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Hypoxic viable tissue in human chronic cerebral ischemia due to unilateral major cerebral artery steno-occlusive disease

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Abstract

Background and Purpose: Positron emission tomography (PET) with radiolabeled 2-nitroimidazoles directly detects hypoxic but viable tissue present in an acute ischemic area in the human brain. The present study using PET with 1-(2-^{18}F-fluoro-1-[hydroxymethyl]ethoxy) methyl-2-nitroimidazole (^{18}F-FRP170) aimed to determine whether tissue with an abnormally elevated uptake of ^{18}F-FRP170 exists in human chronic cerebral ischemia due to unilateral atherosclerotic major cerebral artery steno-occlusive disease.

Methods: ^{18}F-FRP170 PET was performed, and cerebral blood flow (CBF) and metabolism were assessed using ^{15}O-gas PET in 20 healthy subjects and 52 patients. A region of interest (ROI) was automatically placed in three segments of the middle cerebral artery territory in both cerebral hemispheres with a three-dimensional stereotaxic ROI template using SPM2, and each PET value was determined in each ROI. The ratio of values in the affected versus contralateral hemispheres was calculated for the ^{18}F-FRP170 PET image.

Results: A significant correlation was observed between oxygen extraction fraction (OEF) and ^{18}F-FRP170 ratios (ρ=0.509; P<0.0001) in a total of 156 ROIs in 52 patients. The specificity and positive-predictive value for a combination of an elevated OEF and a moderately reduced cerebral oxygen metabolism for detection of an abnormally elevated ^{18}F-FRP170 ratio (19 ROIs: 12%) were significantly greater than those for the individual categories (elevated OEF, moderately reduced cerebral oxygen metabolism, or reduced CBF).

Conclusions: Tissues with abnormally elevated uptake of ^{18}F-FRP170 exist in human chronic cerebral ischemia characterized by a combination of misery perfusion and

moderately reduced oxygen metabolism due to unilateral atherosclerotic major cerebral artery steno-occlusive disease.

Cerebrovascular autoregulatory mechanisms act via dilation of precapillary resistance vessels to maintain cerebral blood flow (CBF) in the context of reductions in cerebral perfusion pressure.[1,2] However, autoregulatory capacity is not sufficient to compensate for severe reductions in cerebral perfusion pressure, thereby leading to a decline in CBF. In this context, referred to as "misery perfusion",[3] cerebral oxygen metabolism is dependent on a progressive increase in oxygen extraction fraction (OEF).[1,4] When CBF is further reduced beyond compensation of the increase in OEF, cerebral oxygen metabolism begins to decline, leading to the irreversible brain damage that characterizes cerebral infarction.

In acute ischemic stroke, the ischemic penumbra is defined as peri-infarct tissue that is functionally impaired but structurally intact and remains potentially salvageable.[5,6] Positron emission tomography (PET) using ^{15}O identifies areas of “misery perfusion” in a patient with acute ischemic stroke.[7,8] ^{18}F-fluoromisonidazole (FMISO) is a PET marker of hypoxic but viable tissue that exists in an acute ischemic area in the human brain,[9-12] and areas with uptake of the tracer reportedly are metabolically compromised tissue at risk of infarction following acute ischemic stroke.[9,10,12] The mechanism of selective retention of 2-nitroimidazoles, including FMISO, in hypoxic tissue is not clearly understood but may involve nitroreductases. Nitroimidazole molecules enter cells by passive diffusion and undergo nitroreduction to products that are covalently bound to intracellular macromolecules. These products are reoxidized and diffuse out of the cells under normoxic conditions, while remaining trapped by macromolecules within cells under hypoxic conditions.[13-15] Therefore, PET with radiolabeled 2-nitroimidazoles may allow detection of hypoxic tissue,[16] although the products of the tracer also remain trapped when cells are no longer hypoxic after

recovery of perfusion.[17]

