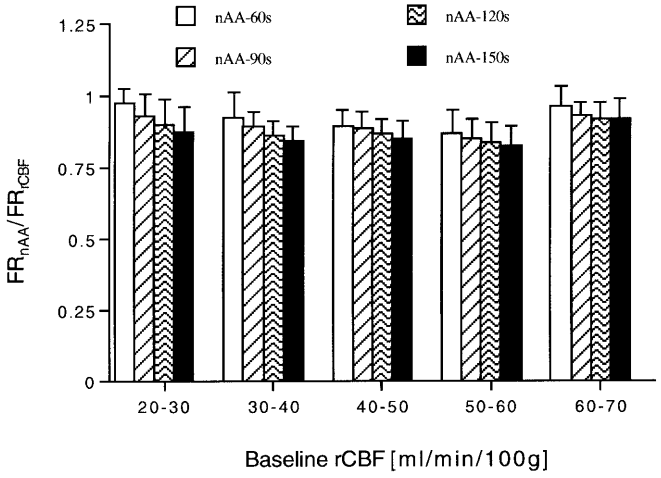

Fig. 3. Effect of using progressively increasing accumulation intervals on the perfusion reserve (PR). Demonstrated is the ratio of PR calculated with nAA and PR calculated with rCBF (PR_{nAA}/PR_{rCBF}) for accumulation intervals of 60, 90, 120 and 150 s. Shown are mean values + SD

r=0.90). The result is shown in the bottom panel on the left. The mean of the residuals was –3% and STD was 17%. The correlation of PR using nAA and rCBF is depicted in the top right panel of Fig. 2. Mean PR based on rCBF was 1.39; the range was 0.93–1.88. Accordingly, values for nAA were 1.27 and 0.75–1.73. As for rCBF vs nAA, the correlation of PR_{rCBF} vs PR_{nAA} was determined and the residuals expressed as percentage deviation from PR_{rCBF}. The result is displayed in the middle panel on the right. The mean of the residuals was –0.2% and the standard deviation (SD) was 7.2%. The result of the Bland-Altman analysis is demonstrated in the bottom panel on the right. It indicates that PR based on nAA underestimates the value calculated with rCBF by 0.126. Eighty-four of the differences evaluated in the 90 regions (93%) lay within the range defined by 2 STD above and below the mean difference.

Figure 3 demonstrates the effect of using consecutively longer accumulation intervals for the calculation of PR. PR using nAA is closest to the value calculated with

