Can the detection of misery perfusion in chronic cerebrovascular disease be based on reductions in baseline CBF and vasoreactivity?

Can reductions in baseline CBF and vasoreactivity detect misery perfusion in chronic cerebrovascular disease?

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Abstract

Purpose: To investigate diagnostic accuracy for misery perfusion using criteria defined by baseline cerebral blood flow (CBF) and cerebral vasoreactivity (CVR) in the acetazolamide (ACZ) challenge, patients with chronic cerebrovascular disease (CVD) were studied.

Methods: Oxygen extraction fraction (OEF) and other hemodynamic parameters were measured in 115 patients (64±9y) with unilateral cerebrovascular stenoocclusive disease (>70% stenosis) using ^{15}O-gas and water PET. A significant elevation of OEF greater than mean+2SD of healthy controls was defined as misery perfusion. CBF, CVR determined by %change in CBF after ACZ administration, OEF, and other hemodynamic parameters in territories of bilateral middle cerebral arteries were analyzed. Diagnostic accuracy in detection of misery perfusion using the criteria determined by baseline CBF and CVR was evaluated in all patients and only in patients with occlusive lesions.

Results: Ten of 24 patients with misery perfusion showed a significant CVR decrease. Using criteria determined by significant decreases in CVR and baseline CBF, misery perfusion was detected with sensitivity of 42% and specificity of 95% in all patients. Patients with occlusive lesions (n=50) showed higher sensitivity with slightly lower specificity. Threshold determined by baseline CBF alone provided similar diagnostic accuracy in all patients as well as patients with occlusive lesions, which was more accurate than the detection by asymmetry index of OEF (OEF-AI).

Conclusion: Reductions of CVR and baseline CBF in the ACZ challenge for CVD would detect misery perfusion with high specificity. Decrease in baseline rCBF is more accurately detect misery perfusion than reduced CVR alone.

Key words: misery perfusion, cerebral vasoreactivity, acetazolamide, cerebral blood flow, chronic cerebrovascular disease

Introduction

Detection of misery perfusion, an elevation of oxygen extraction fraction (OEF) in the brain, is reported to be a good predictive indicator of recurrent stroke in patients with chronic cerebrovascular disease (CVD) [1-3]. Positron emission tomography (PET) is usually used in those studies for measurements of hemodynamic parameters such as cerebral blood flow (CBF) and oxygen metabolism. The acetazolamide (ACZ) challenge, which assesses cerebral vasoreactivity (CVR), has also been reported to be useful in evaluating the residual vasodilatory capacity of resistance vessels and in predicting the risk of cerebral hemodynamic impairment in patients with major cerebral arterial occlusive diseases [4, 5]. The reduced response of regional cerebral blood flow (rCBF) in the vascular territory affected by CVD after a vasodilatory stimulus has been ascribed to the exhaustion of the vasodilatory capacity caused by autoregulatory maximal vasodilation in response to reduced cerebral perfusion pressure [6, 7]. Such affected cerebral regions may reveal misery perfusion, defined as stage II ischemia, where CBF reduction and remaining oxygen consumption causes a relative elevation of OEF in the brain [8-10].

However, approximately half of the patients with severe cerebrovascular stenoocclusive disease who show a significant CVR reduction at the ACZ challenge do not show elevation of absolute OEF in the affected area [11-13]. The relationships between the hemodynamic parameters at baseline and results of the ACZ challenge seem to be more complicated in brain regions affected by stenoocclusive CVD, because the variable degree of collateral circulation development influences the hemodynamic response to vasodilators especially in chronic phase [14]. In a previous PET ACZ challenge study, a significant increase in arterial-to-capillary blood volume, which is expected to be correlated to the diameter of resistance vessels, was observed at the ACZ challenge even in the affected regions of patients with severe CVD who showed a paradoxical reduction in rCBF [11].

This suggests that the reduction of rCBF response to ACZ is not necessarily associated with the degree of vasodilatory capacity, and thus the reduced CVR alone may not be associated with stage II.

The aim of this study is to clarify whether decreases in both baseline rCBF and residual CVR assessed by the ACZ challenge, which may reveal critical hemodynamic status in CVD [15], can appropriately detect misery perfusion represented by the elevation of OEF. PET measurement of CBF and oxygen metabolism was performed in patients with chronic stenoocclusive CVD for this purpose. Significant decreases of CVR and baseline CBF, which can be evaluated using SPECT with a quantitative method, were considered to be indicative of hemodynamic impairment [15]. The asymmetry index (AI) of OEF was also analyzed to assess misery perfusion determined by elevation of absolute OEF in the affected hemisphere as used in several studies [2, 16, 17]. In the present study, baseline CBF, CVR and oxygen metabolism were measured by a series of PET scans within 1.5 hours, which could evaluate hemodynamic parameters at the same condition in each subject compared with studies done in separate days.

Materials and methods

Subjects

One hundred and fifteen patients (88 men and 27 women) aged 31-79 years (mean = 64 ± 9 y) with unilateral major cerebral atherothrombotic stenoocclusive disease were involved in this study. All patients had arterial lesions of occlusion or stenosis with >70% diameter reduction. They underwent PET studies for evaluation of hemodynamic status, and also underwent MRI, MR angiography and/or conventional angiography to examine any and all cerebral and arterial lesions. Details of patient information are given in Table 1. The percent reduction in diameter of stenoocclusive lesions was measured by conventional

angiography and/or ultrasonography in the cervical lesions and by conventional angiography in the intracranial lesions. Fifty patients had occlusion or severe intracranial stenosis (>98% diameter reduction) in a unilateral internal carotid artery (ICA; 34 patients) or middle cerebral artery (MCA; 16 patients). These 50 patients consisted of a subgroup of patients with symptomatic occlusive lesions, and the purpose of PET scans for them was to determine an indication for bypass surgery. The mean interval between an ischemic event and the PET examination of the 50 patients with occlusive disease was 3.8 ± 4.5 months. Twenty-five patients in the occlusive group had minor infarction, and the remaining 25 patients in this group did not have visible ischemic lesions on MRI. All 25 patients with occlusion and 12 patients with severe stenosis in the major cerebral arteries had collateral circulation from the contralateral hemisphere via anterior or posterior communicating arteries, or through ophthalmic and leptomeningeal arteries on the same side as the occlusion. The remaining 13 patients with unilateral severe stenosis did not have any visible collateral circulation. In the remaining 65 patients with stenotic lesions in ICA or MCA (≦98 % of diameter reduction), PET was performed for evaluation of hemodynamic status or as a reference study before neurosurgical treatment such as carotid endoatherectomy (CEA) or stenting. Fourteen healthy volunteers (9 men, 5 women) aged 28-79 years (mean = 51 ± 15 y) underwent ^{15}O-gas and water PET study as controls. This study was approved by the Ethical Committee of University of Fukui, Faculty of Medicine. Written informed consent was obtained from each subject.

