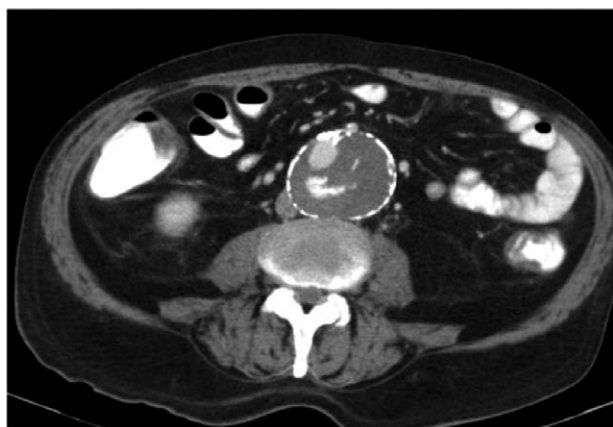


## Novel Molecular Imaging Approaches to Abdominal Aortic Aneurysm Risk Stratification

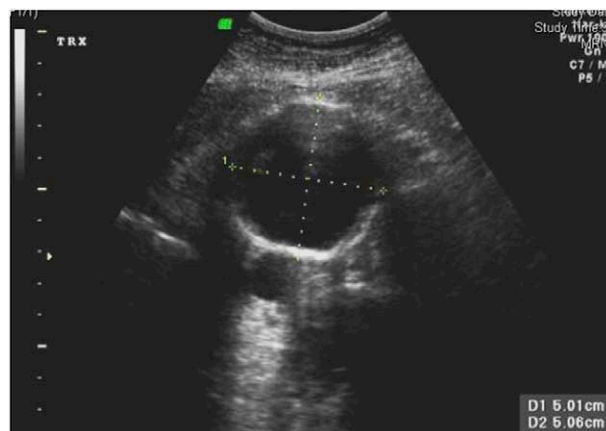
Jakub Toczec, PhD; Judith L. Meadows, MD; Mehran M. Sadeghi, MD

**Abstract**—Selection of patients for abdominal aortic aneurysm repair is currently based on aneurysm size, growth rate, and symptoms. Molecular imaging of biological processes associated with aneurysm growth and rupture, for example, inflammation and matrix remodeling, could improve patient risk stratification and lead to a reduction in abdominal aortic aneurysm morbidity and mortality.  $^{18}\text{F}$ -fluorodeoxyglucose-positron emission tomography and ultrasmall superparamagnetic particles of iron oxide magnetic resonance imaging are 2 novel approaches to abdominal aortic aneurysm imaging evaluated in clinical trials. A variety of other tracers, including those that target inflammatory cells and proteolytic enzymes (eg, integrin  $\alpha_v\beta_3$  and matrix metalloproteinases), have proven effective in preclinical models of abdominal aortic aneurysm and show great potential for clinical translation. (*Circ Cardiovasc Imaging*. 2016;9:e003023. DOI: 10.1161/CIRCIMAGING.115.003023.)

**Key Words:** aorta ■ aortic aneurysm, abdominal ■ fluorodeoxyglucose F18 ■ inflammation ■ magnetic resonance imaging ■ molecular imaging ■ positron-emission tomography



**Figure 1.** Computed tomographic image of a large abdominal aortic aneurysm in a patient with multiple medical comorbidities.



**Figure 2.** Ultrasound image of a patient with a medium abdominal aortic aneurysm.

- Sixty-year-old male with history of acute myelogenous leukemia status post bone marrow transplantation, hypertension, dyslipidemia, tobacco use, and peripheral arterial disease status post right carotid endarterectomy who underwent a computed tomography (CT) of abdomen for nausea and concern of graft versus host disease. CT demonstrated a large infrarenal aortic aneurysm that measures 6.2×6.5 cm with mural thrombus (Figure 1). Can molecular imaging assist in determining need and timing for abdominal aortic aneurysm (AAA) repair?
- Seventy-two-year-old female with history of poorly controlled hypertension, diabetes mellitus, tobacco use, and chronic renal insufficiency. Ultrasound performed for evaluation of renal disease noted infrarenal aorta of 4.7×4.6 cm. Repeat study at 6 months demonstrated growth to 5.0×5.0 cm (Figure 2). Can molecular imaging identify risk of rapid expansion and rupture?

