Am J Nucl Med Mol Imaging 2023;13(2):51-63
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0149470

Review Article

Stroke and molecular imaging: a focus on FDG-PET

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Received February 2, 2023; Accepted March 23, 2023; Epub April 25, 2023; Published April 30, 2023

Abstract: Stroke is the leading cause of disability worldwide, the second most common cause of dementia and the third leading cause of death. Though the etiology of stroke has been explored extensively, there remains open questions in the scientific and clinical study of stroke. Traditional imaging techniques, such as magnetic resonance imaging and computed tomography, have been applied extensively and remain mainstays in clinical practice. Nevertheless, positron emission tomography has proven to be a powerful molecular imaging tool in exploring the scientific aspects of neurological disease, and stroke remains an area of great interest. This review article examines the role of positron emission tomography in the study of stroke including its contributions to elaborating related pathophysiology and delving into possible clinical applications.

Keywords: PET, stroke, ischemic stroke, infarction, molecular imaging

An overview of stroke

Strokes are broadly defined as an acute reduction of cerebrovascular blood flow (CBF) which often culminates in subsequent loss of normal neuronal function and potential irreversible tissue injury. Immediate causes assist in categorizing strokes as ischemic or hemorrhagic (**Figure 1**). Ischemic strokes refer to a lack of circulatory delivery leading to ischemia whereas hemorrhagic strokes are defined as a loss of structural vascular integrity precipitating in hemorrhage and distal ischemia [1]. Ischemic stroke is of particular interest as it accounts for most strokes and can further be caused by thrombotic, embolic, systemic hypoperfusion, and venous thrombotic causes.

The combination of factors including specific causes, affected region of the cerebrovascular circulation, and prevalence of collaterals often determines the resultant effect of the stroke [2]. The ischemic stroke culminates in a core region of cerebral tissue where blood supply is severely restricted, and necrosis occurs. Radially distal to the core exists the penumbra where blood flow is limited to a less extreme magnitude. Penumbra tissues have reduced functioning but take longer to undergo necrosis. Depending on the location of the stroke, clinical manifestations vary respectively [1].

The pathophysiological consequence of cerebral ischemia is of great interest. The primary insult appears to be the lack of oxygen delivery that compromises oxidative phosphorylation, which is the main source of ATP production. Subsequent neuronal dysfunction culminates in an inability to maintain membrane potential and subsequently, a loss of membrane integrity [3]. Importantly, physiological blood flow allows for the exchange of local cellular byproducts, which can accumulate to harmful levels during acute stasis. Following the initial insult, secondary injury signals, including free radicals and inflammatory cytokines, further exacerbate cellular damage. Returning blood flow, often as a result of treatment, can solve the aforementioned issues but may also lead to reperfusion injury [4].

Patients presenting with acute neurological deficits consistent with stroke often undergo