In chronic cerebral ischemia due to severe stenosis of the cervical internal carotid artery (ICA), preoperatively impaired cognitive function occasionally improves after carotid endarterecomy;[18] the reversible cognitive impairment is related to a state of reduction in metabolism due to moderate, but potentially reversible, downregulation of cortical neurotransmitter receptors in response to more severe reduction in brain perfusion due to ICA stenosis[19] and the cognitive improvement is associated with postoperative normalization of the cerebral metabolism followed by postoperative recovery of cerebral perfusion.[19-21] These findings suggest that functionally impaired but structurally intact tissue may exist in areas of chronic cerebral ischemia with a combination of misery perfusion and reduced cerebral metabolism and that such tissue may be viable under hypoxic conditions. To our knowledge, there is only one previous study that has imaged hypoxic tissue in the context of human chronic cerebral ischemia.[22]

While a high OEF is an indirect marker of hypoxic tissue,[23,24] a new radiolabeled 2-nitroimidazole, 1-(2-^{18}F-fluoro-1-[hydroxymethyl]ethoxy) methyl-2-nitroimidazole (^{18}F-FRP170), has been recently developed to directly image hypoxic tissue using clinical PET.[13,25-27] PET using ^{18}F-FRP170 clearly detects viable tissues under hypoxic conditions as an accumulation of the tracer in malignant brain tumors.[28,29]

Therefore, the purpose of the present study, using ^{15}O-gas and ^{18}F-FRP 170 PET, was to demonstrate the presence of tissue with abnormally elevated uptake of ^{18}F-FRP170 in the context of human chronic cerebral ischemia due to unilateral atherosclerotic major cerebral artery steno-occlusive disease.

Subjects and Methods

Healthy subjects

This study evaluated 20 healthy male subjects aged 30 to 67 years (mean, 55 years) who underwent screening based on past history, physical examination, and neurological and cognitive testing. The subjects had no past history of hypertension, diabetes mellitus, atrial fibrillation, or pulmonary disease, and magnetic resonance (MR) imaging did not reveal any organic lesions, leukoaraiosis or asymptomatic lacunar infarction.

Patients

This study also included 52 patients (18 women and 34 men) aged 42 to 82 years (mean, 62 years) with unilateral middle cerebral artery (MCA) or ICA steno-occlusive diseases. All patients had experienced prior cerebral ischemic events. Conventional MR imaging was performed in all patients, and no infarct in the basal ganglia, internal capsula or cerebral cortex was observed in any of the patients; 40 patients exhibited the rosary-like infarcts located at the corona radiate and/or the subcortical white matter in the centrum semiovale and/or the anterior and/or posterior watershed zone, which were defined as subcortical border zone infarction; and the remaining 12 did not have any infarction. Twenty-seven patients had transient ischemic attacks with (15 patients) or without (12 patients) definite subcortical border zone infarction on MR imaging. The remaining 25 patients had minor complete strokes with definite subcortical border zone infarction on MR imaging. Cerebral angiography with arterial catheterization or MR angiography demonstrated ICA stenosis (greater than 70%) in 8 patients, ICA occlusion

in 27 patients, MCA stenosis (greater than 50%) in 10 patients, and MCA occlusion in 7 patients. No patient had occlusion or stenosis of greater than 50% in the contralateral ICA or MCA.

The study protocol was approved by the local ethics committee, and all subjects gave written informed consent before the study.

Positron Emission Tomography

PET studies were performed using a SET-3000GCT/M scanner (PET/CT; Shimadzu Corp.).[30] This modality uses gadolinium silica oxide detectors and provides 59 slices with 2.6 mm slice thickness. The axial field of view was 156 mm, and the spatial resolution was 3.5 mm FWHM at 1 cm in-plane and 4.2 mm FWHM at center axially. The scanner was operated in static scan mode with dual-energy window acquisition for scatter correction. The coincidence time window was set to 10 ns. A shield module consisting of 7 mm thick lead plates attached to the gantry bed and covering the breast and shoulder of the subject was used to reduce the counting rate of random coincidence and scatter coincidence attributable to radioactivity outside the field of view.

