Misery Perfusion and Tau Deposition in Atherosclerotic Major Cerebral Artery Disease: A 18 F-Florzolotau Positron Emission Tomography Study

Article *in* Stroke · November 2022

DOI: 10.1161/STROKEAHA.122.040493

CITATION
1

READS
20

5 authors, including:

Hiroshi Yamauchi
Kyoto University
147 PUBLICATIONS **5,012** CITATIONS
SEE PROFILE

Chio Okuyama
Shiga Medical Center Research Institute
83 PUBLICATIONS **1,049** CITATIONS
SEE PROFILE

Stroke

BRIEF REPORT

Misery Perfusion and Tau Deposition in Atherosclerotic Major Cerebral Artery Disease: A ^{18}F-Florzolotau Positron Emission Tomography Study

Hiroshi Yamauchi, MD, PhD; Shinya Kagawa, PhD; Kuninori Kusano, RT; Miki Ito, RT; Chio Okuyama, MD, PhD

BACKGROUND: Studies using animal models have shown that cerebral hypoperfusion causes hyperphosphorylation of tau protein, leading to neuronal damage. However, the relationship between hypoperfusion and tau deposition in humans is unclear. Hence, we aimed to determine whether cerebral hypoperfusion leading to decreased blood flow relative to metabolic demand [increased oxygen extraction fraction (OEF), misery perfusion] is associated with increased tau deposition in patients with atherosclerotic internal carotid artery or middle cerebral artery disease.

METHODS: We prospectively evaluated the distribution of tau aggregate deposition using positron emission tomography and ^{18}F-florzolotau (PMPBB3 [1-fluoro-3-((2-((1E,3E)-4-(6-(methylamino)pyridine-3-yl)buta-1,3-dien-1-yl)benzo[d]thiazol-6-yl) oxy)propan-2-ol)]) in 8 patients with atherosclerotic disease of the internal carotid artery or middle cerebral artery. The standardized uptake value ratio of ^{18}F-florzolotau at 100 to 110 minutes after injection was calculated using the cerebellar cortex as a reference region and was correlated with OEF obtained from ^{15}O-gas positron emission tomography in the middle cerebral artery distributions.

RESULTS: Significant decreases in cerebral blood flow and cerebral metabolic rate of oxygen and increases in OEF were found in the hemisphere ipsilateral to the arterial lesion. ^{18}F-florzolotau standardized uptake value ratio in this region was also greater than that in the contralateral hemisphere. In the ipsilateral hemisphere, ^{18}F-florzolotau standardized uptake value ratio positively correlated with OEF values.

CONCLUSIONS: This pilot study with a small sample size suggests that increases in OEF–misery perfusion–may be associated with increased tau aggregates deposition in atherosclerotic internal carotid artery or middle cerebral artery disease.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cerebrovascular disorders ■ perfusion ■ positron emission tomography ■ tau protein

Studies using animal models have shown that cerebral ischemia causes hyperphosphorylation of tau protein.[1] Tau hyperphosphorylation causes the dissociation of tau from microtubules and increases the propensity for self-oligomerization and fibril formation, which may lead to neuronal degeneration in the course of neurofibrillary tangle formation.[1] However, the relationship between cerebral hypoperfusion and tau deposition in humans is unclear.

See related article, p XXX

Correspondence to: Hiroshi Yamauchi, MD, PhD, Department of Psychiatry, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawahara-cho, Kyoto 606-8507, Japan. Email yamauchi@kuhp.kyoto-u.ac.jp

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.122.040493.
For Sources of Funding and Disclosures, see page xxx.