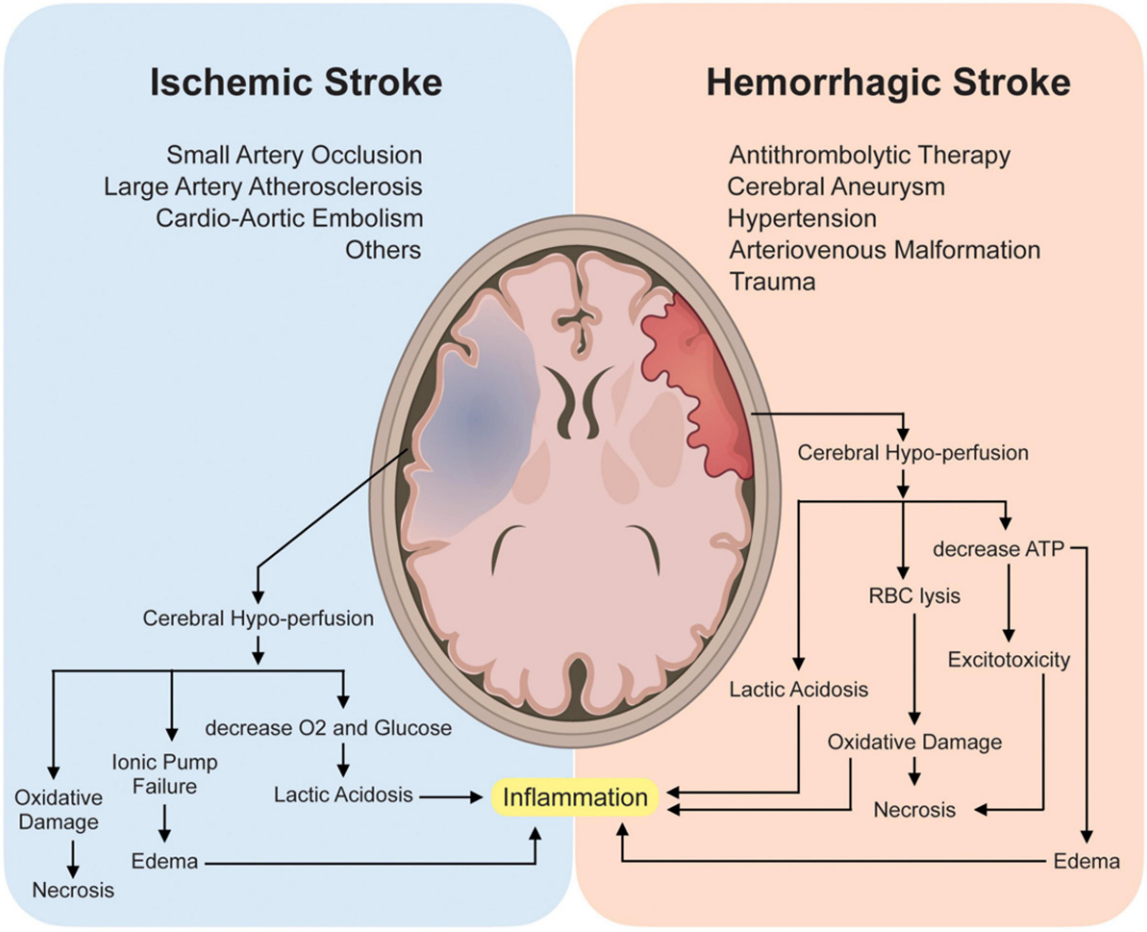

Figure 1. The diagram illustrates the pathophysiology of the two main types of strokes: ischemic stroke (left) and hemorrhagic (right). Reproduced with permission from Peng et al. [7].

computed tomography (CT) scans to differentiate ischemic from hemorrhagic stroke. Occasionally, patients with negative CT images are taken for magnetic resonance imaging (MRI) in proper settings to better characterize the etiology of the neurological deficits [5]. Absent radiological evidence of hemorrhagic stroke, patients are primed for intervention should proper clinical criteria be met. Specifically, patients may undergo thrombolytic therapy which targets thrombo-embolic strokes by "clot busting" and restoring perfusion. Patients with occlusions in larger arteries may be candidates for mechanical thrombectomy which is an interventional procedure that resolves the occluding structure within the artery; notably, interventional procedures are not available in lower resource settings [2].

The core region of the stroke is subject to liquefactive necrosis and not salvageable regardless of intervention. Often the penumbra can be rescued from complete necrosis though function may or may not be fully recovered. Post-stroke patient courses may be complicated with seizures, aspiration, decline of respiratory drive, hemorrhage, pain syndromes, etc. [6]. However, recovery of function in the penumbra often correlates to improvements in neurological deficits in the short-term. On the scale of weeks to months, other recovery processes may occur to differing degrees allowing for the regaining of function [4]. Interventions that have proven to aid in functional recovery include rigorous physical therapy, nerve stimulation, etc.

An overview of PET imaging and exemplary applications in stroke

Positron Emission Tomography (PET) is fundamentally a functional imaging modality which

relies upon the biological activities of radiolabeled molecules, known as radiotracers, that often mimic the structures of biological substances in the body. For instance, fluorine-18 fluoro-2-deoxy-D-glucose (FDG) is a glucose analogue that is radiolabeled with fluorine-18 [8]. These qualities of FDG allow the molecule to mirror the distribution of glucose and process of glycolysis in the body upon intravenous administration. As the radiotracer's isotope decays and expels positrons, the PET scanner is able to deduce the spatial location of the radiotracer thus allowing for the complete ascertainment of tracer distribution in the anatomical region scanned [9].

In research and clinical contexts, there are efforts taken to ensure that PET scans can be compared among patients and benchmarks with respect to radiotracer uptake. Further advancements in reconstruction, resolution enhancement, and unbiased quantitative measure of radiotracer concentration have taken place including partial volume correction [8]. Of note is the standardized uptake value (SUV) which is an accepted method in which one can standardize radiotracer concentration by augmenting the measure by radiotracer injection activity by a measure of initial injection radiotracer activity, decay rate, and a normalizing factor such as body weight. Further, normalization can be performed using body surface area or even ratios between the region of interest measured and a background region unrelated to the inquiry of interest. Alternatively, some studies take more accurate, though invasive, measures using compartmental kinetic analysis and the Ki coefficient [10].

FDG-PET has proven to be a useful technique in characterizing metabolic activity and certain inflammatory processes. As it pertains to stroke, FDG-PET is a method that can be used to assess the pathophysiology of the stroke in many contexts. FDG-PET brain imaging has shown decreased metabolic activity in regions of ischemia and necrosis, but in perihematomal regions associated with hemorrhagic stroke higher uptake was observed. With respect to etiology, PET's ability to measure inflammation allows for superior measurement of atherosclerosis and plaque vulnerability compared to structural measures [11]. On the contrary, similar modalities such as NaF-PET give way to displaying long-term arterial wall microcalcification [12]. FDG-PET has also been widely used to image metabolic activity in the brain in the context of the ischemic insult. Post-stroke recovery remains a complex process that is augmented by other factors including age, stroke size, and use of therapy [13].

PET has been applied in conjunction with other methods such as transcranial magnetic stimulation (TMS) to better understand the mechanisms underlying post-stroke brain reorganization regarding clinical recovery and therapeutic strategies. Repetitive TMS (rTMS) has been used in attempts to improve upper extremity motor function in post-stroke patients though its mechanisms remain uncertain [14]. Using a rTMS/PET protocol with fMRI-guided stimulation (n = 18 healthy controls, n = 2 stroke patients), Conchou et al. [15] compared the effects of rTMS on cerebral blood flow to the primary motor cortex, contralateral to the side of movement. Repetitive TMS to the contralesional primary motor cortex led to increased cerebral blood flow and increased activation in the primary sensory-motor areas with hand motor testing, which was exclusive to the stroke population. Though severely limited in sample size, these findings along with large fMRI studies of rTMS implicate substantial roles for contralesional hemisphere reorganization and motor cortex plasticity in post-stroke motor recovery [15, 16].