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## AAA: Clinical Context and Diagnostic Gaps

*“There is no disease more conducive to clinical humility than aneurysm of the aorta”*

–Sir William Osler

AAA accounts for 10 000 to 15 000 deaths annually in the United States, although this may be a gross underestimation given that half of patients who experience aneurysm rupture fail to survive long enough for initiation of treatment. In screening ultrasound studies, 4% to 8% of men aged 60 to 80 years have occult aneurysm, with a lower prevalence in women. These studies typically identify small aneurysms, whereas a minor fraction (0.3%–0.6%) of screened patients have aneurysms detected with sizes  $\geq 5.5$  cm, a size for which guidelines and evidence suggest need for repair.<sup>1</sup> Despite this prevalence, only a subset of patients with AAA die from a ruptured aneurysm; instead, most will die from other causes, including other cardiovascular diseases.<sup>2</sup>

Prevalence of aneurysmal dilation of the abdominal aorta is associated with advancing age. Other significant risk factors of AAA development include male sex, obesity, white race, positive family history, smoking, the presence of other vessel aneurysms, and atherosclerosis.<sup>1,3</sup> The natural history of the asymptomatic AAA is characterized by a progressive dilation of the aorta. The current approach to screening and surveillance is based almost entirely on size and rate of growth of aneurysms and uses ultrasound and CT scan for anatomic measures. The US Preventive Task Force recommends a 1-time ultrasound screening of men aged  $\geq 65$  years who have ever smoked with selective screening in male nonsmokers and women with a smoking history. The size of AAA at baseline determines the frequency of surveillance ultrasound screening.<sup>3</sup>

Similarly, management strategy of AAA is determined by aortic size, growth rate, and symptoms. Aneurysm size is a strong predictor of rupture risk with annual risk of rupture increasing from  $\leq 1\%$  for AAA  $< 5.5$  cm to 32.5% for those  $\geq 7.0$  cm.<sup>3</sup> In part, on the basis of these data, elective repair (either open surgical repair or endovascular aneurysm repair [EVAR]) of AAA is currently the recommended management to reduce morbidity and mortality in asymptomatic patients with aneurysms  $\geq 5.5$  cm or when AAA has expanded  $> 0.5$  cm in a 6-month period. More rapid aortic expansion is associated with larger initial aortic sizes, tobacco use, and elevated diastolic blood pressure, whereas diabetes mellitus seems to be protective.<sup>4</sup> Beside rapid expansion, female sex, smoking, and hypertension increase the risk of rupture.<sup>1</sup> Many AAA ruptures occur in patients who do not meet the current criteria for AAA repair.<sup>5</sup> However, the low rate of rupture in smaller aneurysms (0.6%–1% for AAA, 4–5.5 cm) and the risks associated with aneurysm repair do not justify routine repair of smaller AAA. Beside smoking cessation, it is recommended that patients with AAA be prescribed medical management for reduction of cardiovascular risk although there is limited evidence that these strategies reduce AAA-related morbidity and mortality.<sup>3</sup>

During the past 25 years, there has been a decline in the incidence of ruptured AAA that may be attributed to more widespread screening and abdominal imaging, the expanded

use of EVAR, or possibly the broader use of medications that lower cardiac risk.<sup>6</sup> Unfortunately, this decline in adverse events is not consistent across all subgroups, particularly female sex. The improvements in cardiovascular risk management and advances in invasive therapy could change the landscape with regard to risk/benefit ratio of repair in AAA of different sizes. A comparison of the 2 approaches of repair has shown that EVAR is associated with a lower 30-day mortality than open repair (1 versus 4%–5%), but longer term mortality is equivalent.<sup>3</sup> Current decision making about repair strategy incorporates information on aneurysm and aorta anatomy (size, tortuosity, angulation, distal vasculature and vascular access, and patterns of calcification), patency of involved mesenteric vessels, the presence of inflammatory aorta, medical comorbidities and perioperative risk, and the ability to comply with post-EVAR surveillance imaging for endoleak (continued blood flow in the aneurysm sac outside the stent graft detected in  $\approx 25\%$  of patients during follow-up)<sup>7</sup> and aneurysm expansion.