Stroke is available at www.ahajournals.org/journal/str

BRIEF REPORT

Nonstandard Abbreviations and Acronyms

CBF	cerebral blood flow
CBV	cerebral blood volume
CMRO$_2$	cerebral metabolic rate of oxygen
MCA	middle cerebral artery
OEF	oxygen extraction fraction
PET	positron emission tomography
ROI	region of interest
SUVR	standardized uptake value ratio

Recently, the development of tau ligands for positron emission tomography (PET) has enabled the in vivo visualization of tau aggregate deposition in humans. However, to the best of our knowledge, no studies have demonstrated the association of cerebral hypoperfusion with tau deposition. ^{18}F-florzolotau, a second-generation tau ligand, has recently become available for tau imaging.[2]

In this study, we evaluated the degree of cerebral hypoperfusion and tau deposition in patients with atherosclerotic internal carotid artery or middle cerebral artery (MCA) disease using ^{15}O-gas PET and ^{18}F-florzolotau PET to determine whether an increased oxygen extraction fraction (OEF)–misery perfusion[3]–is associated with an increase in tau aggregate deposition.

METHODS

Detailed methods are available in the Supplemental Material. This article follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline (https:www.goodreports.org). Additional data can be made available via the corresponding author to qualified researchers upon reasonable request.

Subjects

We studied 8 male patients aged 69±6 years (mean±SD) with symptomatic atherosclerotic occlusion or stenosis of the internal carotid artery or MCA within an 18-month period (Table S1). We also studied the 10 healthy controls (5 men and 5 women) aged 55±11 years.

All protocols were approved by the Shiga General Hospital Institutional Review Board and the Human Study Committee (approval number: 20201020-01). All the participants provided written informed consent.

Positron Emission Tomography

We performed PET scans using a whole-body PET/computed tomography scanner, the Siemens True Point Biograph 16 (Siemens/CTI, Erlangen, Germany).[4]

Patients received ^{18}F-florzolotau by slow intravenous injection.[2] A 10-minute static PET acquisition was performed 100 minutes after injections. The standardized uptake value (SUV) for ^{18}F-florzolotau was calculated as follows: SUV=C (kBq/mL)/ID (kBq)/body weight (g), where C represents the tissue activity concentration measured by PET and ID is the injected dose.

^{15}O-gas experiments were performed the day after the ^{18}F-florzolotau study.[5] We calculated the cerebral blood flow (CBF), cerebral metabolic rate of oxygen (CMRO$_2$), and OEF using the steady-state method.[5]

Data Analysis

For ^{18}F-florzolotau PET scanning analysis, we employed a template-based predefined region of interest (ROI) approach using an in-house computed tomography template.[4] The SUV ratio (SUVR) of each region that indicates tau deposition was calculated as follows: SUVR=SUV brain/SUV cerebellar cortex.[2]

To obtain quantitative regional SUVR values, we performed automated ROI analyses. The automated anatomical labeling atlas was used for the template-based predefined ROIs.[6]

The mean MCA values were calculated as the average of the SUVR value of the anatomical labeling atlas ROIs for the cerebral cortex within the MCA distribution. The ROIs including cerebral infarction were excluded from the analysis.

Statistical Analysis

PET variable values between the 2 hemispheres were compared using Wilcoxon signed-rank tests. The relationships between the 2 variables were analyzed using Spearman correlation analysis. Multiple linear regression analysis (forward stepwise selection) was used to assess the independent predictive value of the CBF, CMRO$_2$, and OEF with respect to the ^{18}F-florzolotau SUVR. Statistical significance was set at $P<0.05$.

RESULTS

Significant decreases in CBF and CMRO$_2$ along with increases in OEF were found in the hemisphere ipsilateral to the arterial lesion compared with the contralateral hemisphere. Also, ^{18}F-florzolotau SUVR values were higher in this region than those in the contralateral hemisphere (Table).