Though not of focus here, various tracers have proven to offer utility in studying stroke. A study conducted by Dundar et al. [11] used F-FDG, 11C-Choline, and 68Ga-DOTATATE. Choline tracers have been used extensively in prostate cancer research as a measure of choline kinase activity, which increases in hypoxic cells; DOTATATE acts as a somatostatin analogue that interacts with the respective receptor. Greater 11C-Choline and 68Ga-DOTATATE uptake was observed in patients with acute or subacute ischemic stroke. It was explained that increasing choline uptake in inflammatory and repair processes relate to stroke. 68Ga-DOTATATE uptake correlated with carotid somatostatin receptor subtype 2 mRNA levels; this allowed 68Ga-DOTATATE uptake to correctly differentiate culprit carotid arteries from non-culprit carotid arteries in patients with transient ischemic attack or stroke.

FDG PET imaging of the corporal arteries

FDG-PET has allowed for detection of arterial loci which correlate to inflammatory events that are predictable markers of unstable atherosclerosis and potentially thromboembolic events.

Van der Valk et al. [17] enrolled 83 patients (25 healthy patients, 23 patients with increased risk of cardiovascular disease (CVD), and 35 patients with diagnosed CVD) and found significant differences between the healthy and diseased patients in all 18F-FDG uptake measurements from the carotids and aorta. The 90th percentile maximum target to background ratio (TBR) SUVs in healthy patients were 1.84 and 2.68 in the carotids and aorta, respectively. Fifty-two percent of patients with elevated CVD risk and 67% of diagnosed CVD patients exhibited higher TBR SUVs. From this, the authors concluded to have established a baseline threshold for 18F-FDG uptake in major vessels, including in healthy patients, and confirmed that 18F-FDG PET was a reproducible marker of inflammation. However, they also noted that the small sample size limits generalizability and heightens the need for future, larger studies.

Tawakol et al. [18] had shown that TBR SUV is strongly correlated with the degree of plaque in patients using histological analysis. Several studies have demonstrated that arterial FDG uptake can be a potential biomarker for high-risk carotid plaques that ultimately lead to ischemic stroke events in patients, including Rominger et al. [19] and Müller et al. [20]. S. Kim et al. [21] used FDG-PET/CT to explore differences in carotid artery inflammation between acute coronary syndrome (ACS, n = 39) and chronic stable angina (CSA, n = 35) patients in Seoul. Like Hyafil et al. [22], carotid PET signals via TBR SUV were significantly higher in ACS than CSA patients bilaterally, and high-sensitivity C-reactive protein (hs-CRP) also showed a significant association with carotid FDG uptake bilaterally. As such, the authors concluded ACS survivors may have bilateral carotid inflammation; they hypothesized systemic immune activation leading to arterial dysfunction (via disseminated trans-coronary neutrophil activation with coronary plaque instability) and subsequent symptomatic atherosclerosis could be a linkage between ACS and ischemic stroke. Multiple similarly designed FDG-PET studies of patients with symptomatic internal carotid artery stenosis and atherosclerosis found serum LDL and total cholesterol were associated with carotid plaque inflammation and FDG uptake thereby corroborating a significant role of lipids in plaque development [23-25].

Studies have suggested that FDG PET can identify vulnerable plaques when used in conjunction with structural imaging modalities. Carotid ultrasound of plaques has been shown to help stratify patients by stroke risk, where Græbe et al. [26] report that FDG-PET further improves stroke risk prediction by quantifying active levels of inflammation among high-risk plaques. Piri et al. [27] reported positive correlations between FDG uptake and CT imaging parameters such as vessel wall, lipid-rich necrotic core, and fibrous tissue volumes. On the contrary, FDG localization has been shown to negatively correlate with carotid artery calcium scoring via CT imaging. MRI imaging of vessel wall volume, fibrous tissues volume, plaque ruptures, and intra-plaque hemorrhage has also been found to be more prevalent with FDG uptake [27].

Hyafil et al. [22] used combined FDG-PET/MRI in a sample of 18 patients admitted for cryptogenic, ischemic stroke to evaluate morphological and biological features of non-stenotic carotid plaques (**Figure 2**). MRI was used to explore the presence of complicated lesions in the carotid arteries ipsilateral and contralateral to the stroke, while FDG-PET uptake was quantified using TBR SUV with the internal jugular vein as background. High-risk morphological plaque features and complicated lesions were observed significantly more in the carotid artery ipsilateral to the stroke (39%) relative to the contralateral side (0%). Specifically, MRI showed that ipsilateral carotid arteries exhibited significantly larger maximal wall areas and necrotic cores, while FDG PET uptake was significantly increased in ruptured atherosclerotic plaques with thin fibrous caps, particularly those > 5 mm or ones with necrotic core or intra-plaque hemorrhage. Said features could contribute to risk stratification of symptomatic patients with non-stenotic plaques and in turn, earlier diagnosis and intervention. While the authors concluded their findings highlight a potential causative role of diffuse inflammation