PET procedures

In all subjects (patients and volunteers), PET scans were performed with a whole-body tomography scanner (ADVANCE, General Electric Medical System, Milwaukee, WI, USA), which permits simultaneous acquisition of 35 image slices in a 2-dimentional acquisition mode with inter-slice spacing of 4.25 mm [18]. Performance tests showed the intrinsic

resolution of the scanner to be 4.6 to 5.7 mm in the transaxial direction and 4.0 to 5.3 mm in the axial direction. A transmission scan was performed for 10 min using $^{68}Ge/^{68}Ga$ for attenuation correction in each subject before the tracer administration. The PET data were reconstructed using a Hanning filter with a resolution of 6.0-mm full width at half maximum in the transaxial direction.

Subjects were positioned on the scanner bed with their heads immobilized using a head holder. A small cannula was placed in the brachial artery for blood sampling. $H_2{}^{15}O$-PET was performed with the bolus injection of tracer in approximately 740 MBq as described in detail elsewhere [19, 20]. In each scan, a 3-min dynamic PET scan was started at the time of tracer administration from the antecubital vein with frame durations of 5 sec x 12, 10 sec x 6 and 20 sec x 3. Radioactivity in the arterial blood was counted continuously using an automatic blood sampling system (ABSS) which included a positron radioactive counter (Apollomec Co. Ltd., Kobe, Japan) [21] and a mini-pump (AC-2120; Atto Co., Tokyo, Japan). Arterial blood was sampled and counted continuously with the ABSS at a constant rate of 7 mL/min for the first 2 min, followed by manual sampling of 0.5 mL of blood every 20 sec during the remaining scan time. Radioactivity, as counted by the ABSS, was calibrated with the blood sampled manually. Decay of the radioactivity from PET and blood data was corrected to the starting point of each scan. Dispersion for the external tube in the arterial curves was corrected with a double-exponential dispersion function [22].

CBF (mL/100g/min) images for the two conditions of pre- and post-ACZ administration were calculated from the dynamic PET data and arterial input functions measured above. The 3-weighted integral method based on a 2-compartment (one-tissue compartment) model was used for image calculation [11, 19, 20]. The time delay of arterial input was corrected automatically in the program and a time constant of $\tau = 4$ sec

was used for internal dispersion correction [19, 23]. After baseline CBF measurement and ^{15}O-gas scans, 1g ACZ in 10 mL of saline was administered from the venous line over 1 minute, and $H_2{}^{15}O$-PET was started 10 min after ACZ administration to evaluate changes in CBF [20].

In the steady-state method [24, 25], $C^{15}O_2$ (370 MBq/min) and $^{15}O_2$ (740 MBq/min) were inhaled continuously for approximately 8 min, followed by static data acquisition for 5 min to obtain images of the CBF, OEF and cerebral metabolic rate of oxygen ($CMRO_2$) (mL/100g/min). Arterial blood was sampled during each procedure and the radioactivity in the blood was immediately measured with a scintillation counter. During continuous inhalation of $^{15}O_2$ in the steady-state method, the sampled blood was divided into two aliquots in order to count the radioactivity of both whole blood and plasma. Each subject also inhaled a single dose of $C^{15}O$ (1000 MBq) to obtain a CBV image. The static PET scan was then started at least 40 sec after the arrival of the peak count of $C^{15}O$ in the brain and continued for 3 min [20]. Arterial blood was sampled twice during each $C^{15}O$ study, and the radioactivity in the blood samples was immediately measured with a scintillation counter. Individual CBV image was used for correction of the effect of intravascular radioactivity in calculation of OEF image. During the PET scanning with $^{15}O_2$ inhalation, total O_2 content (tO_2c) in the arterial blood was measured from one blood sample to calculate $CMRO_2$. The arterial blood gas data of tensions for CO_2 (P_aCO_2) and O_2 (P_aO_2), pH, and hematocrit were also measured in the same blood sample. The blood pressure of each subject was measured continuously through the arterial line and displayed on a monitor during the PET study. The blood gas data were also obtained during $H_2{}^{15}O$-PET scan after ACZ administration.

Data analysis

Regional values for each parametric image in the 115 patients were determined using multiple regions of interest (ROIs) placed on the cortical territories of the MCA of the 2 hemispheres (Fig. 1). To avoid including areas of infarction in the ROIs, PET images were co-registered to individual MRI image before drawing ROIs. A total of 30 small circular ROIs with fixed size of 10 mm in diameter were placed on each hemisphere at several slice levels using co-registered MRI so as not to include stroke regions, and were applied to all images of CBF, OEF, $CMRO_2$ and CBV for each subject. The 30 ROI values were averaged in each hemisphere and parametric data thus obtained were compared between hemispheres and among subject groups [1, 3, 12, 22]. Patients were divided into 2 groups according to their lesions. The occlusive lesion group included patients with occlusion or severe stenosis (> 98%), and the stenotic lesion group consisted of all the remaining patients ($\leqq$98 % stenosis). For group comparison, control data included 28 hemispheres from 14 healthy volunteers who performed ^{15}O-water study for baseline CBF, as well as ^{15}O-gas PET for CBV and oxygen metabolism.