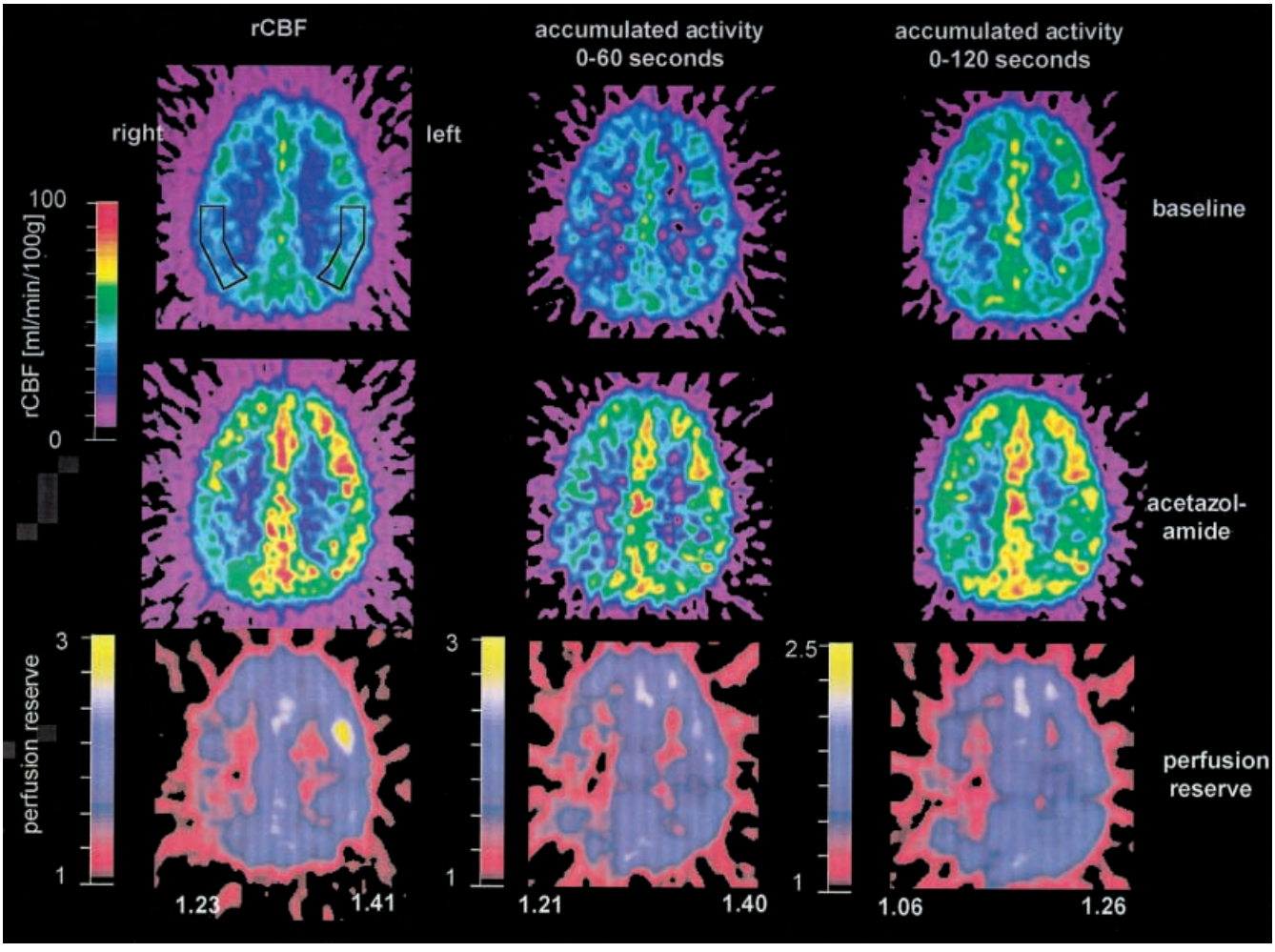

Fig. 4. Example of rCBF, accumulated activity over 60 and 120 s and perfusion reserve maps of one patient with reduced PR in the right parietal region. The numbers at the bottom represent PR calculated in the ipsi- and contralateral regions indicated in the top left image

rCBF for the shortest of the tested intervals (60 s). For low baseline rCBF (20–30 ml/min/100 g), PR_{nAA60} underestimates PR_{rCBF} by 3%. This value rises to 13% at high baseline rCBF (60–70 ml/min/100 g). The degree of the underestimation grows with increasing accumulation interval. Using a 150-s interval, the underestimation was as high as 18%. Univariate analysis demonstrated that this effect was significant (df=4, F=10.34, P=0.0001).

An example of maps of rCBF, nAA_{60} (accumulated activity over 60 s) and nAA_{120} (accumulated activity over 120 s) at baseline and following acetazolamide and PR in a single patient is demonstrated in Fig. 4. At baseline there is a slight defect in the right parietal region, which becomes more pronounced following acetazolamide. The reduced PR is best appreciated in the PR images themselves. PR in the pathological region was similar when determined on rCBF and nAA_{60} maps (1.23 and 1.21 respectively) but lower when determined using nAA_{120} maps (1.06). The same trend is seen on the contralateral healthy side, PR determined with rCBF and nAA_{60} was similar, while PR based on nAA_{120} was considerably lower. On the other hand, image quality was superior with nAA_{120} compared with nAA_{60}.

Discussion

The major purpose of this work was to address the question of whether the perfusion reserve could be measured quantitatively with $H_2{}^{15}O$ PET without arterial blood sampling. Before discussing PR, it should be noted that there is already a high correlation between the accumulated counts over 60 s and rCBF. This is not surprising. Herscovitch et al. have previously shown that the $H_2{}^{15}O$ counts acquired over the shorter interval of 40 s correlate highly with rCBF [20]. In theory one might expect the correlation to increase with decreasing accumulation intervals. This is easily explained by the cerebral kinetics of $H_2{}^{15}O$. The tracer diffuses virtually freely into permeable space and then progressively washes out. Immediately following the arrival of the bolus in the brain, the tracer kinetics is mainly determined by the diffusion of $H_2{}^{15}O$ from the vascular space into the tissue, the degree of this diffusion being directly proportional to the amount of delivered tracer, e.g. rCBF. In the washout phase, backdiffusion of $H_2{}^{15}O$ from tissue to vascular space becomes dominant and the total amount of accumulated $H_2{}^{15}O$ reflects rCBF to a decreasing extent. From this point of view, shorter accumulation intervals should lead to nAA maps that better mirror rCBF and PR. This is confirmed in the present study. With longer accumulation intervals, PR was progressively underestimated (Fig. 3). On the other hand, longer intervals are associated with a better count statistics, e.g. better image quality, as is demonstrated in Fig. 4. Therefore the optimal duration of the accumulation interval depends on the situation. If image quality is a major concern, one would opt for a longer interval, while if quantitative reflection of rCBF is the issue, one would choose a shorter interval. For practical purposes, 60 s seems a reasonable choice. An easy solution is to acquire multiple scans that can be summed to yield images of various accumulation intervals.

