Review Article

Role of molecular imaging with positron emission tomographic in aortic aneurysms

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Abstract: Aortic aneurysms (AA) are often asymptomatic before the occurrence of acute, potentially fatal complications including dissection and/or rupture. Beyond aortic size, the ability to assess aortic wall characteristics and processes contributing to aneurysm development may allow improved selection of patients who may benefit from prophylactic surgical intervention. Current risk stratification for aneurysms relies upon routine noninvasive imaging of aortic size without assessing the underlying pathophysiologic processes, including features such as inflammation, which may be associated with aneurysm development and progression. The use of molecular imaging modalities with positron emission tomographic (PET) scan allows characterization of aortic wall inflammatory activity. Elevated uptake of Fuorine-2-deoxy-D-glucose (FDG), a radiotracer with elevated avidity in highly-metabolic cells, has been correlated with the development and progression of both abdominal and thoracic AA in a number of animal models and clinical studies. Other novel PET radiotracers targeting matrix metalloproteinases (MMPs), mitochondrial translocator proteins (TSPO) and endothelial cell adhesion molecules are being investigated for clinical utility in identifying progression of disease in AA. By further defining the activation of molecular pathways in assessing aortic regions at risk for dilatation, this imaging modality can be integrated into future clinical decision-making models.

Keywords: Aortic aneurysms (AA); positron emission tomographic (PET); molecular imaging

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Introduction

Although the past few decades have witnessed great progress in clinical aortic imaging, medical care and surgical techniques, patients with aortic aneurysms (AA) continue to have high rates of morbidity and mortality. Based on current AA consensus guidelines, aortic size is the guiding metric for use in diagnosis and surveillance, and criterion for elective surgical intervention (1). The standard anatomic-based imaging approaches, which mainly focus on measures of aortic size, reflect relatively late stage pathology, when structural dilation has already occurred. Beyond anatomic imaging, focusing on primary and aggravating pathological functional processes such as aortic wall inflammatory activity and perturbed biomechanics requires application of molecular and functional imaging techniques, such as hybrid positron emission tomographic (PET) imaging. This approach has the potential to accelerate diagnosis, refine prognosis, and guide treatments. The ability to identify aortic characteristics or underlying processes associated with increased aortic growth would be tremendously valuable, both in guiding selection of patients for prophylactic

surgical repair and for optimizing timing of intervention to prevent aortic complications.

Thoracic AA

Clinical problem

Thoracic aortic aneurysms (TAAs) are silent, but life-threatening conditions (2). Approximately 95% of TAAs are asymptomatic before the occurrence of often fatal acute complications, such as aortic dissection or rupture (3-5). Although prophylactic surgical correction is guided by anatomic measures of aortic size, diameter alone poorly predicts the risk for life-threatening complications (6,7). For example, it has been recently demonstrated that up to 60% of genetically-mediated TAA patients who developed aortic dissections had aortic diameters below the conventional threshold of 5.0 cm for prophylactic surgery (8,9). In non-genetic TAAs, is has been demonstrated that nearly 60% of type A dissection patients had aortic diameters <5.5 cm, the current cutoff for prophylactic surgery in this population; and 40% had diameters <5.0 cm. Moreover, recent data from our group and others have indicated that risk for aortic complications remains elevated even after prophylactic AA surgery. For example, among a cohort of 1,991 patients with genetically-mediated TAAs [22% Marfan Syndrome (MFS), 39% bicuspid aortic valve (BAV)], 52% of dissections, including 68% in MFS, occurred in patients who had previously undergone prophylactic graft repair of other aortic segments (8). Taken together, given the poor predictive value of aortic size to risk stratify patients, additional markers of thoracic aortic vulnerability are crucial to better encompass patients' risk for TAA complications.