Differences in rCBF were statistically compared between the 2 hemispheres and the 2 conditions before and after ACZ administration using repeated-measures analysis of variance (ANOVA) and a paired *t*-test. For evaluation of CVR, percent change in rCBF (= [(post-ACZ CBF) – (baseline CBF)] / (baseline CBF) x 100 %) was calculated for all patients. Differences in each parameter between the 2 hemispheres of patients were analyzed using repeated-measures ANOVA and a paired *t*-test. Differences among the 3 groups were compared using one-way ANOVA and a post-hoc Scheffé's *F*-test. A probability value of less than 0.05 was considered to indicate a statistically significant difference. Correction for multiple comparison was applied to the threshold probability value to keep an overall $\alpha = 0.05$ when testing multiple null hypotheses.

To evaluate diagnostic accuracy for the detection of misery perfusion defined by increase in absolute OEF, rCBF and CVR of all patients were analyzed using the criteria determined by baseline rCBF and CVR at the ACZ challenge, and then those of the patients who had only occlusive lesions more than 98 % (50 patients). The thresholds for this method were defined as the lower 95% confidence limit of the mean of control values (i.e. mean – 2SD) and lower values than the threshold were considered to be a significant decrease [11, 26]. As for CVR reduction at the ACZ challenge, the threshold of 10.5 % was used as determined by data from healthy volunteers in the previous study [11, 20]. Cerebral regions with a significant OEF increase in the affected hemisphere greater than mean + 2SD of controls were considered to be affected by misery perfusion [1, 3], which was used as the ground truth in this analysis. In the application of threshold using AI of OEF (OEF-AI: ipsilateral/contralateral ratio) for estimation of misery perfusion, significantly high OEF-AI was determined by the point at which the regression line of OEF-AI and CVR correlation was crossing the line of CVR = 10.5 %.

Results

Table 2 shows the average values of the physiological data and the changes in rCBF for the bilateral MCA regions measured in 115 patients. The $P_{a}O_2$ and tO_2c increased and $P_{a}CO_2$ decreased significantly after the ACZ injection. The mean CBF was significantly different between the 2 hemispheres at both conditions ($P < 0.005$ and $P < 0.0001$, respectively). The hemispheres both showed a significant rCBF increase after ACZ administration ($P < 0.0001$), although the percent change in rCBF in the ipsilateral hemisphere was significantly lower than that in the contralateral hemisphere ($P < 0.0001$).

The relationship between OEF and percent change in CBF after ACZ administration is shown in Figure 2. Absolute OEF did not show any correlation with vasodilatory capacity

measured in CBF response to ACZ (Fig. 2A). However, OEF-AI showed a negative correlation with percent change in CBF (Fig. 2B). The regression coefficient was not excellent, but the correlation was significant ($F = 23.6 > F(1, 113) = 3.93$). This regression line ($y = -152x + 180$) along with the threshold of significant reduction of CBF response (10.5 %) identified the AI of 1.12 as the critical OEF increase on the basis of vascular response.

All parameters obtained from PET studies and changes in physiological data are given in Table 3. Patients were divided into 2 groups with (n = 50) or without (n = 65) occlusive lesions (see above). All patients without occlusive lesions had stenosis less than 95 % of diameter reduction on conventional angiography or ultrasonography. Baseline CBF and $CMRO_2$ were significantly lower in the ipsilateral hemisphere of both patient groups compared with the contralateral hemisphere ($P < 0.001$ and $P < 0.01$, respectively) and those of the control group ($P < 0.01$). OEF and CBV were significantly increased only in the ipsilateral hemisphere of patients with occlusive lesions ($P < 0.001$ and $P < 0.01$, respectively). Mean blood pressure at baseline was significantly higher ($P < 0.05$) and P_aO_2 at both conditions was significantly lower ($P < 0.01$) in both patient groups than the control group. The threshold for critical reduction in baseline CBF derived from the mean of control data (mean – 2SD) was calculated to be less than 33.3 (mL/100g/min) at baseline. The threshold for critical elevation of OEF was determined as greater than 51.0 % calculated from mean + 2SD of control data.

The relationship between baseline rCBF and rCBF response to ACZ (CVR) is plotted in Figure 3. When the criteria determined by baseline rCBF and CVR reductions were applied, diagnostic accuracy for misery perfusion (significant elevation of absolute OEF) was as follows; sensitivity 41.7 %, specificity 94.5 %, positive predictive value (PPV) 66.7 % and negative predictive value (NPV) 86.0 % (Fig. 3A, Table 4). When the analysis

was limited to unilateral occlusive lesions (n = 50), sensitivity and PPV for diagnosis of misery perfusion using baseline rCBF and CVR were increased because of decrease in false negatives and few change in false positives (Fig. 3B, Table 4). Sixteen patients in the group of occlusive lesions had OEF elevation, and 13 of them showed a significant decrease in baseline rCBF (81.3 %). If a threshold of baseline rCBF is set at 31.5 (mL/100g/min), which is the 98 % confidence limit of the mean baseline rCBF, significant rCBF reduction alone could detect 10 patients out of 16 with misery perfusion (62.5 %) and two moderate OEF increase (Fig. 3B, Table 4). Diagnostic accuracy for misery perfusion using three different criteria including this simple threshold by baseline rCBF is presented in Table 4.

In Figure 4, three representative cases of true and false positive, and false negative are presented. These cases were patients with right ICA stenosis, left ICA occlusion and right ICA occlusion, respectively. Both true and false positive cases showed reduction in baseline CBF and CVR in the ipsilateral hemisphere, whereas OEF was increased in the former and no change in the latter. In the third case (Fig. 4C), CBF and CVR were in the normal range, although OEF increased as a global change. Fifteen out of 24 patients with misery perfusion in the present study showed a moderate decrease in ipsilateral $CMRO_2$ (< mean – SD of control data). Twenty-six patients showed a significant decrease in $CMRO_2$ (< mean – 2SD of control data) and four of them had OEF elevation in the ipsilateral hemisphere. The remaining 22 patients had normal OEF, and 8 of them showed reduced CVR. These 22 patients showed parallel decreases in CBF and $CMRO_2$, although 14 of them had normal CVR.