The ^{18}F-florzolotau SUVR was positively correlated with OEF (ρ=0.83, P=0.027; Figures 1 and 2). One patient with the highest OEF value exhibited an increased SUVR value beyond the control range. Six patients exhibited increased SUVR ratios (ipsilateral to contralateral

Table. Positron Emission Tomography Values in the Hemisphere Ipsilateral and Contralateral to the Diseased Artery

	Hemisphere	
Variable	Ipsilateral	Contralateral
CBF, mL/(100 g per min)	27.7±3.5*	30.5±4.1
CMRO$_2$, mL/(100 g per min)	2.09±0.21*	2.20±0.28
OEF, %	46.3±7.0*	44.2±7.7
^{18}F-florzolotau (SUVR)	0.86±0.09*	0.84±0.09

Values are reported as mean±SD. CBF indicates cerebral blood flow; CMRO$_2$, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction; and SUVR, standardized uptake value ratio.

*P=0.0117 versus contralateral hemisphere.

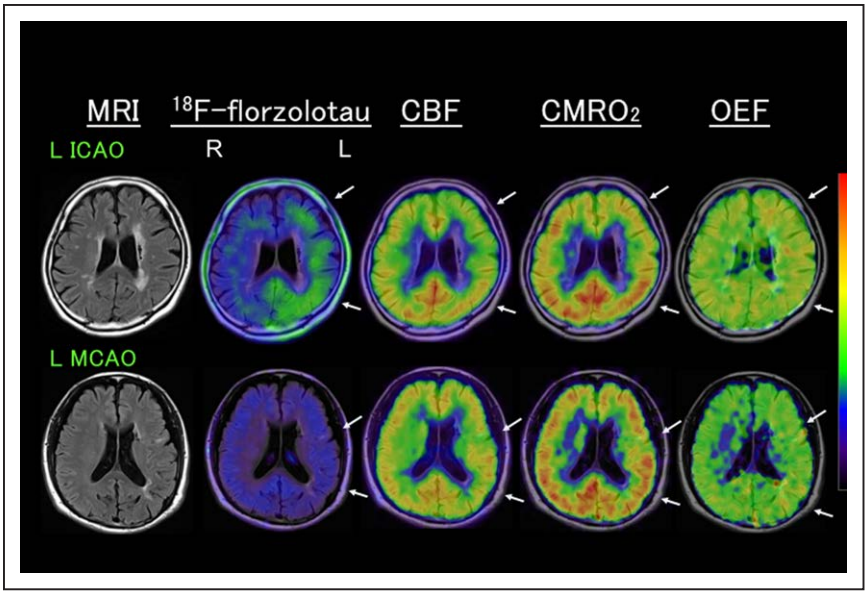

Figure 1. Representative positron emission tomography images.
Upper, Increased ^{18}F-florzolotau standardized uptake value ratio (SUVR; 0.94, ipsilateral/contralateral, 1.12), with decreased cerebral blood flow (CBF) and increased oxygen extraction fraction (OEF; 50.5%), despite a reduction in cerebral metabolic rate of oxygen ($CMRO_2$), in a patient with left (L) internal carotid artery occlusion (ICAO) (fetal type). Note a relatively lower 18F-florzolotau uptake in the anterior middle cerebral artery (MCA) region with a relatively lower $CMRO_2$. Lower row: a low ^{18}F-florzolotau SUVR (0.77, ipsilateral/contralateral, 1.02) in a patient with LMCA occlusion (O) with mild decreases in both CBF and $CMRO_2$ and normal OEF (46.0%). Arrows indicate the affected regions. Both patients were negative for amyloid positron emission tomography (PET).[7] MRI indicates magnetic resonance imaging. R indicates right.

ratio) beyond the control range (median, 1.016, range, 1.0–1.121).

There was no significant correlation between ^{18}F-florzolotau SUVR and CBF (ρ=–0.21, P=0.57) or $CMRO_2$ (ρ=0.02, P=0.94). However, multiple linear regression analysis created a model including the values of OEF (%; coefficient: 0.012, P<0.005) and $CMRO_2$ (mL/100 g per min; coefficient: 0.207, P<0.05) with a correlation coefficient of 0.92 for the ^{18}F-florzolotau SUVR (P<0.01).