Scope of the problem

According to the Centers for Disease Control and Prevention, AAs account for 43,000 to 47,000 deaths annually (9). In patients with TAAs, nearly 40% die in the field due to aortic rupture or dissection, and out-of-hospital mortality is ≥1–2% per hour (10). Among those that reach a hospital alive, the perioperative mortality for emergent surgical repair is ~25% (11,12). Each year, an estimated 10–11 per 100,000 people are diagnosed with a TAA (13). This number is expected to rise due to recently adopted imaging guidelines employing chest CT for lung cancer screening, which will incidentally detect more TAAs, previously undiagnosed until a lethal aortic complication. An estimated 7 million patients meet criteria for chest CT screening, which will detect an estimated 280,000 new TAAs (14). For all these reasons, the National Institutes of Health (NIH) has classified this disease as a significant burden on the health care system. In light of these data, improved stratification of patients at risk for TAAs and optimization of management are essential, and represent an important public health and research focus. Current risk stratification is reliant on routine noninvasive imaging assessment of aortic anatomy—aortic size. However, it is evident that standard anatomic-based imaging assessment of aortic size alone does not capture underlying functional processes related to aneurysm dilation, such as inflammation.

Basis for arterial fluorine-2-deoxy-D-glucose (FDG) uptake for localization of inflammation

Accelerated glucose metabolism is the basis for the use of FDG with PET in detecting inflammation. FDG is taken up by glucose-requiring activated inflammatory cells via the glucose transporter protein system (GLUT). After FDG enters the inflammatory cell, it undergoes phosphorylation by the hexokinase enzyme system to FDG-6-phosphate. However, unlike glucose-6-phosphate, FDG-6-phosphate is not metabolized further along the glycolytic pathway (i.e., not dephosphorylated by glucose-6-phosphatase), resulting in metabolic trapping of 18 FDG-6-PO4 in the cell in direct proportion to its overall metabolic state (15).

Activated macrophages and other inflammatory cells demand substantially greater glucose for accelerated cellular metabolic processes. Importantly, inflammatory cells have a distinctly higher rate of glucose uptake than non-inflammatory cells residing within an arterial wall, resulting in increased FDG uptake and facilitating the detection of an inflamed locus. In addition, the hypoxic plaque environment favors anaerobic metabolism, and in turn, stimulates macrophages to metabolize glucose rather than oxygen-dependent metabolism of free fatty acids (16). Thus, glucose becomes the main energy source for inflammatory cells within an inflamed arterial wall (17).

Several studies have established a strong correlation between arterial FDG uptake and macrophage content in a variety of animal models (18-20). In murine experiments, a strong correlation between FDG uptake and gene expression of inflammatory molecular markers has been demonstrated (21). Building on these early findings, in rabbits, it has been shown that inflamed aortic lesions accumulate up to 20 times more

Table 1 Clinical studies of PET imaging in AAs

Studies	Year	Study population	AAA expansion	Subjects with PET uptake	Results
Nchimi *et al.* (22)	2014	47 AAA, 6 TAA	4/53	38% of examinations	Subjects with higher uptake had higher rate of clinical events and no correlation with aortic size
Barwick *et al.* (23)	2014	151 AAA, 159 controls (age/sex/risk factor matched)	NA	36/151 (SUV_{max}: 1.8±0.4), 30/159 (SUV_{max}: 1.9±0.3)	No correlation between AAA and AAA size with uptake
Kuehl *et al.* (24)	2008	33 with AAS (5 TAA)	NA	11/33	Subjects with high uptake were likely to have progression of AAS
Blockmans *et al.* (25)	2008	46 with biopsy proven giant cell arteritis	NA	22/46	Subjects with high uptake had a larger thoracic aortic diameter and volume on serial follow up
Truijers *et al.* (26)	2008	17 AAA 17 controls (age matched)	NA	SUV_{max}: 2.52±0.52, SUV_{max}: 1.78±0.45	Subjects with AAA had significantly higher uptake; no correlation with maximal aneurysmal diameter
Sakalihasan *et al.* (27)	2002	26 AAA	6/26	10/26	Near 50% of subjects with high uptake required urgent repair compared to none in the low uptake group

AAA, abdominal aortic aneurysm; TAA, thoracic aortic aneurysm; SUV, standardized uptake value; AAS, acute aortic syndrome.

FDG than non-inflamed arterial lesions, thereby enabling reliable noninvasive detection of inflamed loci within arterial wall with FDG-PET (20). From these studies, it becomes clear that the PET derived FDG signal can be reliably used as a beacon for arterial wall inflammation.