Discussion

In the present study with chronic cerebral stenoocclusive CVD, specificity of detection of misery perfusion was improved when the reductions of baseline rCBF and CVR are

combined as compared with using CVR alone. The lack of correlation between absolute OEF and percent change in rCBF at the ACZ challenge supports this result. If a threshold determined by only CVR is applied for detection of misery perfusion, approximately half of the patients with reduced CVR are classified as false positive, which is consistent with the previous reports [11-13]. On the other hand, the threshold defined by baseline rCBF alone showed better diagnostic accuracy than the other two criteria studied when patients with occlusive lesions were analyzed (Table 4). This result indicates the importance of quantitative measurement of rCBF at baseline for assessment of hemodynamic status in chronic stenoocclusive CVD. Since misery perfusion should be accompanied by an rCBF decrease at baseline, results of the ACZ challenge for detection of compromised circulation should be evaluated in association with baseline rCBF [15].

Misery perfusion is considered to be the effect of rCBF decrease in regions of normal oxygen consumption [7-10]. However, considerable number of the patients with misery perfusion also show a reduction in $CMRO_2$ in the affected region as both patient groups showed a significant decrease in ipsilateral $CMRO_2$ (Table 3). In the present study, 63 % of patients with misery perfusion showed a moderate decrease in ipsilateral $CMRO_2$, and 85 % of patients with significant decrease in $CMRO_2$ showed parallel decreases in CBF and $CMRO_2$. This means that chronic CBF reduction due to decreased perfusion pressure caused various degrees of $CMRO_2$ reduction as well. Those patients who showed parallel decreases in CBF and $CMRO_2$ with reduced CVR resulted in false positives in evaluation by the ACZ challenge, although surgical treatment may recover both CBF and $CMRO_2$ when the reduction is caused by neuronal hypofunction including diaschisis. On the other hand, the false negatives in the present study tended to have an OEF increase in both hemispheres (Fig. 2B, 3A, 4C). This global change of OEF elevation would be caused by various reasons such as tentative CBF decrease due to increase in hematocrit [27], arteriosclerosis in

small vessels [28], as well as anemia observed in a few cases. Conservative treatment may improve these kinds of misery perfusion, and follow-up studies will be needed for them.

In the evaluation of hemodynamic impairment, we used diagnostic criteria defined by the 95 % confidence limit of the mean values obtained from healthy volunteers, which is considered to identify significant changes in the affected hemisphere [1, 3, 26]. The criteria showed fair results in specificity and accuracy for detection of OEF elevation in CVD patients, although sensitivity was lower than 65 %. If the criteria were applied to the patients with occlusive lesions who are expected to be candidates for neurosurgical bypass treatment, the critical problem will be to identify the 37 % of them with misery perfusion that could not be detected with the ACZ test alone. However, the major reason for such elevation in the false negatives may not have been caused by focal hemodynamic impairment as discussed above. If such OEF elevation due to systemic or whole brain changes is excluded, the criteria used in this study would provide better results in the diagnosis of critical brain regions.

Patients with CVD who have misery perfusion in the affected cerebral region showed a significantly high risk of recurrent stroke as reported in several prospective studies [1-3, 16]. Similar prospective studies using CVR evaluation showed a significantly higher recurrent stroke risk (about 30-40 % of patients) in the reduced CVR group than in the normal CVR group [4, 5]. This ratio is similar to that of OEF elevation in the patients with reduced CVR in the present study. These results indicated that hemodynamic impairment of cerebral circulation should be evaluated by baseline CBF associated with CVR. The most critical factor for reduction of CVR in regions of hypoperfusion would be insufficient collateral circulation from regions with sufficient blood supply [14]. The impairment of hemodynamic autoregulation, which might be associated with poor collateral circulation, would also cause CVR reduction. Thus, hemodynamic deficiency due to poor collateral

circulation would be a high risk factor for stroke, as suggested by the evidence that a severe reduction in cerebral perfusion pressure was associated with a history of stroke [29]. Another possible reason for CVR reduction might be the decrease in neuronal activity or neuronal loss in the hypometabolic regions as revealed by $CMRO_2$ reduction, which may result in reduced baseline rCBF and a decreased response to ACZ without OEF elevation. A few cases of false positives in the current study may have been in this status (Fig. 4B).

The threshold determined by OEF-AI is considered to be a fair diagnostic method for detection of misery perfusion [17], although sensitivity in detecting misery perfusion was inferior to that achieved using the ACZ challenge (Fig. 2B, Table 4). In the present study, OEF-AI was calculated from absolute OEF. The results may slightly different from those of count-based OEF-AI because count-based OEF-AI includes the effects of CBV increase [16]. CBV was used only for correction of absolute OEF in the present analysis because it includes both arterial and venous volume and dilatation of resistance arteries caused by impaired circulation should be assessed using other parameters [11, 30].

In the present study, mean age of control group was younger than patient groups. Since the thresholds for criteria were determined by this control data, diagnostic accuracy may vary by classification of patients in the border zone. However, CVR in the ACZ challenge was not different between the contralateral hemisphere of patients and control data. Although mean of baseline rCBF may tend to be lower in the older subjects, a lower threshold of baseline rCBF would improve specificity and accuracy in diagnosis of misery perfusion as observed in Fig. 2. P_aCO_2 was significantly decreased after the ACZ challenge because of an increase in respiratory ventilation induced by ACZ [31], which may reduce CBF reaction to ACZ. However, these effects of ACZ would provide CBF changes equally both in patient and control groups. The criteria for the ACZ challenge could be

determined by similar thresholds with the quantitative normal values even in other diagnostic modalities, and would provide fair prediction of stroke recurrence.

Conclusion

Detection of misery perfusion reached high specificity and fair accuracy by using thresholds defined by significant decreases in baseline rCBF and CVR after the ACZ challenge. Quantitative measurement of baseline rCBF would be essential for evaluation of critical hemodynamic impairment although additional studies for measurement of CVR or oxygen metabolism will provide useful information to correctly evaluate the hemodynamic status. Pathophysiology of CVD including global changes in OEF would be well elucidated by observation from multiple phases of hemodynamic changes.

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Figure legends

Figure 1.

Multiple circular ROIs (10 mm in diameter) placed on MCA territories of the bilateral hemispheres. PET images were co-registered to individual MRI image, and 30 ROIs were placed on each hemisphere using several image slices of MRI. The same ROIs were applied to the parametric PET images.