Before the emission scans, a transmission scan (3 min) with a ^{137}Cs point source was performed with a bismuth germanate transmission detector ring coaxially attached to the gadolinium silica oxide emission detector ring. CBF was determined while the subject continuously inhaled $C^{15}O_2$ through a mask. Measurements of $CMRO_2$ and OEF were obtained during continuous inhalation of $^{15}O_2$. Data were collected for 5 min. A single breath of $C^{15}O$ was used to measure cerebral blood volume. CBF, $CMRO_2$ and OEF were calculated using the steady state method,[31] and $CMRO_2$ and OEF were

corrected by cerebral blood volume.[32]

The ^{18}F-FRP170 was synthesized using on-column alkaline hydrolysis according to previously described methods.[27] The final formulation for injection was prepared in normal saline containing 2.5 % v/v ethanol using solid-phase extraction techniques. At 60 min after intravenous injection of approximately 370 MBq of ^{18}F-FRP170, data were collected for 10 min.[29]

Patients underwent PET studies more than two months after the last ischemic event, and the interval between ^{15}O-gas PET and ^{18}F-FRP170 PET ranged from one to four days.

Data Analysis

All PET images were transformed into the standard brain size and shape by linear and nonlinear transformation using SPM2 for anatomic standardization.[33] Thus, brain images from all subjects had the same anatomic format. Three hundred and eighteen constant regions of interest (ROIs) were automatically positioned in both cerebral hemispheres using a three-dimensional stereotaxic ROI template (3DSRT) with SPM2 (FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan).[34] The ROIs were grouped into ten segments (callosomarginal, pericallosal, precentral, central, parietal, angular, temporal, posterior, hippocampus, and cerebellar) in each hemisphere according to the arterial supply. Of these ten segments, the precentral and central segments were combined and defined as an ROI of the frontal cortex perfused by the MCA ($ROI_{f\text{-}MCA}$); the parietal and angular segments were combined and defined as an ROI of the parietal cortex perfused by the MCA ($ROI_{p\text{-}MCA}$); the temporal segment was defined as an ROI of the temporal cortex perfused by the MCA ($ROI_{t\text{-}MCA}$) (**Figure I in the online-only Data**

Supplement). CBF, $CMRO_2$ and OEF on ^{15}O-gas PET images were measured in the $ROIs_{f\text{-}MCA}$, $ROIs_{p\text{-}MCA}$ and $ROIs_{t\text{-}MCA}$ in the cerebral hemisphere ipsilateral to the lesion. Radioactive counts on ^{18}F-FRP170 PET images were measured in the bilateral $ROIs_{f\text{-}MCA}$, $ROIs_{p\text{-}MCA}$ and $ROIs_{t\text{-}MCA}$; the ratio of the value in the affected cerebral hemisphere to that in the contralateral cerebral hemisphere was then calculated for each ROI in ^{18}F-FRP170 PET images.

Healthy subjects were assigned to one of two groups, each consisting of 10 subjects who underwent ^{15}O-gas PET or ^{18}F-FRP170 PET assessments. In the former group, CBF, $CMRO_2$, and OEF were measured in the bilateral hemispheric ROIs. In the latter group, the ^{18}F-FRP170 ratio was calculated when the left cerebral hemisphere was defined as the affected side; mean and standard deviation (SD) of the ^{18}F-FRP170 ratio was then calculated in each ROI ($ROIs_{f\text{-}MCA}$, $ROIs_{p\text{-}MCA}$ or $ROIs_{t\text{-}MCA}$). Of these three MCA ROIs, the highest value of the mean+2 SDs of ^{18}F-FRP170 ratio was determined. Any patient with an MCA ROI with ^{18}F-FRP170 ratio greater than the highest value was defined as having an abnormally elevated ^{18}F-FRP170 ratio.

In addition, mean data in the whole MCA territory ($ROIs_{whole\text{-}MCA}$ = mean value of [$ROIs_{f\text{-}MCA}$ + $ROIs_{p\text{-}MCA}$ + $ROIs_{t\text{-}MCA}$]) in healthy subjects and patients were calculated and analyzed in the same manner as that for each MCA ROI ($ROIs_{f\text{-}MCA}$, $ROIs_{p\text{-}MCA}$ or $ROIs_{t\text{-}MCA}$).