Clinical studies of FDG-PET imaging of inflammation in thoracic AA

Though molecular inflammation imaging has been mostly been performed in the context of abdominal aortic aneurysm (AAA), a few studies have demonstrated utility of inflammation imaging in TAAs (see *Table 1*). For example, one clinical study demonstrated a correlation of FDG-avidity in the aortic wall and progression of AA. Blockmans *et al*. studied 46 patients with biopsy proven giant cell arteritis and FDG PET scan at baseline. After a mean follow up of 46.7±29.9 months, a single CT scan of the aorta was performed. They noted patients with increased FDG uptake in the aorta at diagnosis of giant cell arteritis had a significantly larger thoracic aortic diameter (in both ascending and descending aorta) and volume compared those with minimal to no FDG uptake (25). In multivariate regression model, FDG uptake was significantly associated with late volume of the thoracic aorta.

In another study, by Kuehl *et al.*, 33 patients with acute aortic syndrome (thoracic aortic aneurysm 5, thoracic aortic dissection 14, penetrating aortic ulcer 8, intramural hematoma 6) and FDG-PET scan at baseline were studied. Of those with increased aortic uptake [standardized uptake value $(SUV)_{max}$ >2.5], 9 of 11 patients (82%) had progression of disease or received definitive surgical treatment, while a majority of patients (55%) without elevated tracer uptake displayed stability or regression of disease and did not require intervention at follow-up (24).

AAA

Clinical problem and magnitude

AAA is a localized dilation of the aorta with a diameter of 3 cm or greater. Advanced AAA eventually leads to rupture, which is associated with a mortality of 90% (28). AAA leads to 30,000 deaths every year, of those 15,000 are due to rupture (29,30). The mechanism of AAA involves changes in the aortic wall's extracellular matrix thought to be associated with increased matrix metalloproteinases (MMPs). Inflammation is associated with an increase in these enzymes that are produced by macrophages, lymphocytes, and mast cells (31,32). Prevalence of AAA

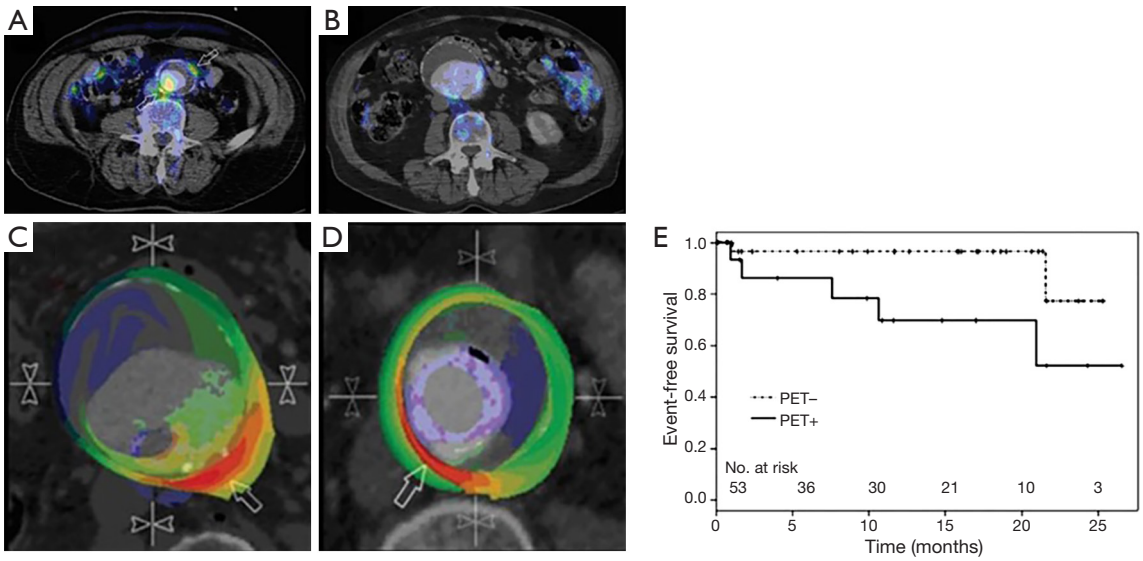

Figure 1 FDG PET/CT imaging (A and B) and finite element analysis (C and D) of two patients with AAA showing discordances between the two measures. The first patient (A) has a region of increased FDG uptake in AAA with increased wall stress (D, wall stress =161 kPa) in the corresponding region. The second patient has no FDG uptake in AAA (B) and a large area of increased wall stress (C, arrow, wall stress =315 kPa). The intensity scale ranges from deep blue to red. (E) Event-free survival curves in FDG PET-positive and PET-negative patients according to their last examination (22).