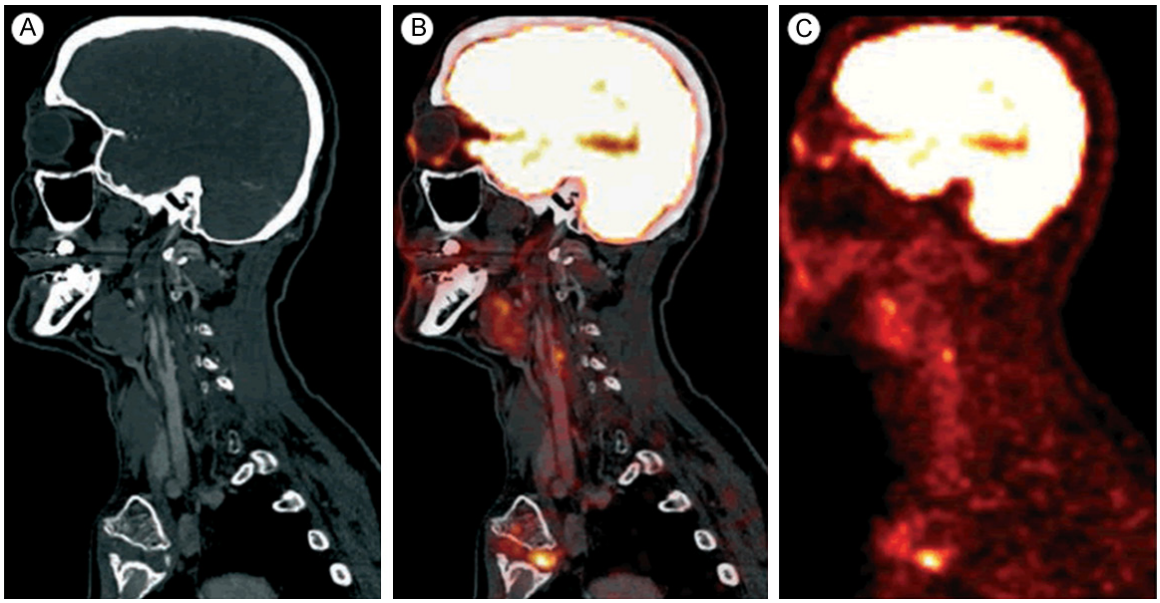

Figure 2. The left carotid contains a suspected culprit plaque in a symptomatic patient and illustrates the high FDG uptake in (A) CT angiography, (B) fused PET/CT, and (C) PET alone. Reproduced with permission from Græbe et al. [26].

and plaque formation in stroke, they acknowledged their study was limited by a small, homogenous sample, imperfect outcome measurements in TBR SUV, and a lack of histological validation of plaque morphology.

Similar limitations and fewer promising findings were noted in a case-control study by Vesey et al. [28] which assessed the efficacy of both NaF and FDG in identifying culprit and high-risk carotid plaques. Twenty-six patients with recent transient ischemic attack (TIA) or minor ischemic stroke were enrolled and divided into two groups-symptomatic stenosis while awaiting carotid endarterectomy (n = 18) and non-symptomatic stenosis as a control group (n = 8). SUVs were computed for both imaging modalities and associations between radiotracer uptake, plaque phenotype, and predicted cardiovascular risk (i.e., ASSIGN scores) were calculated. While NaF identified culprit and high-risk plaques, FDG identified no differences in overall uptake between carotid artery plaques ipsilateral to the stroke with either contralateral plaques or patients with non-symptomatic stenosis. FDG uptake was also not significantly associated with complicated plaque morphology.

Mikail et al. [29] evaluated concurrent use of FDG PET with CT angiography (CTA) as a hybrid imaging modality to evaluate non-stenotic plaque buildup in the carotid arteries of patients who suffered from strokes of unknown origin. Their analysis of 44 stroke patients (67 ± 15 years; 34% female) suggested high risk plaques are more likely to arise on the ipsilateral carotid artery versus the contralateral artery. They found that the most diseased segment TBR SUV on FDG PET was significantly higher in the ipsilateral artery compared to the contralateral artery (2.24 ± 0.80 vs. 1.84 ± 0.50; $P < 0.05$). Additionally, the ipsilateral carotid arteries had significantly greater FDG uptake (SUVmax 2.6 ± 0.8 vs. SUVmax 2.1 ± 0.6; $P = 0.001$), hypodense plaque prevalence (41% vs. 11%; $P < 0.05$), and extent of hypodense plaque (0.72 ± 1.2 mm^2 vs. 0.13 ± 0.43 mm^2; $P < 0.05$) relative to the contralateral carotid artery. The authors conclude that CTA has limited use when dealing with non-stenotic, non-calcified plaques in the carotid due to inadequate contrast between plaque and vessel lumen. Combining CTA with FDG PET helps overcome this limitation as FDG PET allows for favorable sensitivity to identify sites of inflammation which CTA could not pinpoint otherwise when used alone.