Statistical Analysis

Data are expressed as the mean ± SD. Differences in various parameters between the controls and patients were evaluated using the Mann-Whitney U test. Correlations between various parameters were determined using the Spearman's rank correlation

coefficient. Statistical significance was set at the $P<0.05$ level. To verify an assumption that the ^{18}F-FRP170 ratio is abnormally elevated when the CBF or $CMRO_2$ is reduced or the OEF is elevated and to investigate which of these three parameters or which combination is more strongly associated with an abnormally elevated ^{18}F-FRP170 ratio, the accuracy of using CBF, $CMRO_2$ or OEF to detect an abnormally elevated ^{18}F-FRP170 ratio was determined using a receiver operating characteristic (ROC) curve. When a CBF or $CMRO_2$ in an MCA ROI in a patient was less than the cut-off point lying closest to the left upper corner of the ROC curve for detection of an abnormally elevated ^{18}F-FRP170 ratio, the ROI was categorized as having a reduced CBF or $CMRO_2$, respectively; when a OEF in an MCA ROI in a patient was greater than the cut-off point lying closest to the left upper corner of the ROC curve for detection of an abnormally elevated ^{18}F-FRP170 ratio, the ROI was categorized as having an elevated OEF. Exact 95% confidence intervals (CIs) of sensitivity, specificity, positive- and negative-predictive values were computed using the binomial distributions. The differences in sensitivity, specificity, positive- or negative-predictive values between the categories of reduced or elevated PET value were analyzed using the 95% CIs.

Results

Mean, SD and range of ^{18}F-FRP170 ratio, CBF, $CMRO_2$, and OEF in $ROIs_{f\text{-}MCA}$, $ROIs_{p\text{-}MCA}$ and $ROIs_{t\text{-}MCA}$ in 10 healthy subjects and 52 patients are shown in **Table 1**. ^{18}F-FRP170 ratios did not differ between healthy subjects and patients in all three MCA ROIs. CBF and $CMRO_2$ were significantly lower in patients than in healthy subjects in all three MCA ROIs, while OEF was significantly greater in patients than in healthy

subjects in $ROIs_{f\text{-}MCA}$ and $ROIs_{t\text{-}MCA}$; in $ROIs_{p\text{-}MCA}$, OEF did not differ between healthy subjects and patients. The mean+2 SDs of ^{18}F-FRP170 ratio obtained in healthy subjects was 1.094 for $ROIs_{f\text{-}MCA}$ and $ROIs_{p\text{-}MCA}$; 1.092 for $ROIs_{t\text{-}MCA}$. Thus, when ^{18}F-FRP170 ratio in each MCA ROI in each patient was >1.094, the ROI was defined as having an abnormally elevated ^{18}F-FRP170 ratio. As a result, of the 156 ROIs in 52 patients, 19 (12%) were classified as having abnormally elevated ^{18}F-FRP170 ratio.

Figure 1 compares the ^{18}F-FRP170 ratio and CBF in each ROI from the patients, with no significant correlation identified between the two parameters. The sensitivity, specificity, positive- and negative-predictive values for CBF at the cut-off point lying closest to the left upper corner of the ROC curve for detection of an abnormally elevated ^{18}F-FRP170 ratio are shown in **Figure II in the online-only Data Supplement** and **Table 2**. The cut-off point was 35.9 ml/100 g/min (**Figure 1**) and an ROI with CBF less than this value was categorized as having a reduced CBF. The value represents mean – 1.5 SD (for $ROIs_{f\text{-}MCA}$ and $ROIs_{p\text{-}MCA}$) or mean – 1.8 SD (for $ROIs_{t\text{-}MCA}$) of the control value obtained from healthy subjects. The lowest CBF of ROIs with an abnormally elevated ^{18}F-FRP170 ratio was 23.7 ml/100 g/min.