is higher in men and with advanced age (33). Other risk factors for AAA include white race, obesity, family history, smoking, and known atherosclerosis. The US Preventive Task Force recommends screening for AAA in men aged ≥65 years who have smoked with imaging to determine the size of AAA at baseline (34). Over the last few decades, the incidence of ruptured AAA has declined. This is attributed to the implementation of AAA screening programs and new therapeutics (35). However, novel imaging modalities are required to better stratify AAA at risk of rupture and those that will benefit from repair. By noninvasively detecting inflammation, as with 18F-FDG PET scan, healthcare providers may be able to detect those at high risk of clinical events and those that may benefit the most from elective repair.

Clinical studies of FDG-PET imaging of inflammation in abdominal AA

There have been more studies in AAA utilizing PET imaging given the established association of the presence of inflammation with AAAs (see *Table 1*). FDG is the most commonly used agents and is recognized as a surrogate for aortic wall inflammation. Sakalihasan *et al.* first reported the correlation of FDG-PET to clinical aortic events. In 26 patients with AAA, 10 patients demonstrated increased uptake of FDG. Those with no or minimal uptake did not require urgent surgery, whereas, 5 out of the 10 patients who showed increased uptake required urgent surgery within 2 to 30 days (27).

In another well-known study, Nchimi *et al.* studied 53 patients with descending AAA =131 areas, TAA =54 areas. This study showed that nearly one third of subjects had increased (i.e., positive) FDG PET uptake. After 11 months of follow-up to monitor for clinical events (defined as rupture, dissection, or aortic growth >1 cm), those with increased FDG uptake had a significant increase in clinical events compared to those without uptake [5 of 18 (28%) versus 2 of 35 (6%); P=0.03; see *Figure 1*]. In addition, finite element analyses were performed and showed that areas of high FDG uptake did not significantly correlate with areas that harbored the highest wall stress (including stress/strength index) (22). This latter point suggests that inflammation (i.e., FDG uptake) may provid additional information to biomechanical wall stress and lumen diameter.

Truijers *et al.* conducted a retrospective study of 17 asymptomatic patients with AAA (maximal diameter >3.0 cm)

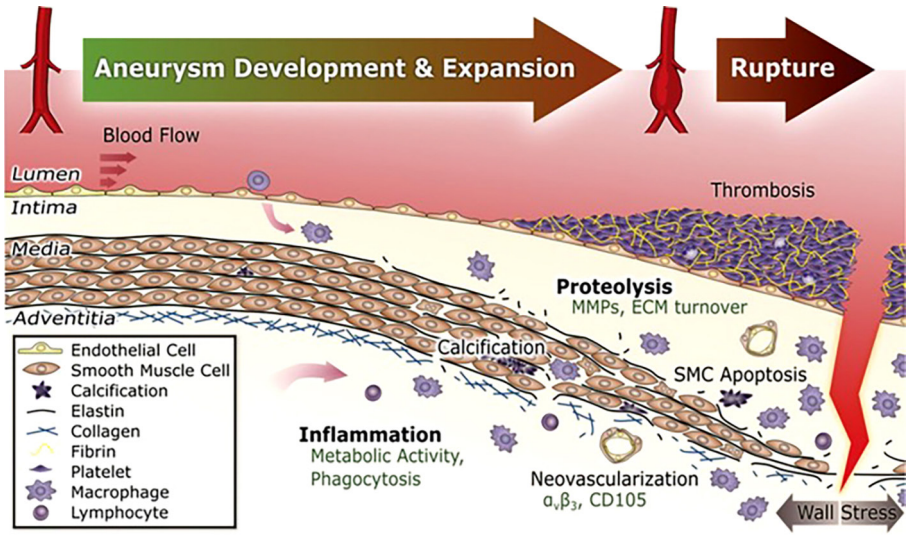

Figure 2 Pathophysiology of abdominal aortic aneurysm (AAA). Note the possible targets of molecular imaging including inflammation and proteolysis (45).