Several studies aimed to assess the robustness of FDG-PET uptake commonly used to quantify vascular inflammation, which is a

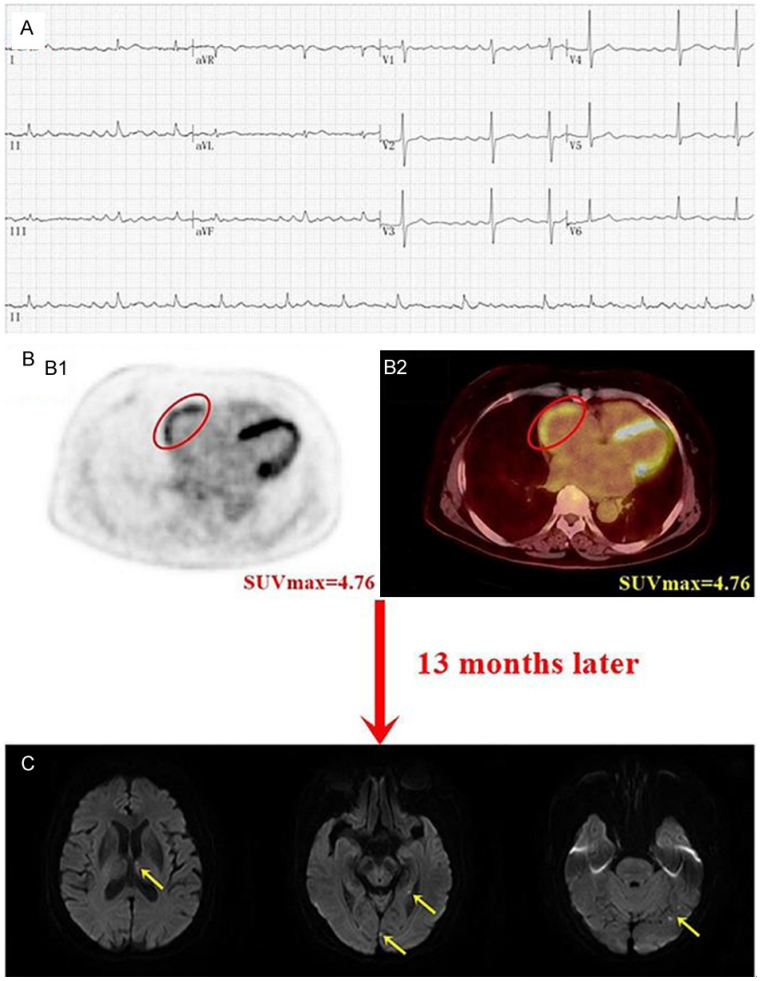

Figure 3. A 75-year-old woman with persistent atrial fibrillation for 8 years underwent positron emission tomography (PET)/computer tomography (CT) due to elevated CEA marker (final diagnosis of gastric cancer) and developed stroke after 13 months of the follow-up. (B) Shows the red oval circle outlines the RA FDG uptake (SUVmax = 4.76). (C) Shows acute infarcts in the left thalamus, hippocampus, and occipital lobe (yellow arrow) (A. Electrocardiogram; B1. PET image; B2. PET/CT image; C. DWI image). Reproduced with permission from B. Wang et al. [34].

known risk factor of stroke. Johnsrud et al. [30] assessed inter-reader variability using different methods of FDG uptake quantification. In their study of 45 patients with > 70% stenosis of the carotid artery, they found that FDG quantification methods which do not correct for background blood pooling yielded improved optimal inter-reader agreement which was in agreement with similar studies Kwee et al. [31] and Marnane et al. [32]. Johnsrud et al. assessed inter-reader variability using the intraclass correlation coefficient (ICC) and reported highest ICC for uncorrected SUVs (0.97-0.98), followed by cSUVs (0.89-0.94), TBR SUVs (0.74-0.79), and 0.77 for the background blood pool. They recommended using SUVmax in future studies that aim to assess inter-reader variability in patients who have less than 70% stenosis in the carotid artery, as ultimately 18-FDG PET's utility for clinical decision making will be best used in patients who have low grade stenosis of arteries.

Cardiac PET imaging in the prediction of stroke

Recently, there has been increased attention paid to atrial cardiomyopathy in the clinical care of ischemic stroke patients as atrial cardiomyopathy is associated with an increased risk of embolic stroke. Identifying high-risk individuals has become paramount for early intervention and prevention.

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting up to 33 million individuals worldwide. AF has been identified to increase stroke risk. Diagnosing AF continues to remain challenging as up to 40% of patients with underlying AF may not exhibit symptoms that meet diagnostic criteria [33]. Sinigaglia et al. conducted a retrospective single center study consisting of 128 matched patients with a 3D-time-of-flight PET/CT hybrid system resulting in a non-enhanced CT and a whole-body PET. Greater atrial FDG uptake was associated with a higher prevalence of stroke in atrial fibrillation patients. Multivariate analysis found that right atrium uptake of FDG tracer and active smoking were significant factors that increased stroke risk. Increased FDG uptake seen in the right atria could be related to an increased metabolic activity, cardiac remodeling, and inflammation in the right atrial tissue and endocardial cells.

B. Wang et al. [34] used right atrial FDG uptake to identify patients at increased risk for stroke (**Figure 3**). B. Wang et al. enrolled 230 patients

(115 with AF and 115 without AF) using a whole-body PET/CT resulting in an unenhanced CT and an attenuated 3D PET collection. They reported that that FDG uptake in the atria was higher in the atrial fibrillation patients compared to non-atrial fibrillation patients and that right atrium FDG uptake is an independent risk for stroke, such that FDG uptake may be better than CHA2DS2-VASc score. Multivariate Cox regression analysis suggested that high RA SUVmax was an independent risk factor for stroke (HR = 4.264, 95% CI 1.368-13.293, P = 0.012).