Figure 2 compares ^{18}F-FRP170 ratio and $CMRO_2$ in each ROI from the patients. Again, no significant correlation was identified between the two parameters. The sensitivity, specificity, positive- and negative-predictive values for $CMRO_2$ at the cut-off point lying closest to the left upper corner of the ROC curve for detecting an abnormally elevated ^{18}F-FRP170 ratio are shown in **Figure II in the online-only Data Supplement** and **Table 2**. The cut-off point was 3.31 ml/100 g/min (**Figure 2**) and an ROI with $CMRO_2$ less than this value was categorized as having a reduced $CMRO_2$. The value represents mean – 0.4 SD (for $ROIs_{f\text{-}MCA}$) or mean – 0.6 SD (for $ROIs_{p\text{-}MCA}$

and $ROIs_{t\text{-}MCA}$) of control. Further, when the cut-off point was moved in decrements from 3.31 ml/100 g/min of $CMRO_2$, the sensitivity and positive-predictive values became 0% at a cut-off point of 2.51 ml/100 g/min (**Figure 2**), which represents mean – 2.4 SD (for $ROIs_{f\text{-}MCA}$ and $ROIs_{t\text{-}MCA}$) or mean – 2.0 SD (for $ROIs_{p\text{-}MCA}$) of control. When $CMRO_2$ less than 2.51 ml/100 g/min or between 3.31 ml/100 g/min and 2.51 ml/100 g/min was categorized as severely or moderately reduced, respectively, the specificity for a moderately reduced $CMRO_2$ for detection of an abnormally elevated ^{18}F-FRP170 ratio was significantly greater than that for a reduced $CMRO_2$ (**Table 2**).

Figure 3 compares the ^{18}F-FRP170 ratio and OEF in each ROI from the patients. The correlation between the two was significant (P<0.0001), with a correlation coefficient of 0.509. The sensitivity, specificity, positive- and negative-predictive values for OEF in the cut-off point lying closest to the left upper corner of the ROC curve for detecting an abnormally elevated ^{18}F-FRP170 ratio are shown in **Figure II in the online-only Data Supplement** and **Table 2**. The cut-off point was 46.3% (**Figure 3**) and an ROI with OEF greater than this value was categorized as having an elevated OEF. The value represents mean + 1.6 SD (for $ROIs_{f\text{-}MCA}$) or mean + 1.3 SD (for $ROIs_{p\text{-}MCA}$ and $ROIs_{t\text{-}MCA}$) of control. Further, the specificity and positive-predictive value for a combination of an elevated OEF and a moderately reduced $CMRO_2$ for detection of an abnormally elevated ^{18}F-FRP170 ratio were significantly greater than those for the individual categories (elevated OEF, moderately reduced $CMRO_2$, or reduced CBF); significant differences in the sensitivity and negative-predictive value were not observed among the combined category and the individual categories (**Figure 3**, **Table 2**).

Mean data in the $ROIs_{whole\text{-}MCA}$ in healthy subjects and patients and analysis

in the same manner as that for each MCA ROI are presented in **Tables I and II, Figures III, IV and V in the online-only Data Supplement**.

Representative PET images in one patient with an abnormally elevated ^{18}F-FRP170 ratio are shown in **Figures 4**.

Discussion

The present study used ^{15}O-gas and ^{18}F-FRP 170 PET to demonstrate that tissues with abnormally elevated uptake of ^{18}F-FRP170, a direct marker of hypoxic but viable tissue, are present in human chronic cerebral ischemia with a combination of misery perfusion and moderately reduced oxygen metabolism due to unilateral atherosclerotic major cerebral artery steno-occlusive disease.

The rosary-like infarcts located at the subcortical white matter in the centrum semiovale or the anterior or posterior watershed zone are associated with hemodynamic impairment in ICA occlusive diseases.[35] The same pattern infarcts located at the corona radiate appears to be related to hemodynamic impairment in MCA occlusive diseases.[36] These infarcts were defined as subcortical border zone infarction and the present study tried to enroll patients with such infarcts to investigate relationship between misery perfusion and ^{18}F-FRP 170 PET findings.