Figure 2.

Plots for relationship between resting OEF and CVR (% Change in rCBF) at the ACZ test in the ipsilateral hemisphere. Absolute OEF and CVR did not show any correlation (A). However, asymmetry index (AI) of OEF and CVR showed a negative correlation (B), although the regression constant was weak (solid line: $y = -152x + 180$, $R = 0.42$). Open circles (○) show values with normal OEF and gray filled square (■) represents significant elevation of OEF (> mean + 2SD) in the affected hemisphere. Open triangles (Δ) show moderate OEF increase greater than mean + 1 SD. Horizontal dashed line is the threshold for significant CVR reduction and vertical dashed line is the crossing point of the regression line and the threshold.

Figure 3.

Relationship between baseline CBF and CVR in all 115 patients studied (A) and 50 patients with occlusive lesions (B). The dashed lines represent the threshold determined in the current study (baseline CBF < mean – 2SD, and CVR < mean – 10.5% of healthy controls). The square in bold lines represents the region where these criteria indicate a severely impaired cerebral circulation (= misery perfusion). See Table 4 for diagnostic accuracy.

Figure 4.

Representative cases of true positive (A), false positive (B) and false negative (C) in patients with right ICA stenosis, left ICA occlusion and right ICA occlusion, respectively. Both true and false positive cases showed reduction in baseline CBF and CVR in the ipsilateral hemisphere, whereas OEF was increased in the former and no change in the latter. In case C, CBF and CVR were normal, although OEF increased as a global change. Same color scale is used for the same parametric images.

Table 1. Patient information

		Total	Occlusive[1)]	Stenosis[2)]
Number of patients		115	50	65
Age (years)		63.8 ± 9.2	63.8 ± 9.0	63.8 ± 10.3
Sex	Male	88	45	43
	Female	27	5	22
Symptoms	Stroke	41	25	16
	TIA	34	22	12
	Others[3)]	15	3	12
	Asymptomatic[4)]	25	0	25
Period[5)] (months)		4.5 ± 7.1	3.8 ± 4.5	5.7 ± 9.7

[1)] Unilateral occlusion or severe stenotic lesion (> 98%), [2)] Unilateral stenosis of 70-98 %, [3)] Other minor symptoms such as headache, ischemic occulopathy etc., [4)] Stenosis in aymptomatic patients was found by MRA or US in health check up, [5)] Mean interval between ischemic events and the PET examination. Asymptomatic patients were excluded in calculation.

Table 2. Changes in physiological data and CBF (mean ± SD) in 115 patients under two conditions

	Baseline	ACZ	Difference[1)]
pH	7.42 ± 0.03	7.42 ± 0.03	0.002 ± 0.025
$P_{a}CO_2$ (mmHg)	39.9 ± 3.5	38.5 ± 3.4[*]	- 1.4 ± 2.6
$P_{a}O_2$ (mmHg)	78.0 ± 9.5	90.9 ± 11.2[*]	13.0 ± 10.3
tO_2c (%)	16.8 ± 2.2	17.5 ± 2.3[*]	0.7 ± 0.6
Ht (%)	38.9 ± 4.9	39.9 ± 5.0	0.9 ± 1.2
Mean Blood Pressure (mmHg)	96.8 ± 12.1	98.9 ± 14.2	2.2 ± 6.9
CBF (mL/100g/min)			% Change
Ipsilateral hemisphere	35.9 ± 6.3[‖]	44.4 ± 11.0[†,‡]	23.6 ± 21.8[‡]
Contralateral hemisphere	38.2 ± 5.4	52.0 ± 9.6[†]	36.2 ± 17.5

ACZ: acetazolamide, $P_{a}CO_2$: arterial carbon dioxide tension, $P_{a}O_2$: arterial oxygen tension, tO_2c: total arterial oxygen content, Ht: hematocrit, % change = [(post-ACZ CBF) – (baseline CBF)] / (baseline CBF) × 100 %

[1)] Mean ± SD of the absolute change in each subject for each parameter

[*]$p < 0.0085$ comparing physiological data in the 2 conditions using paired *t*-test (a statistically significant difference analyzed with correction for multiple comparison).

[†]$p < 0.0001$ comparing conditions before and after ACZ injection (repeated-measures ANOVA and paired *t*-test).

[‖]$p < 0.005$, [‡]$p < 0.0001$ comparing the 2 hemispheres in each condition (repeated-measures ANOVA and paired *t*-test).

Table 3. Comparing the 2 hemispheres in each group (mean ± SD)

	Occlusive (n = 50)		Stenosis (n = 65)		Control (n = 14)	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	28 hemispheres	
CBF (mL/100g/min)						
Baseline	35.0 ± 6.8$^{*,\|\|}$	38.6 ± 5.5	36.7 ± 6.2$^{\dagger,\|\|}$	38.3 ± 5.6¶	43.3 ± 5.0	
Post-ACZ	39.3 ± 10.0*,§	52.1 ± 9.3‡	48.5 ± 10.5*,‡	52.1 ± 9.9‡		
% Change	12.1 ± 19.8*	35.3 ± 16.5	32.4 ± 19.2†	36.7 ± 18.2	(37.5 ± 13.5)[1)]	
$CMRO_2$ (mL/100g/min)	2.72 ± 0.44$^{*,\|\|}$	2.91 ± 0.41	2.78 ± 0.47$^{\dagger,\|\|}$	2.88 ± 0.45	3.23 ± 0.39	
OEF (%)	47.3 ± 8.1*	44.5 ± 6.4	45.0 ± 6.2	44.6 ± 5.4	43.6 ± 3.7	
AI	1.06 ± 0.07$^{\|\|}$		1.01 ± 0.05		1.02 ± 0.01	
CBV (mL/100g)	4.25 ± 0.95†	4.00 ± 0.92	3.85 ± 0.82	3.76 ± 0.73	4.04 ± 0.54	
Physiological data	Baseline	ACZ	Baseline	ACZ	Baseline	ACZ
P_{aCO_2} (mmHg)	39.8 ± 3.3¶	38.2 ± 3.5§	40.0 ± 3.6	38.8 ± 3.5§	42.0 ± 2.8	40.6 ± 3.3
P_{aO_2} (mmHg)	77.7 ± 10.0$^{\|\|}$	90.9 ± 11.6$^{\ddagger,\|\|}$	78.4 ± 9.3$^{\|\|}$	90.9 ± 10.9$^{\ddagger,\|\|}$	93.2 ± 3.9	99.0 ± 6.1
tO_2c (%)	17.2 ± 2.3	17.9 ± 2.4	16.6 ± 2.2	17.3 ± 2.3	17.2 ± 1.6	17.6 ± 1.8
Ht (%)	39.9 ± 4.9	40.6 ± 5.2	38.3 ± 4.9	39.5 ± 5.0	39.4 ± 4.1	40.1 ± 4.2
Mean Blood Pressure (mmHg)	96.0 ± 11.3¶	98.6 ± 15.0	97.5 ± 12.6¶	99.2 ± 13.5	88.9 ± 9.4	91.7 ± 9.1