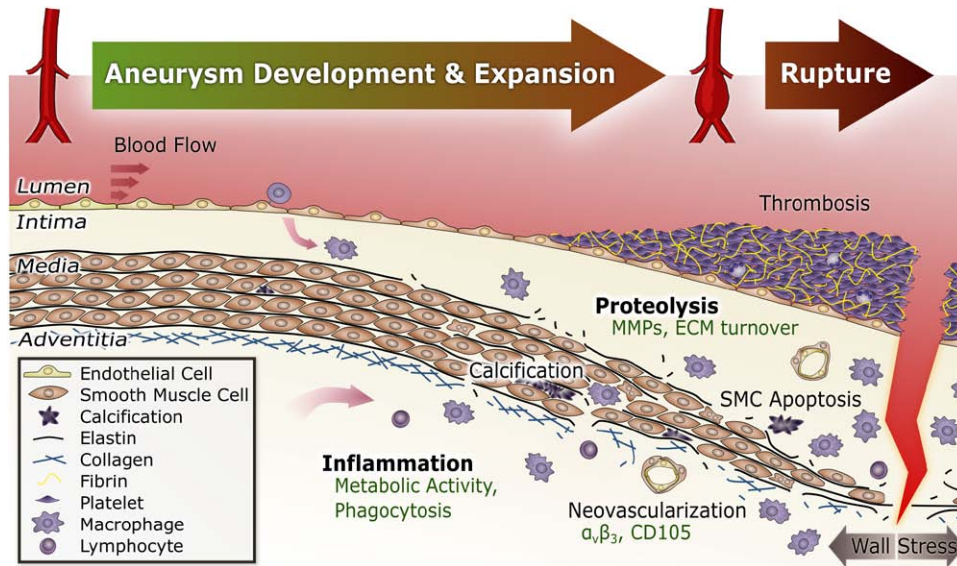
There is a clinical need for novel imaging and improved AAA risk models to overcome the limitations in current screening and surveillance strategies. Novel imaging techniques based on vessel wall biology could identify patients who will benefit from AAA repair and support the development of therapies that might alter the pathophysiologic processes that underlie aneurysm development, expansion, and rupture. In addition, new imaging approaches to predict endograft failure are needed.

## Pathophysiology

Inflammation, matrix remodeling with elastin degradation and compensatory collagen deposition, and medial smooth muscle cell rarefaction are the main pathological features of AAA (Figure 3). Both local and systemic (eg, smoking) factors play a role in aneurysm development. Traditionally, AAA is thought to be associated with atherosclerosis, but the protective role of diabetes mellitus in AAA and differences in the predilection sites point to a more complex picture. Single-gene mutations of matrix proteins that are major players in thoracic aortic aneurysm seem to be less prevalent in AAA where focal vessel wall inflammation is associated with upregulation of proteolytic pathways, smooth muscle cell apoptosis, enhanced oxidative stress, and neovascularization.<sup>1</sup> The combination of extracellular matrix and more specifically elastin breakdown, in part, mediated by matrix metalloproteinases (MMPs), and smooth muscle cell loss is responsible for the thinning of the media and aortic dilation. Intraluminal thrombus, present particularly in patients with advanced AAA, is associated with increased local inflammation and proteolysis.<sup>8</sup> Aneurysm expansion is a consequence of the interaction of local hemodynamic forces with a weakened vessel wall. Rupture occurs when wall stress exceeds tensile strength. The sites of low tensile strength are associated with inflammation, matrix remodeling, and neovascularization.<sup>9,10</sup> These issues have been summarized in an excellent recent review.<sup>1</sup>

## Molecular Imaging for AAA Risk Stratification

Through visualization, characterization, and quantification of biological processes involved in (or associated with) AAA



**Figure 3.** Schematic representation of abdominal aortic aneurysm (AAA) pathophysiology. Inflammation, proteolysis, smooth muscle cell (SMC) apoptosis, neovascularization, calcification, and intraluminal thrombosis may be targeted by molecular imaging. These in conjunction with biomechanical forces contribute to AAA development and rupture. ECM indicates extracellular matrix; and MMP, matrix metalloproteinase.

expansion and rupture, molecular imaging could help improve AAA risk stratification, personalize therapeutic decisions beyond existing paradigms, and potentially lead to a reduction in AAA morbidity and mortality. Similar to their key role in AAA complications, inflammation and matrix remodeling play a major role in many other cardiovascular pathologies. As such, these processes may be promising practical targets for molecular imaging and have a good prospect for advancing to the clinic. Unfortunately, of many molecular imaging agents that have been introduced for detection of inflammation and matrix remodeling in cardiovascular pathology, only a small subset has been evaluated in clinical studies and preclinical models of aneurysm.