PET with ^{18}F-FMISO has been commonly used to detect hypoxic tissue.[37-39] However, ^{18}F-FMISO has various limitations, such as slow accumulation in hypoxic tissues, low target-to-background contrast, and significant amounts of radioactive metabolic products.[28,40] The ^{18}F-FMISO agent is relatively lipophilic, whereas high hydrophilicity is associated with rapid blood clearance and high target-to-background

ratios.[28] In contrast, the ^{18}F-FRP 170 used in the present study has high image contrast, fast clearance[28], and readily crosses the blood-brain barrier;[25] therefore, it is more suitable for visualizing hypoxic brain tissue than ^{18}F-FMISO.[28] Interestingly, a study using intratumoral oxygen pressure measurements with microelectrodes during resection of malignant glioma has directly demonstrated that an accumulation on ^{18}F-FRP 170 PET represents viable tissue under the hypoxic condition.[29]

While hypoxic tissue exhibiting increased uptake of ^{18}F-FMISO may be doomed to die in acute stroke, a recent study using diffusion/perfusion MR or CT perfusion imaging and ^{18}F-FMISO in acute ischemic stroke demonstrated that ^{18}F-FMISO trapping overlapped the ischemic core presented as high intensity on diffusion MR as well as the ischemic penumbra.[41] PET studies using ^{15}O in acute stroke also often show a high OEF in the ischemic core as well as the ischemic penumbra, suggesting that the ischemic core under such conditions may remain viable at the time when PET is performed, although it is likely to die soon after that.[23,24] Thus, cerebral tissue with increased uptake of ^{18}F-FMISO in acute ischemia may represent a situation where increased OEF is combined with reduced $CMRO_2$, which corresponded with our results using ^{15}O-gas and ^{18}F-FRP 170 PET in chronic ischemia.

In the present study, while a positive correlation was observed between the OEF and ^{18}F-FRP170 ratios, the area with an elevated OEF did not exhibit an elevated ^{18}F-FRP170 ratio when the area had a normal $CMRO_2$. Several investigators showed that the degree of ^{18}F-FMISO uptake is often greater in the ischemic core than in the ischemic penumbra in acute ischemia.[41] Oxygen metabolism is theoretically reduced to a greater degree in the core versus penumbra. Thus, reduced $CMRO_2$ in addition to increased OEF may be an essential characteristic of hypoxic tissue in cerebral ischemia.

In contrast, areas with severely reduced $CMRO_2$ did not exhibit elevated ^{18}F-FRP170 ratios, suggesting that the cerebral tissue in these areas might be non-viable.

Kuroda et al.[42] suggested that reduced CBF in the normal-appearing cerebral cortex includes two pathophysiologically different conditions: misery perfusion due to hemodynamic compromise; and matched hypometabolism due to border zone infarction. ^{18}F-FRP170 ratio may be elevated in the former condition. In contrast, for the latter condition, border zone infarction may cause selective neuronal damage in the normal-appearing cerebral cortex beyond the regions of infarcts, resulting in reduced metabolism in the cerebral cortex.[43] In addition, metabolism in the cerebral cortex with border zone infarction may be reduced due to diaschisis from the infarction.[43] Under such conditions, CBF was reduced with reduction in cerebral metabolism, resulting in non-elevated OEF and non-elevated ^{18}F-FRP170 ratio. This may be a reason why the majority of areas with an abnormally elevated ^{18}F-FRP170 ratio exhibited reduced CBF, although no correlation between CBF and ^{18}F-FRP170 ratios was observed. In addition, the lowest CBF of ROIs with an abnormally elevated ^{18}F-FRP170 ratio was 23.7 ml/100 g/min. CBF in the ischemic penumbra is reported to be < 20 ml/100 g/min.[23] Our data suggested that non-infarcted tissue under hypoxic conditions may exist in the chronic ischemic regions with CBF values above the penumbra threshold.

Hypoxic tissue presenting as increased uptake of ^{18}F-FMISO is metabolically compromised and at risk of infarction following acute ischemic stroke.[9,10,12] Our data suggested that cerebral tissue may become hypoxic when oxygen metabolism begins to decline at the end stage of misery perfusion with deterioration of chronic cerebral ischemia due to atherosclerotic major cerebral artery steno-occlusive disease. If this hypothesis is correct, the following research questions are raised. Does hypoxic tissue

presenting as increased uptake of ^{18}F-FRP170 in chronic cerebral ischemia subsequently succumb to irreversible brain damage over time? Does the hypoxic tissue disappear with recovery of CBF and oxygen metabolism after arterial reconstructive surgery? Is the disappearance of hypoxic tissue associated with improvement of cerebral function including cognition? Further studies aimed at answering these questions would be of benefit.