An interesting question is whether a regression line like that established in the top left panel of Fig. 2 or of the inverse relation (rCBF vs nAA) could be used to derive rCBF from nAA values in individual patients. Such a procedure would have considerable limitations, as is demonstrated by the residuals in the bottom left panel of Fig. 2. Since positive residuals mean underestimation of true rCBF, rCBF values derived from nAA and the correlation line would underestimate true rCBF at higher flow values and overestimate lower rCBF values. Furthermore, the relatively high SD of the residuals (17%) limits the accuracy of converting nAA into absolute values of rCBF. The reasons for this are manifold. For instance, the amount of accumulated $H_2{}^{15}O$ activity in the brain relative to injected activity depends on factors such as the fraction of the total cardiac output diverted to the brain. Such factors will vary among subjects. However, for many clinical purposes, knowledge of rCBF in absolute units is not mandatory. In the evaluation of patients with CVD it may be sufficient to establish the rCBF pattern and determine PR. Since the latter is a ratio of two measurements in the same subject, some systematic errors in each measurement can be expected to cancel in the ratio. Indeed, one of the major results of this study is the high correlation of PR derived from nAA and from rCBF maps. Although there is a slight underestimation of PR using nAA relative to PR_{rCBF}, it is small. The Bland-Altman plot further suggests that, despite the small underestimation, PR_{nAA} and PR_{rCBF} are very similar and PR_{nAA} can be considered to reflect the PR in a quantitative manner. This is further supported by the low SD of the residuals in the correlation PR_{rCBF} vs PR_{nAA}, i.e. 7.2%, which is considerably lower than the SD of the residuals in the correlation rCBF vs nAA.

A prerequisite for PR_{nAA} to be quantitative is that only brain perfusion increases following the administration of acetazolamide. If the fractional increase in perfusion were equally distributed throughout the body, the fraction of the injected $H_2{}^{15}O$ activity diverted to the brain would not increase and a count-based method would not work. In this respect, several studies suggest that the increase in cerebral perfusion induced by acetazolamide is indeed not accompanied by increased peripheral perfusion. [21, 22]. The relative increase in global cerebral perfusion after acetazolamide in this study (39%±16%) is in keeping with the effect reported in the literature [5, 12, 13, 23]. Another important factor is a consistent injection procedure. An automatic injection device like the one used in this study is ideal. It yields a reproducible time course of the arterial $H_2{}^{15}O$ activity, as is illustrated in Fig. 1. Another point in favour of automatic injection

is the accurate measurement of the actually injected activity. Considering the short physical half-life of ^{15}O, the accuracy of such a measurement would be impaired when using manual injection.

Other methods for the evaluation of cerebral perfusion without arterial blood sampling have been described. Nelson et al. described a method involving the measurement of the flux of photons emanating from the superior lobe of the right lung as a parameter for arterial blood activity after intravenous bolus of $H_2{}^{15}O$ [24]. Iida et al showed the usefulness of a PET system where the activity in the left cardiac ventricle, subsequently used as the input curve, is simultaneously measured with brain activity [25]. Both methods require specialized equipment limited to a few specialized PET centres. Different methods of data analysis which potentially permit the avoidance of arterial blood sampling have also been described [26, 27, 28]. Drawbacks of these methods are the complicated data processing and the fact that reproducibility has not yet been proven beyond doubt.

The presented non-invasive count-based method allows the qualitative evaluation of the pattern of baseline rCBF and the quantitative assessment of PR. In principle, this could also be achieved with SPET and the use of flow tracers such as technetium-99m labelled hexamethylpropylene amine oxime and ethyl cysteinate dimer. However, there are some drawbacks of the SPET method. Because of the variable geometry of the SPET scanners, the required conversion of the injected activity into the units of the SPET system is less reliable than in PET, with its fixed geometry of the gantry. Furthermore, the longer half-life of ^{99m}Tc mandates that the two required examinations be carried out on different days, whereas the total duration of the PET examinations is only 30 min on one day.

In summary the presented non-invasive count-based method allows the qualitative evaluation of the pattern of baseline rCBF and the quantitative assessment of PR following the administration of acetazolamide. Using ^{15}O-labelled water and PET, a full examination encompassing two emission scans and a transmission scan lasts only 30 min.

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