$^{*}p < 0.001$, $^{\dagger}p < 0.01$, comparing the 2 hemispheres in each group (repeated-measures ANOVA and paired *t*-test).

$^{\ddagger}p < 0.0001$, $^{\S}p < 0.01$, comparing conditions before and after ACZ injection (repeated-measures ANOVA and paired *t*-test).

$^{\|\|}p < 0.01$, $^{\P}p < 0.05$ comparing among 3 groups (ANOVA with post-hoc Scheffé's *F*-test)

% change = [(post-ACZ CBF) – (baseline CBF)] / (baseline CBF) x 100 %,

AI = asymmetry index of OEF = (ipsilateral OEF)/(contralateral OEF) in patients and = (higher OEF)/(lower OEF) in control hemispheres.

[1)]Mean of % change in the ACZ challenge was obtained in the previous study[20)].

Table 4. Diagnostic accuracy for misery perfusion (significant OEF elevation) (%)

	Sensitivity	Specificity	PPV[1)]	NPV[2)]	Accuracy
Total (N = 115)					
Baseline CBF & CVR[3)]	41.7	94.5	66.7	86.0	83.5
OEF-AI[4)]	25.0	96.7	66.7	83.0	81.7
Baseline CBF	58.3	88.0	56.0	89.0	82.6
Occlusive (N=50)					
Baseline CBF & CVR	56.3	88.2	69.2	81.1	78.0
OEF-AI	37.5	91.2	66.7	75.6	74.0
Baseline CBF	62.5	91.2	76.9	79.5	82.0

[1)]PPV = Positive predictive value, [2)]NPV = Negative predictive value, [3)]CVR = cerebrovascular reactivity, [4)]AI = asymmetry index [=(ipsilateral OEF)/(contralateral OEF)]. Diagnostic accuracy determined by OEF-AI was calculated using the threshold of AI = 1.12 (see Fig. 2B) for detection of misery perfusion.