Conclusions

The present study using ^{15}O-gas and ^{18}F-FRP 170 PET demonstrated that tissue with an abnormally elevated uptake of ^{18}F-FRP170, a direct marker of hypoxic but viable tissue, is present in human chronic cerebral ischemia with a combination of reduced perfusion, moderately reduced oxygen metabolism and misery perfusion due to unilateral atherosclerotic major cerebral artery steno-occlusive disease.

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Disclosures

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Figure Legends

Fig. 1

Correlation between cerebral blood flow (CBF) and 1-(2-^{18}F-fluoro-1-[hydroxymethyl]ethoxy) methyl-2-nitroimidazole (^{18}F-FRP170) ratio in patients. The dashed horizontal line denotes mean + 2 standard deviations (SD) of ^{18}F-FRP170 ratios obtained in healthy subjects. The dashed vertical line denotes 35.9 ml/100 g/min, which represents mean – 1.5 SD (for region-of-interest of the frontal cortex perfused by the middle cerebral artery [$ROI_{f\text{-}MCA}$] and region-of-interest of the parietal cortex perfused by the middle cerebral artery [$ROIs_{p\text{-}MCA}$]) or mean – 1.8 SD (for region-of-interest of the temporal cortex perfused by the middle cerebral artery [$ROIs_{t\text{-}MCA}$]) of CBF obtained in healthy subjects.

Fig. 2

Correlation between cerebral metabolic rate of oxygen ($CMRO_2$) and ^{18}F-FRP170 ratio in patients. The dashed horizontal line denotes mean + 2 SD of ^{18}F-FRP170 ratios obtained in healthy subjects. The right and left dashed vertical lines denote 3.31 ml/100 g/min and 2.51 ml/100 g/min, respectively. The former represents mean – 0.4 SD (for $ROIs_{f\text{-}MCA}$) or mean – 0.6 SD (for $ROIs_{p\text{-}MCA}$ and $ROIs_{t\text{-}MCA}$) of $CMRO_2$ obtained in healthy subjects; the latter represents mean – 2.4 SD (for $ROIs_{f\text{-}MCA}$ and $ROIs_{t\text{-}MCA}$) or mean – 2.0 SD (for $ROIs_{p\text{-}MCA}$) of $CMRO_2$ obtained in healthy subjects.

Fig. 3

Correlation between oxygen extraction fraction (OEF) and ^{18}F-FRP170 ratio in

patients. The dashed horizontal line denotes mean + 2 SD of ^{18}F-FRP170 ratios obtained in healthy subjects. The dashed vertical line denotes 46.3%, which represents mean + 1.6 SD (for $ROIs_{f\text{-}MCA}$) or mean + 1.3 SD (for $ROIs_{p\text{-}MCA}$ and $ROIs_{t\text{-}MCA}$) of OEF obtained in healthy subjects. Open, half-tone and closed circles denote $CMRO_2$ > 3.31 ml/100 g/min, between 3.31 ml/100 g/min and 2.51 ml/100 g/min, < 2.51 ml/100 g/min, respectively.

Fig. 4

Positron emission tomography (PET) images from a 63-year-old woman with symptomatic right middle cerebral artery occlusion. CBF is severely reduced, $CMRO_2$ is moderately reduced, and OEF is elevated in the right temporal cortex when compared with the left cerebral hemisphere. That region exhibits relatively high accumulation of ^{18}F-FRP170.