There was no correlation between ^{18}F-florzolotau SUVR and the time elapsed from symptoms (ρ=–0.57, P=0.12) or from the diagnosis of artery diseases (ρ=0.43, P=0.25).

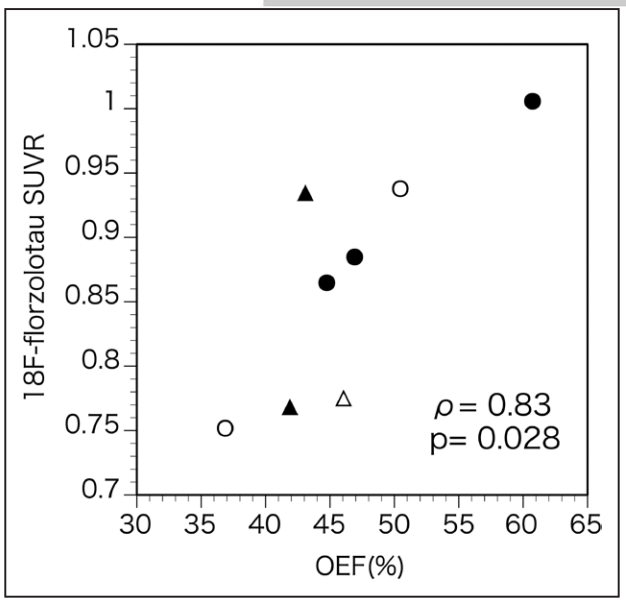

Figure 2. Scatter diagram plotting the ^{18}F-florzolotau standardized uptake value ratio (SUVR) against the value of oxygen extraction fraction (OEF) in the hemisphere with arterial diseases.
Open symbols, left diseases; closed symbols, right diseases; circles, carotid artery diseases; triangles, middle cerebral artery diseases.

DISCUSSION

To our knowledge, this is the first study showing an increase in tau deposition in patients with misery perfusion caused by atherosclerotic internal carotid artery or MCA disease. Increased ^{18}F-florzolotau SUVR in the noninfarcted cerebral cortex was associated with increased OEF.

Hypoperfusion leading to decreased CBF relative to $CMRO_2$ and, in turn, to an increase in OEF (misery perfusion) may be associated with an increase in neurofibrillary tau deposition. In the hemisphere ipsilateral to the arterial lesion with a reduction in CBF and $CMRO_2$ and an elevation in OEF, ^{18}F-florzolotau SUVR was increased compared with the contralateral hemisphere. The ^{18}F-florzolotau SUVR was positively correlated with OEF, which suggested that misery perfusion, defined as an increased OEF, was associated with increased tau deposition. ^{18}F-florzolotau SUVR was not correlated with CBF. This may be because the decrease in the CBF may reflect not only misery perfusion but also secondary CBF decreases due to the decreased $CMRO_2$ by tissue damage or deafferentation.

The decrease in $CMRO_2$ was correlated with a decrease in ^{18}F-florzolotau SUVR. Misery perfusion may cause cortical neuronal damage, which may be accompanied by decreases in $CMRO_2$.[7] As shown in Figure 1, in the hemisphere with increased ^{18}F-florzolotau uptake and OEF, a relatively lower ^{18}F-florzolotau uptake was observed in the anterior MCA region with a relatively lower $CMRO_2$. We speculate that increases in tau deposition due to misery perfusion might not have occurred or might have disappeared in the region with cortical neuronal loss.

BRIEF REPORT

An increased ^{18}F-florzolotau SUVR value beyond the control range was found in only one patient, who showed an SUVR value slightly above the reported threshold for healthy controls and patients with Alzheimer disease.[2] Although 6 patients exhibited increased SUVR hemispheric ratios, the magnitude of the increases was small. However, the distribution of ^{18}F-florzolotau SUVR values was heterogenous, and the mean MCA values may miss regional increases in SUVR values.