B. Wang et al. further constructed a ROC (receiver operating characteristic) model to evaluate predictive value of FDG uptake relative to the CHA2DS2-VASc score for stroke. The CHA2DS2-VASc score is a composition of factors including congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke, vascular disease, age 65-74 years, and sex. Three ROC (receiver operator curve) models were constructed and analyzed: high RA SUVmax, CHA2DS2-VASc score, and high RA SUVmax + CHA2DS2-VASc score. The model found: high RA SUVmax (AUC = 0.636, P = 0.016); CHA2DS2-VASc (AUC = 0.700, P < 0.001); and high RA SUVmax + CHA2DS2-VASc score (AUC = 0.790, P < 0.001). The findings suggest that addition of high RA SUVmax to the CHA2DS2-VASc score ROC model may help predict stroke more effectively, as this combined model has a larger AUC 0.790 (P < 0.001).

Similar studies have used FDG PET for other underlying cardiomyopathies to identify high risk patients. Su et al. [35] used a cohort of 1444 patients who had been hospitalized a month from an individual PET/CT scan and met exclusion criteria which included: age less than 40 years, prior history of: AF, pericardial effusion, intense left ventricular FDG uptake, hemorrhagic strokes, traumatic brain injury, cerebral cancer, cerebral infection, and cerebral surgery. Greater atrial FDG uptake was found in 196 of these patients, while 392 patients served as controls without atrial activity (matched for age, gender, and body mass index). Su et al. reported that patients with atrial cardiomyopathy had greater prevalence of activity in the atria (47.1% vs. 26.0%, P < 0.001), and patients with greater atrial activity had greater prevalence of prior ischemic strokes (12.2% vs. 3.3%, P < 0.001). After adjusting for risk factors, multivariate regression modeling suggested that ischemic stroke (OR 4.02, 95% CI 1.97-8.19, P < 0.001) and atrial cardiomyopathy (OR 3.63, 95% CI 1.51-8.74, P = 0.004) were associated with greater atrial activity.

Mild valvular disease was also identified to be associated with greater atrial FDG uptake. This finding is clinically relevant because valvular disease may induce inflammatory damage to the endothelium, fibrosis, and necrosis of cardiac tissue. More longitudinal studies are needed to prove that increased atrial FDG activity is indicative of ischemic stroke and atrial cardiomyopathy. Su et al.'s findings, if further corroborated by future, well-designed, prospective longitudinal studies, can have vast implications on clinical care of stroke patients as FDG quantitative imaging may be able to identify atrial endothelial damage, which increases risk for ischemic stroke, prior to abnormal structural findings that may be seen on electrocardiogram (ECG).

FDG PET has been useful in identifying increased risk of ischemic strokes in cancer patients. Grandpierre et al. [36] were one of the first to conduct a study investigating the link between prior arterial FDG uptake value and subsequent ischemic cerebrovascular events in cancer patients. Patients referred to FDG PET/CT for conventional oncologic indications were retrospectively included and compared. The aortic arch, from the base of the truncus brachiocephalicus to the aortic isthmus, and the carotid bifurcation regions were segmented and analyzed for uptake. Stroke correlated to the presence of FDG avid lesions in the aortic arch (stroke patients, 86% vs. Controls, 31%; P = 0.03) and more so in carotid bifurcations (stroke patients, 71% vs. Controls, 6%; P = 0.006). Carotid FDG foci show significant promise in predicting ischemic events in cancer patients given their specificity since they are only seen in 29% of atherosclerotic carotid lesions and rare in regions of carotid stenosis. Grandpierre et al.'s study had a limited number of patients and a lack of covariate (e.g., blood factors) measurements that could also play a role in the occurrence of stroke.

J. Kim et al. [37] selected 134 patients, of which 30 patients had an ischemic stroke event. Blood pool SUV was measured by creat-

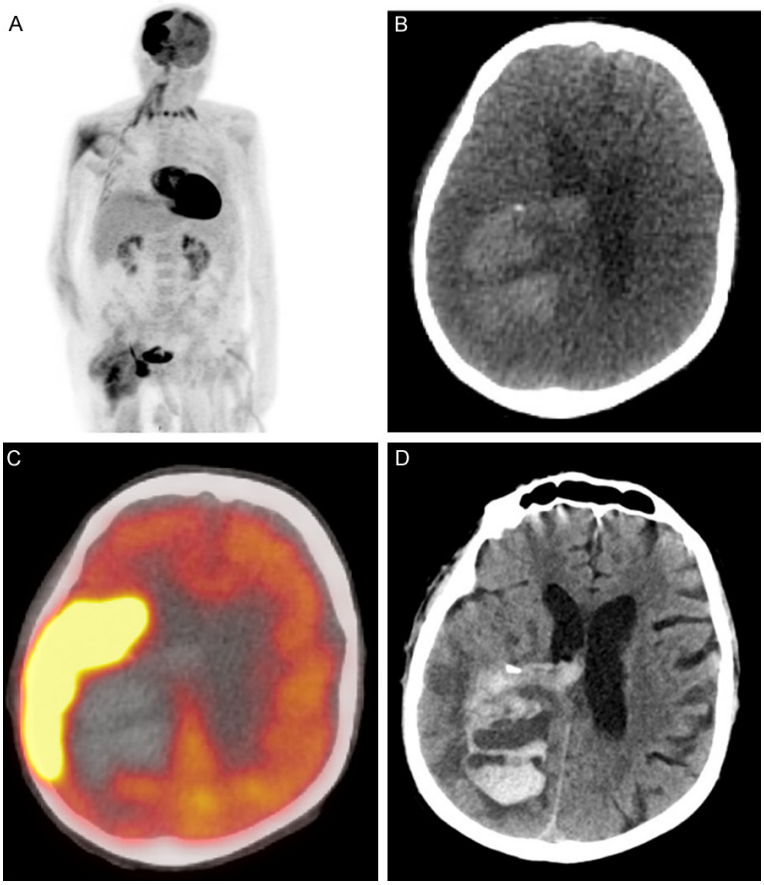

Figure 4. 64-year-old male presented with an acute hemorrhagic stroke on 18F-FDG PET/CT. Maximum intensity projection (A), non-contrast CT axial image (B), fused PET/CT axial (C), and a short-term follow-up enhanced head CT (D). Reproduced with permission from Dundar et al. [11].