Figure 1

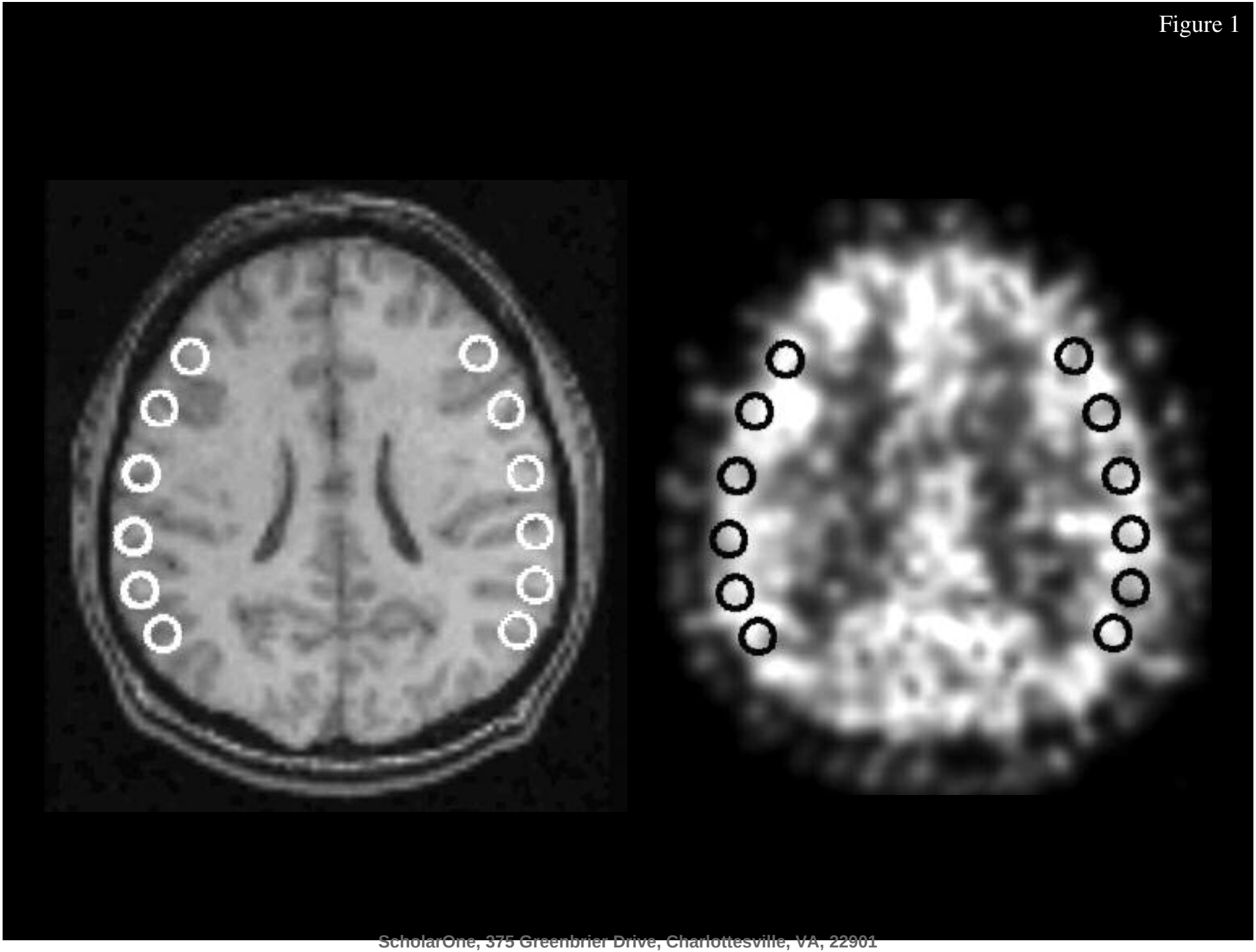


Figure 2

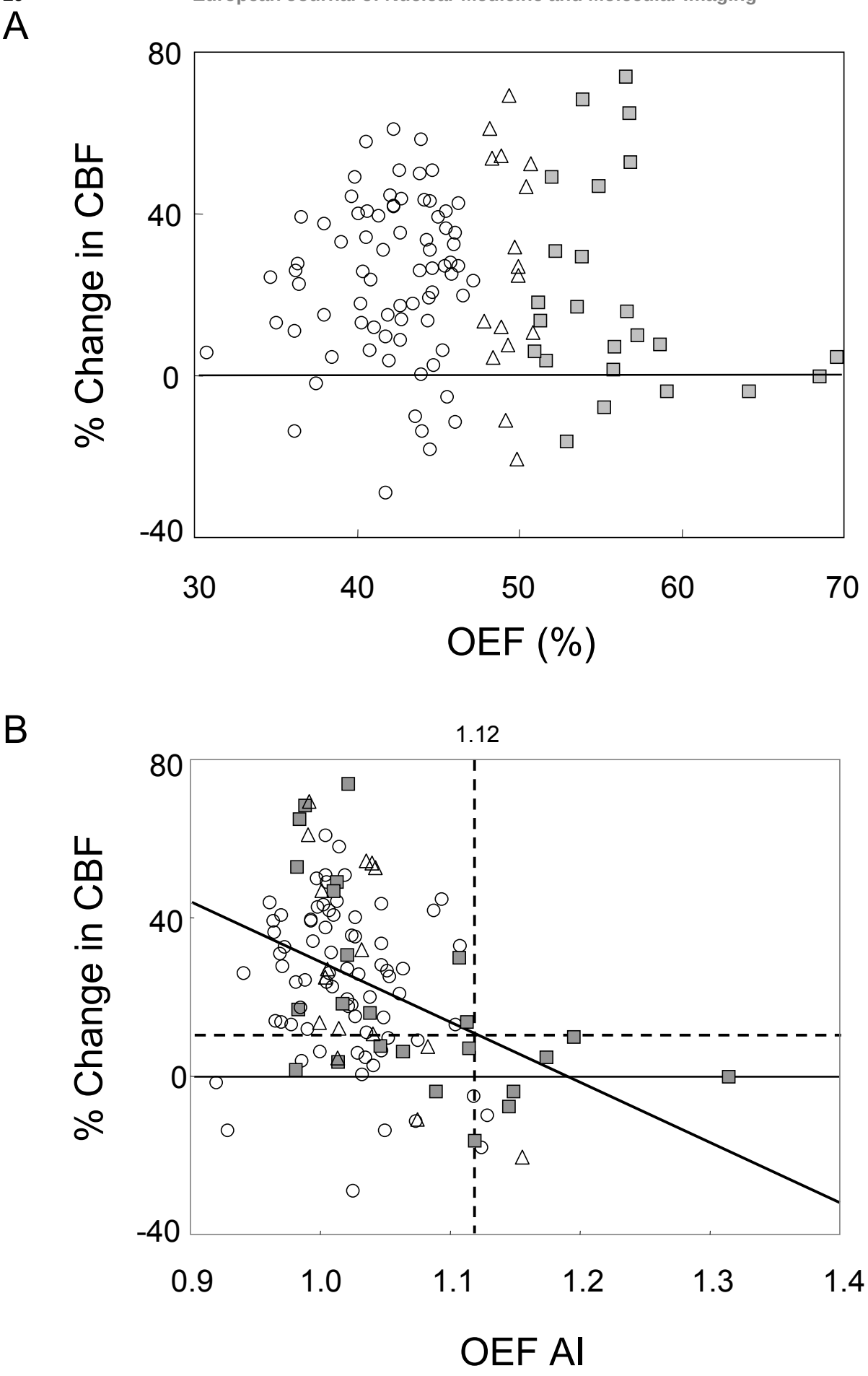
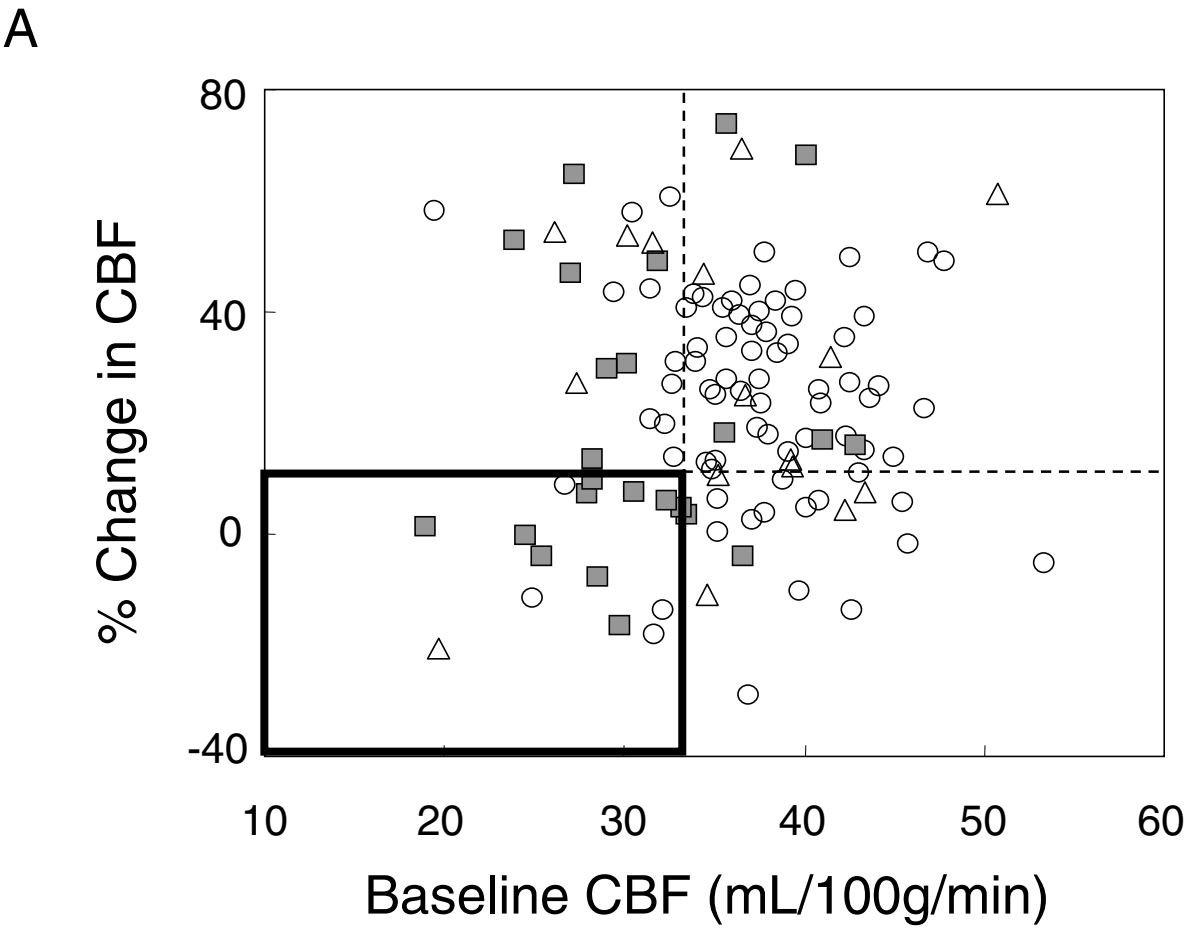