Table 1. PET values obtained from healthy subjects and patients in $ROIs_{f\text{-}MCA}$, $ROIs_{p\text{-}MCA}$ and $ROIs_{t\text{-}MCA}$

		Healthy subjects (N = 10* or 20†)	Patients (N = 52‡)	P value
$ROIs_{f\text{-}MCA}$				
^{18}F-FRP170 ratio	Mean	1.000	1.013	
	SD	0.047	0.058	
	Range	0.925-1.055	0.893-1.180	
				N.S.
CBF (ml/100 g/min)	Mean	46.8	38.6	
	SD	7.2	7.6	
	Range	34.7-57.4	23.7-50.2	
				0.0032
$CMRO_2$ (ml/100 g/min)	Mean	3.44	3.07	
	SD	0.38	0.57	

	Range	2.78-3.83	1.76-3.85	
				0.0477
OEF (%)	Mean	37.9	42.0	
	SD	5.4	5.3	
	Range	31.8-46.2	35.7-60.6	
				0.0336
$ROIs_{p\text{-}MCA}$				
^{18}F-FRP170 ratio	Mean	1.000	1.017	
	SD	0.047	0.063	
	Range	0.935-1.057	0.845-1.182	
				N.S.
CBF (ml/100 g/min)	Mean	47.7	38.2	
	SD	7.7	7.5	
	Range	35.0-56.8	23.7-50.0	
				0.0013

$CMRO_2$ (ml/100 g/min)	Mean	3.65	3.13	
	SD	0.56	0.48	
	Range	2.99-4.41	1.99-3.87	
				0.0176
OEF (%)	Mean	40.8	42.6	
	SD	4.4	5.3	
	Range	35.1-48.3	36.9-60.2	
				N.S.
$ROIs_{t\text{-}MCA}$				
^{18}F-FRP170 ratio	Mean	1.000	1.011	
	SD	0.046	0.057	
	Range	0.935-1.076	0.889-1.172	
				N.S.
CBF (ml/100 g/min)	Mean	47.2	39.1	
	SD	6.3	7.3	

	Range	36.6-57.4	24.2-50.3	
				0.0019
$CMRO_2$ (ml/100 g/min)	Mean	3.60	3.13	
	SD	0.45	0.48	
	Range	3.07-4.34	1.99-3.87	
				0.0336
OEF (%)	Mean	39.5	42.4	
	SD	5.2	5.4	
	Range	32.1-45.9	35.7-58.6	
				0.0493

*, ^{18}F-FRP170 ratio of ROI; †, CBF, $CMRO_2$ and OEF of bilateral hemispheric ROIs; ‡, ^{18}F-FRP170 ratio of ROI and CBF, $CMRO_2$ and OEF of ROI in the hemisphere ipsilateral to lesion.

Table 2. Sensitivity, specificity, PPV and NPV for each PET value for detection of an abnormally elevated ^{18}F-FRP170 ratio

	Reduced CBF	Reduced $CMRO_2$	Moderately reduced $CMRO_2$	Elevated OEF	Elevated OEF and moderately reduced $CMRO_2$
	CBF <35.9 ml/100 g/min	$CMRO_2$ <3.31 ml/100 g/min	$CMRO_2$ <3.31 ml/100 g/min and >2.51 ml/100 g/min	OEF >46.3%	OEF >46.3% and 2.51 ml/100 g/min< $CMRO_2$ <3.31 ml/100 g/min
Sensitivity	89% (17/19)	89% (17/19)	89% (17/19)	79% (15/19)	68% (13/19)
95% CIs	76-103%	76-103%	76-103%	61-97%	48-89%
Specificity	70% (96/137)	55% (75/137)	78% (107/137)	91% (124/137)	99% (135/137)

95% CIs	62-78%	46-63%	71-85%*	86-95%	97-101%†
PPV	29% (17/58)	22% (17/79)	36% (17/47)	54% (15/28)	87% (13/15)
95% CIs	18-41%	12-31%	22-50%	35-71%	72-104%†
NPV	98% (96/98)	97% (75/77)	98% (107/109)	97% (124/128)	96% (135/141)
95% CIs	95-101%	94-101%	96-101%	94-100%	92-99%

PPV, positive-predictive value; NPV, negative-predictive value; *, significantly greater than reduced $CMRO_2$; †, significantly greater than reduced CBF, moderately reduced $CMRO_2$, or elevated OEF.