ing six regions of interest in the center lumen of inferior vena cavas and internal jugular veins. Their study found that patients with strokes were more likely to have higher TBR SUV in: carotid arteries and abdominal aorta ($P < 0.001$), visceral adipose tissue ($P = 0.021$), and total adipose tissue ($P = 0.041$) compared to non-stroke patients where other arteries tended to have different, but statistically insignificant average SUV between stroke patients and non-stroke patients. Although previous studies have reported PET and CT variables to be predictive of stroke, J. Kim et al.'s study was one of the first to combine both FDG and PET/CT variables to assess stroke risk in oncology patients. The authors noted that their cohort of patients all had malignancy and thus exhibited various neurological symptoms, which could have led to a greater frequency of ischemic stroke compared to healthy controls, so they recommended future studies to include a larger cohort of cancer patients without neurological symptoms.

Brain PET imaging in stroke

The evident value of PET in stroke related to brain imaging has been of great interest (**Figure 4**). Nasu et al. [38] used 18F-FDG-PET to assess glucose metabolism in acute stroke patients with higher 18F-FDG uptake indicative of higher glucose metabolism. Twenty out of 24 stroke patients in the study showed reduced 18F-FDG uptake with seven of those 20 showing significantly increased uptake in areas around the area affected by stroke; the authors proposed increased anaerobic glycolysis as well as phagocytosis, gliosis, and neuronal excitation as possible drivers of the increased 18F-FDG uptake.

Karbe et al. [39] investigated the effect of stroke on speech production in the brain. The study found that glucose metabolism in areas of the brain related to speech was a good predictor of stroke impact including that on aphasia. Specifically, FDG uptake was characterized in patients presenting with a single lesion derived from an occlusion of the left middle cerebral artery. The CT scans showed striatocapsular infarcts in seven patients, subcortical white matter lesions in three patients, a frontal cortical lesion in one patient, parietal cortical lesions in three patients, lesions of the insular cortex in three patients, and complete or nearly complete infarcts of the left middle cerebral artery territory in five patients. Functional impairment of language as correlated to FDG uptake in language-producing regions of the brain was in turn correlated with neuronal cell death, thereby corroborating poor prognosis.

Central poststroke pain (CPSP) is a chronic neuropathic pain resulting from cerebrovascu-

lar lesions at the somatosensory pathway possibly implicating the spinothalamic pathway, thalamic nuclei, ventral posterior nucleus-pulvinar border zone, or anterior pulvinar nucleus. N.Y. Kim et al. [40] sought to analyze patients with CPSP after thalamic intracerebral hemorrhagic (ICH) stroke using FDG PET. The CPSP group showed significantly decreased brain metabolism in the ipsilesional precentral and postcentral gyri and the contralesional cuneus when compared to the controls, while significantly increased brain metabolism was found in the medial dorsal nucleus of the contralesional thalamus. Significant positive correlations of pain intensity were found in the ipsilesional Crus I and Crus II of the cerebellum. The findings suggest a change in resting neural activity is a key element in CPSP. Possible limitations included damaged white matter impacting metabolism since lesions extended to extra-thalamic areas.

CPSP can also develop in hemorrhagic pontine strokes. Choi et al. [41] sought to assess metabolic changes in patients with pontine hemorrhage without cortical involvement who developed CPSP. The CPSP group showed significant hypometabolism in the ipsilesional primary motor cortex and contralesional rostral anterior cingulum ($P < 0.001$) when compared to the control. Increased brain metabolism was observed in the contralesional cerebellum (lobule VIIB) and the ipsilesional cerebellum (VI) ($P < 0.001$). Furthermore, decreased metabolism in the ipsilesional supplementary motor area and contralesional angular gyrus corresponded to increased pain intensity.

Nevertheless, FDG-PET is not without limitations for use in brain imaging. From a technical standpoint, standardized procedures and protocols are necessary to acquire FDG-PET images and transfer them between different institutions. For instance, in a literature review of 18F-FDG-PET imaging protocols for the evaluation of atherosclerotic plaques, 53 different acquisition protocols with 46 quantification methods were noted, suggesting no consensus on the most appropriate procedures has been reached and more optimization and dissemination of best practices is necessary [42]. Second, the time between injection of the 18F-FDG radiotracer and PET imaging is often too long for diagnosis and treatment of acute conditions like stroke and conditions like transient hyperglycemia, which are commonly associated with stroke or other hyperacute events, can reduce effectiveness of this imaging [43].