A
80
40
0
-40
% Change in CBF
30
40
50
60
70
OEF (%)
B
1.12
80
40
0
-40
% Change in CBF
0.9
1.0
1.1
1.2
1.3
1.4
OEF AI

Figure 3


A
80
40
0
-40
% Change in CBF
10
20
30
40
50
60
Baseline CBF (mL/100g/min)

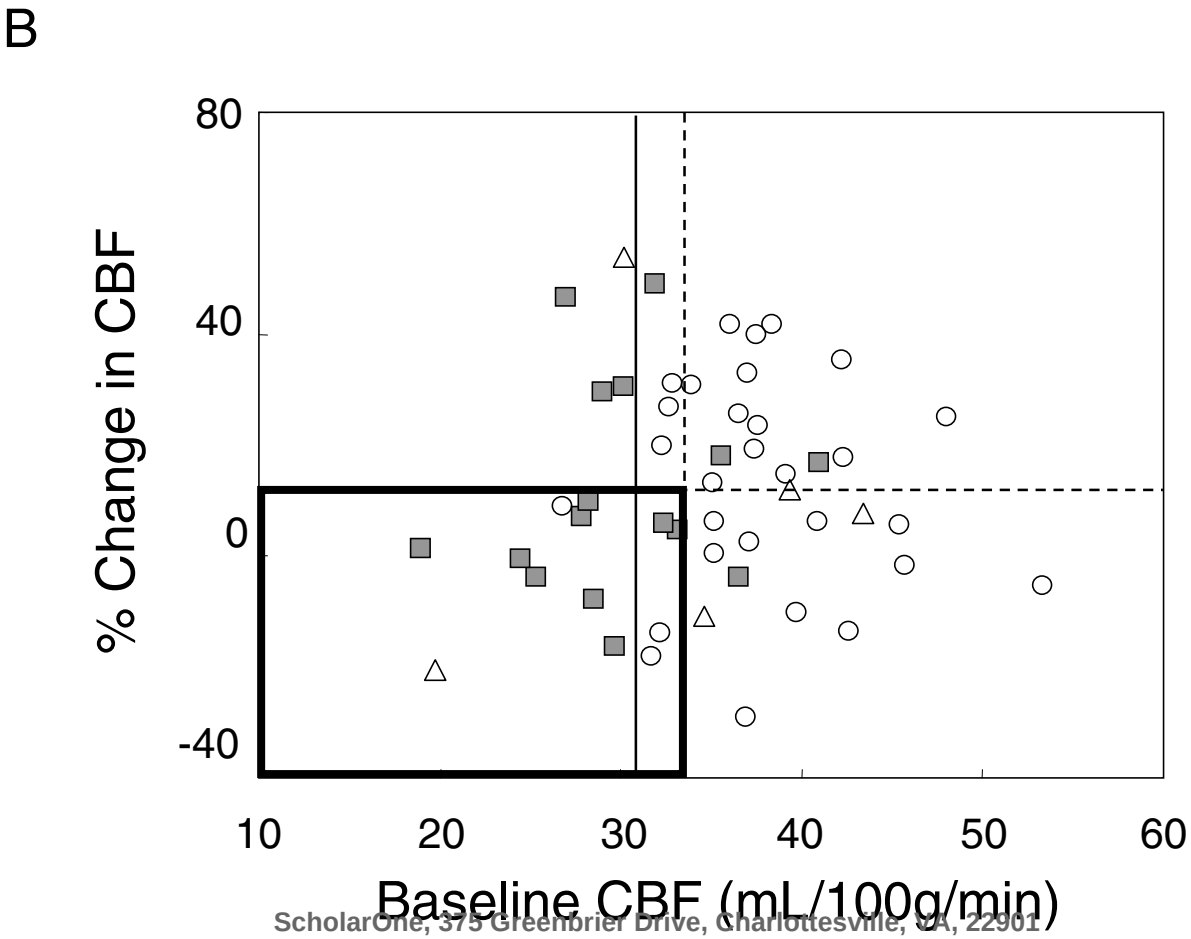

B
80
40
0
-40
% Change in CBF
10
20
30
40
50
60
Baseline CBF (mL/100g/min)

Figure 4