and an age-matched control group that had FDG-PET performed for staging of primary lung cancer. They compared the SUVmax between these two groups. Those with AAA had a significantly higher SUV-max compared to the control group (26). These findings were reproducible and reported by other groups as well (36,37). On other hand, Palombo *et al.* evaluated the PET-measured SUV in the aortic wall of 50 male patients with asymptomatic AAA and 44 age-matched controls (24 males, 20 females), 44 age-matched controls subjects (mean age: 71 years, range: 59-85 years, 24 males, 20 females) with no known atherosclerotic disease. They noted a lower mean and SUV_{max} in those with AAA compared to adjacent non-aneurysmal segments in controls. This finding has been reported by several other groups as well (38-40). Barwick *et al.* published a case control study that involved 151 patients with AAA and 159 controls, and reported no difference in FDG uptake or SUVmax between those with AAA and controls (23). Several other studies have looked at the relationship between FDG uptake and recent AAA expansion (36,41-44). Whether FDG uptake in the aortic wall in AAA holds clinical meaning remains to be fully clarified. Large, prospective studies will need to be performed to resolve the equivocal results from prior studies.

Novel molecular radiotracers on the horizon

AAs are a complex microenvironment involving several biologic pathways, with increasing evidence that inflammation is important in both abdominal and thoracic aneurysm pathophysiology. Over the past few years, significant advances have been made in the field of fluorination chemistry and other radiotracer developmental technology, whereby ongoing efforts to synthesize PET-compatible novel tracers directed at various inflammatory processes are underway (see *Figure 2*) (45). For example, tracers targeting endothelial cell adhesion molecules, MMPs, apoptotic caspases, mitochondrial translocator protein (TSPO), integrin receptor, and apolipoprotein E are but a few being investigated (see *Table 2*) (51-54).

Several proteases have been identified as important modulators of vessel wall integrity especially with regards to collagen and elastin fibers, and thus may mediate AA growth and rupture. One family of such proteases are the MMP. In particular, some animal studies have used a protease-activated near-infrared fluorescence probe, such as MMPSense 680, to monitor and quantify MMP activity. These studies have documented upregulated MMP activity within AA. In a study using control mice, mice homozygous for the fibulin-4 reduced-expression allele [fibulin-4 (R/R)] showed an enlarged ascending aorta (46). These mice demonstrated significant increase in the presence of MMP-9. Even slight decrease in expression of fibulin-4 in the heterozygous fibulin-4 (+/R) mice showed mild aneurysm formation. In addition, it was shown that MMP levels are elevated prior to overt enlargement in aortic lumen size, and that higher MMP levels predict increased aneurysm progression (46). Pilot clinical studies are needed to

Table 2 Preclinical studies of novel molecular radiotracers in PET imaging of AAs

Studies	Aortic segment	Radiotracer	Molecular target	Mouse model	Results
Kaijzel *et al.* (46)	Thoracic	MMPSense 680 probe	MMP	Genetically modified fibulin-4 models	Elevated MMP signaling were visualized in locations of future aneurysmal development in mice homozygous to extracellular matrix protein fibrillin-4
Nahrendorf *et al.* (47)	Thoracic abdominal	18-F-CLIO	Dextran-coated iron oxide nanoparticles	AngII-induced murine AAA	Elevated NP uptake was noted in AAA areas 10-12 hours after injection; elevated uptake was associated with increased risk of aneurysmal rupture
Kitagawa *et al.* (48)	Abdominal	18F-FPPRGD2	Integrin αvβ3	AngII-induced murine AAA	RGD uptake corresponds with vascular changes including vascular inflammation and neovessel count but not AAA diameter
Shi *et al.* (49)	Abdominal	64Cu-labeled TRC105 (fab antibody)	CD 105 (endoglin)	Calcium-induced murine AAA	Elevated 64Cu-labeled TRC105 was visualized in the AAA area 6 hours after injection
Tegler *et al.* (50)	Abdominal	11C-PK11195, 11C-d-deprenyl	TSPO	15 patients with asymptomatic AAA undergoing repair	Chronic inflammation seen on histology was not detectable with these radiotracers

AAA, abdominal aortic aneurysm; MMP, matrix metalloproteinase; TSPO, Translocator protein; RGD, Arginine-glycine-aspartate; PET, positron emission tomographic; AAS, acute aortic syndrome.

determine if greater PET signals reflecting increased MMP levels predict human aneurysm progression.