The mechanisms of tau aggregation in the face of hypoperfusion are yet to be elucidated. Chronic hypoperfusion induces tau hyperphosphorylation and deposition.[1] The pathological changes of tau may be caused by oxidative stress, autophagy, excitotoxicity, inflammation, endothelium and angiogenesis, and mitochondrial dysfunction, in ischemic stroke.[1] Increased tau deposition on PET in this study may reflect other processes than neurodegenerative tauopathy.

We acknowledge some limitations. First, the sample size is small, and the patients included only men and a mixture of internal carotid artery and MCA diseases. Furthermore, patients and controls were not matched or age and sex. Additional studies with a larger number of patients are needed to confirm our results. Second, we did not perform correction of multiple comparisons in the statistical analyses since this was an exploratory study, and the use of multiple regression analysis would be inappropriate due to the small sample size. Third, the assessment of amyloid uptake would be valuable for the correct interpretation of the results. However, we could assess amyloid uptake only in 2 patients (both negative). Lastly, we could not correct for partial-volume effects. This effect might lead to the underestimation of ^{18}F-florzolotau SUVR.

ARTICLE INFORMATION

Received June 29, 2022; final revision received September 13, 2022; accepted September 21, 2022.

Affiliations

Department of Psychiatry, Graduate School of Medicine, Kyoto University, Japan (H.Y.). Division of PET Imaging, Shiga Medical Centre Research Institute, Moriyama, Japan (S.K., K.K., M.I., C.O.).

Acknowledgements

The precursor of florzolotau was provided by APRINOIA Therapeutic, Inc (Tokyo, Japan).

Sources of Funding

This study was funded by Japan Society for the Promotion of Science KAKENHI (Grant Number: 22K07683).

Disclosures

None.

Supplemental Material

Supplemental Methods
Table S1
STROBE Statement

REFERENCES

1. Chen X, Jiang H. Tau as a potential therapeutic target for ischemic stroke. *Aging (Albany NY)*. 2019;11:12827–12843. doi: 10.18632/aging.102547
2. Tagai K, Ono M, Kubota M, Kitamura S, Takahata K, Seki C, Takado Y, Shinotoh H, Sano Y, Yamamoto Y, et al. High-contrast in vivo imaging of tau pathologies in alzheimer's and non-alzheimer's disease tauopathies. *Neuron*. 2021;109:421–58.e8. doi: 10.1016/j.neuron.2020.09.042
3. Baron JC, Bousser MG, Rey A, Guillard A, Comar D, Castaigne P. Reversal of focal "misery-perfusion syndrome" by extra-intracranial arterial bypass in hemodynamic cerebral ischemia. A case study with ^{15}O positron emission tomography. *Stroke*. 1981;12:454–459. doi: 10.1161/01.str.12.4.454
4. Higashi T, Nishii R, Kagawa S, Kishibe Y, Takahashi M, Okina T, Suzuki N, Hasegawa H, Nagahama Y, Ishizu K, et al. (18)F-FPYBF-2, a new F-18-labelled amyloid imaging PET tracer: first experience in 61 volunteers and 55 patients with dementia. *Ann Nucl Med*. 2018;2018:206–216. doi: 10.1007/s12149-018-1236-1
5. Okazawa H, Yamauchi H, Sugimoto K, Takahashi M, Toyoda H, Kishibe Y, Shio H. Quantitative comparison of the bolus and steady-state methods for measurement of cerebral perfusion and oxygen metabolism: Positron emission tomography study using ^{15}O gas and water. *J Cereb Blood Flow Metab*. 2001;21:793–803. doi: 10.1097/00004647-200107000-00004
6. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002;15:273–289. doi: 10.1006/nimg.2001.0978
7. Baron JC, Yamauchi H, Fujioka M, Endres M. Selective neuronal loss in ischemic stroke and cerebrovascular disease. *J Cereb Blood Flow Metab*. 2014;34:2–18. doi: 10.1038/jcbfm.2013.188