FDG-PET has also been widely used in basic science animal experiments which can be advantageous when studying acute and transient phenomena such as stroke. J. Wang et al. [44] used FDG PET imaging to measure efficacy of transplanted stem cells (induced pluripotent/iPSC and embryonic/ESC) in rat models of cerebral ischemia. Twenty-four male rats were assigned across control and iPSC and ESC treatment groups with baseline status and treatment response evaluated through weekly FDG PET. Rats receiving iPSC and ESC treatment showed significantly higher FDG uptake in ipsilateral cerebral infarction regions than control rats as well as significant functional improvements. Rats treated with iPSC showed consistent increases in FDG uptake while ESC-treated rats saw uptake decrease after two weeks. Although the authors were unable to assess adverse effects, they acknowledged FDG-PET's utility in measuring therapeutic properties of stem cell therapies, particularly in future experiments with iPSC.

Wu et al. [45] applied FDG/PET to test their hypothesis that electro-acupuncture (EA) could promote cerebral glucose metabolism in rats with ischemia after middle cerebral artery occlusion (MCAO) and reperfusion injury. FDG-PET showed that EA increased glucose metabolism in the caudate putamen, somatosensory cortex, and motor cortex. These three regions also showed increased phosphorylation of AMP-activated protein kinase α (AMPKα) suggestive of increased AMPKα activation post-EA treatment in rats with MCAO.

Hwang et al. [46] used FDG PET imaging to assess regional brain changes in glucose utilization post liposomal delivery of angiogenic peptides with VEGF activity. Forty male Sprague-Dawley rats were subjected to 40 minutes of middle cerebral artery blockage, and the liposome-enveloped angiogenic peptides were administered in 10 rats after a 15-minute reperfusion window. Rats receiving angiogenic peptides exhibited less ipsilateral cortical ischemia than rats in the control group. FDG PET imaging seven days post-treatment showed the angiogenic peptides increased glucose uptake

in ipsilateral ischemic cortices of treated rats, and glucose uptake had a significant, positive association with cerebral perfusion. As such, FDG-PET can be used to evaluate effectiveness of various therapies in ischemic stroke.

Artificial intelligence methods applied to PET and stroke

Acute ischemic stroke represents the most critical situation in which AI and PET can be combined to produce a more favorable outcome. For instance, natural language processing (NLP) algorithms and automated lesion detection networks as applied to CT scans to ultimately increase efficiency in triaging such time-sensitive presentations [47].

Matsubara et al. [48] applied convolutional neural networks (CNN) to learn structural MR images and arterial spin labeling maps (CBV and CBF) to predict oxygen extraction fraction (OEF) as measured by 15O2-PET scans. The predicted OEF maps were similar to the real maps, and the intraclass correlation of 0.60 by the learned model indicated that CNNs trained with PET and MR images can qualitatively predict OEF maps without the 15O2 scan.

This study suggests that the fixation time for the 15O PET scans can be shortened, speedily providing critical information for stroke presentations. In the context of stroke rehabilitation, L. Wang et al. [49] utilized a cross-modal deep learning algorithm to restore PET imaging in situations of missing complete PET image. In this case, deep learning applied to PET can be conducive to the improvement of the final evaluation results of stroke rehabilitation treatment. Using the multimodal data available, the applied deep learning algorithm in the evaluation dataset achieved an accuracy of 98% with respect to an ordinal functional outcome.

Furthermore, after a stroke event, up to one-third of survivors report post-stroke dementia (PSD) or post-stroke cognitive impairment with a worsening cognitive decline over time [50]. However, because stroke patients already have decreased metabolism in their affected brain region, it is often difficult to identify the degree to which the decreased metabolism would predict dementia as shown via FDG PET.

Lee et al. approached this matter by applying a 3D CNN to predict dementia using FDG PET. A model was trained using a large dataset of FDG PET from the Alzheimer's Disease Neuroimaging Initiative (ADNI), and an area under the curve values of receiver operating characteristic curves (AUC-ROC) of 0.94 was achieved in the ADNI. After training on the ADNI data, the algorithm was then transferred to a PET dataset of patients with stroke. It was found that the deep learning model that differentiated Alzheimer's Disease from normal controls was successfully transferred to an independent stroke cohort with an AUC-ROC of 0.75. As such, the resulting FDG PET cognitive signature was an independent risk factor for dementia following stroke.

Concluding remarks

Our review summarizes the utility of FDG PET in the context of ischemic stroke. While the clinical utility of FDG PET imaging is often limited compared to CT and MRI, certain applications of FDG PET imaging have proven useful in stroke patients. FDG PET can augment other imaging modalities when used in combination. For example, CTA can quickly and precisely identify carotid plaques, but falters when imaging non-stenotic, non-calcified plaques. FDG PET with CTA can improve accuracy when attempting to identify tissues and vessels with inflammatory loci. Additionally, FDG may have a role in predicting stroke in cardiac PET imaging, as right atrial FDG uptake has been suggestive of atrial fibrillation and heightened risk of stroke. Brain imaging with FDG PET has been shown to provide additional information regarding functional disability and recovery in the aftermath of a stroke. Furthermore, preliminary applications of artificial intelligence to PET data in stroke patients have shown promise. For instance, recent machine learning methods have been able to reduce PET scan fixation time, improve imaging quality, and supplement radiologist findings and interpretations. Widespread use of whole-body PET/CT imaging and technological advancements in image quality will continue to improve data availability in stroke patient populations. Using the established literature to identify regions of interest, further research can explore comprehensive prediction and prognostication models of stroke derived from the multiple regions.

Disclosure of conflict of interest

None.

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