Arginine-glycine-aspartate (RGD) peptide-based radiotracers targeting integrin alpha-v Beta-3 have been studied in AAA. Integrin alpha-v Beta-3 is upregulated in proliferating macrophages, endothelial cells, and vascular smooth muscle cells (see *Figure 3*) (48,55-57). In a study using angiotensin II (AngII)-induced murine AAA, an 18F-labeled RGD compound (18F-FPPRGD2), was used to detect vascular changes including vascular inflammation and higher neovessel count. This study demonstrated a correlation between RGD-based radiotracer uptake and vascular changes (vascular inflammation and neovessel count) but not with AAA diameter (48). Similar to some clinical studies, aortic inflammation has been identified in both existing aneurysm and normal-caliber segments, whereby in the latter scenario, inflammation appears to provide additional information to aortic size. Longitudinal studies to determine if inflamed normal diameter segments are predisposed to enlargement need to be performed.

Fab-based molecular radiotracers have also been studied in AAA such as copper-64-labeled CD105 fab antibody fragment. CD105, also called endoglin, is a membrane glycoprotein that interacts with transforming growth factor-beta, an important modulator of AAA formation. Upregulation of CD105 is found in endothelial cells of neovessels and macrophages. A study using a murine calcium-induced AAA, increased PET uptake of the copper-64-labeled CD105 fab antibody fragment radiotracer was noted in the abdomen in the AAA area 6 hours post-injection (49). However, its biological significance is yet to be determined. A limitation of this tracer is the high residual blood pool activity (8% injected dose per gram at 24 hours); often seen with Fab-based radiotracers (58).

TSPO is a mitochondrial protein associated with cholesterol transport and immunomodulation. Radiotracers targeting TSPO, 11C-PK11195 and 11C-d-deprenyl, have been studied in various disorders of systemic inflammation including atherosclerosis and aneurysm. A study looking at the use of these tracers in AAA compared to disorders of systemic inflammation did not show a significant difference between groups. This negative results may have been attributed to the so-called control arm (i.e., systemic inflammatory disorders), which are known to harbor higher degree of arterial inflammation, thereby minimizing the ability to determine a meaningful difference (45,50). With the advent of recognition that inflammation plays a role in TAA, a recent study has shown increased TSPO in the context of TAA (Singh *et al.*), namely in MFS—a prototype genetically-medicated TAA disorder. This study is small in

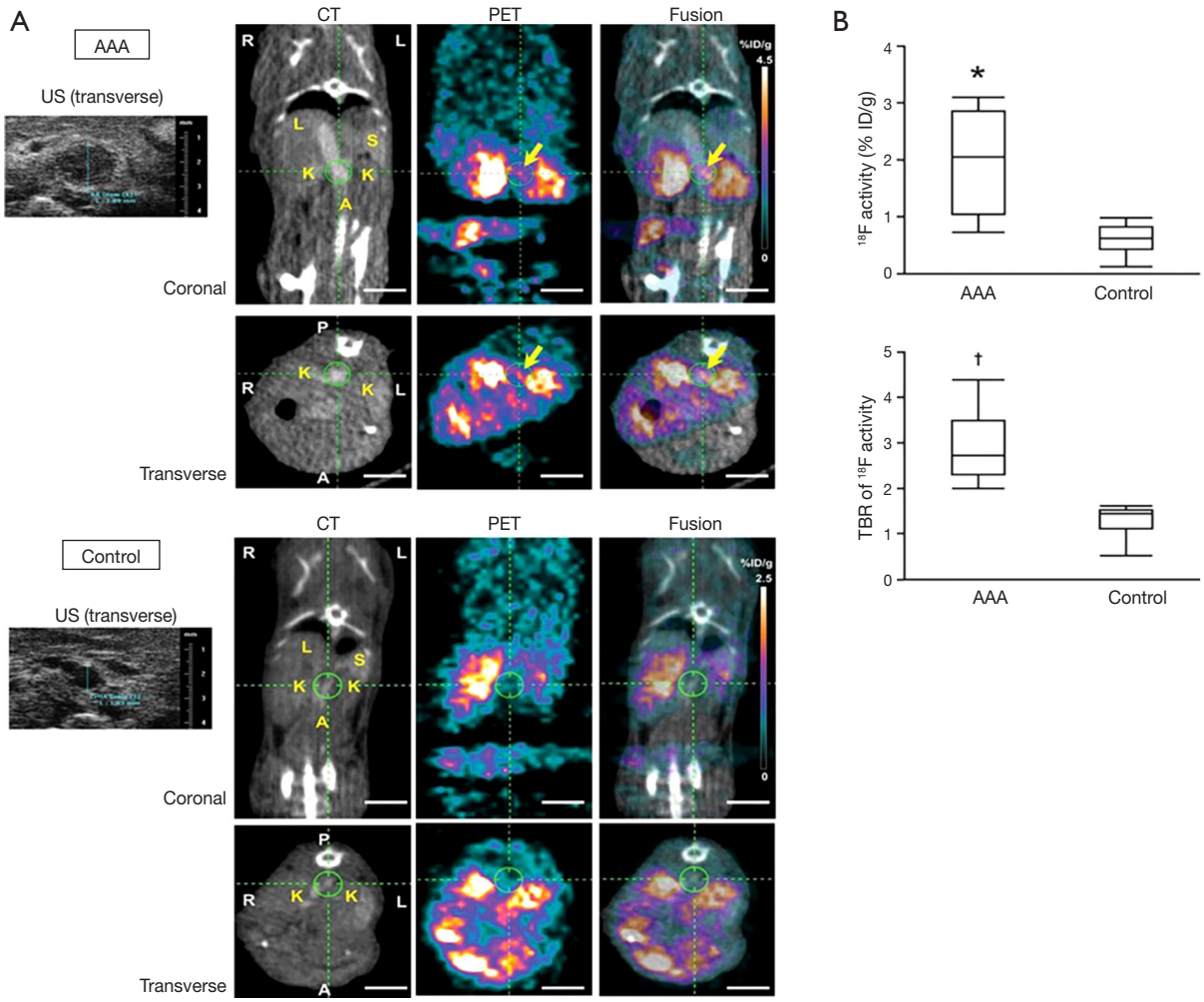

Figure 3 18F-FPPRGD2 PET imaging of AAA and normal aorta (48). (A) AAA mouse model with aortic diameter of 1.89 mm on ultrasound (US) showing increase PET uptake in the AAA lesion (yellow arrows) compared to control mouse aorta that had a diameter of 1.09 mm on US that did not have any uptake. A, anterior; L, left; P, posterior; R, right; (B) quantitative analysis showing both the percentage-injected dose per gram and target to background ration (TBR) that were significantly higher in AAA than normal control aorta. P value <0.05. *, P=0.003 versus control; †, P=0.0008 versus control. PET, positron emission tomographic; AAA, abdominal aortic aneurysm.

size and no longitudinal data are yet available.

Other PET radiotracers that have been utilized in AA imaging include nanoparticles-based agents such as fluorine-18-labelled dextran-coated iron oxide nanoparticles (18F-CLIO). In an experimental model with apoE$^{-/-}$ mice, AngII was injected into experimental mice, creating both thoracic and AAA. PET imaging 10 to 12 hours after injection of this radiotracer noted higher uptake in the aneurysmal thoracic and abdominal aortas than in the control mice aortas. In addition, high uptake in early images was associated with higher risk of aneurysm growth and rupture. A limitation of nanoparticle-based radiotracers is their long circulation time mandating delayed imaging to clear blood pool activity. This may be addressed with smaller nanoparticle radiotracers that are cleared more rapidly (47).

Future of clinical imaging of AA

As hybrid PET-CT camera systems continue to mature into an important diagnostic tool, the integration of MRI into PET scanners has surfaced and offers the advance of superior high spatial resolution. Multimodal imaging combines strengths borne from each individual modality and offers valuable integration of molecular, physiologic, and anatomic

information. Simultaneous image acquisition with PET and MRI seamlessly co-registers acquired images from both modalities, thereby limiting misalignment and partial volume effects with shorter scan times (59). In addition, PET-MRI hybrid imaging permits synchronized evaluation of multiple physiologic and disease processes by incorporating complementary molecular imaging probes (60,61).

Conclusions

Molecular imaging afforded by hybrid PET imaging systems has emerged as a powerful diagnostic tool to identify potentially high-risk AA. The early identification of these aneurysms is critical to effectuating appropriate care to at risk populations and to lower the risk profile of patients. The road ahead for noninvasive imaging of AA is promising, and with continual efforts dedicated to refining the imaging techniques and performance of prospective clinical studies, the integration of these robust imaging modalities into clinical decision algorithms is promising.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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