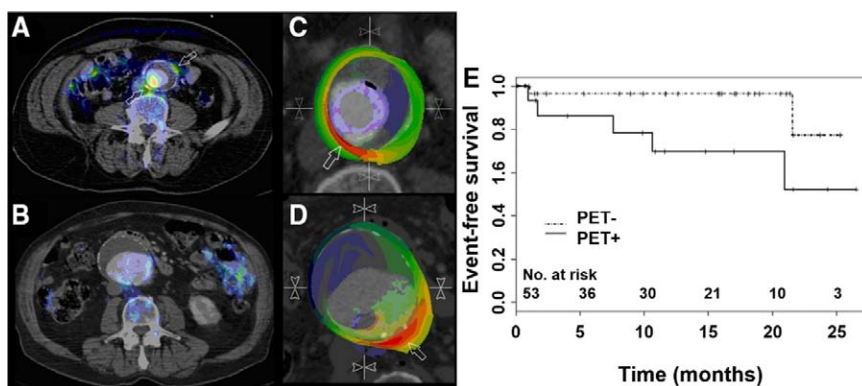
The first step in evaluating emerging molecular imaging agents is the assessment of their performance in detecting a specific process, for example, gene expression *in vivo*. Many

molecular imaging agents bind to multiple targets and can detect several, often related, processes simultaneously. The critical next step is the demonstration that target expression, as detected by the tracer, can predict the development of AAA complications in preclinical models and, ultimately, in clinical studies. The presence of tracers approved for clinical use for other applications has facilitated clinical studies of vascular biology in AAA.

### Clinical Studies

#### Metabolic Activity

<sup>18</sup>F-fluorodeoxyglucose (FDG) is a glucose analog, which after phosphorylation by hexokinase cannot proceed along the glycolytic pathway and is retained in cells with high metabolic activity and glycolysis, such as inflammatory



**Figure 4.** <sup>18</sup>F-fluorodeoxyglucose (FDG)-positron emission tomographic (PET)/computed tomographic imaging (A and C) and finite element analysis (B and D) of 2 patients with abdominal aortic aneurysm (AAA) demonstrating partial discordance between the 2 measures. The first patient (A and B) has 2 distinct areas of FDG uptake in AAA (A, arrows) with average and increased wall stress (B, arrow, wall stress, 161 kPa) in these areas. The second patient has no FDG uptake in AAA (C) and a large area of increased wall stress (D, 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. Reprinted from Nchimi et al<sup>18</sup> with permission of the publisher. Copyright © 2013, Wolters Kluwer Health.

cells. Although there is ongoing debate on the determinants of FDG uptake in the vessel wall,<sup>11</sup> FDG-positron emission tomography (PET) seems as a useful tool for imaging vessel wall inflammation in specific vascular pathologies. Despite a paucity of preclinical FDG-PET studies in aneurysm, the availability of FDG has led to many clinical studies aimed at evaluating the role of this imaging agent in AAA. To date, these studies have yielded contradictory results with some showing or suggesting an association between FDG uptake and AAA extent or evolution,<sup>12–18</sup> whereas others failing to reproduce such results.<sup>19–25</sup> One of the first reports of FDG-PET in AAA showed increased FDG uptake in AAA on qualitative evaluation of PET images in 10 of the 26 high-risk (based on AAA size or clinical presentation) patients, 5 of whom ultimately required urgent surgery, whereas none of the 16 remaining patients required urgent surgery.<sup>12</sup> In a recent study of 53 patients with descending thoracic and AAA (mostly with AAA, half of which with a diameter >5 cm),<sup>18</sup> nearly one third of these subjects had a positive FDG-PET study. During the 11 months of follow-up, the event rate (aneurysm growth of >1 cm per year, dissection, rupture, or emergency surgery) was significantly higher in this FDG-positive group compared with FDG-negative group (28% versus 6%). Interestingly, there was a poor correlation between FDG uptake and wall stress and stress/strength index estimated using commercial software. Furthermore, areas of high FDG uptake poorly matched the areas with the highest wall stress and stress/strength index (Figure 4).<sup>18</sup>

The link between FDG uptake and vessel wall inflammation is addressed in a small number of studies.<sup>13,16,17</sup> A study of 15 patients undergoing open aneurysm repair for clinical indications found higher FDG uptake (expressed as standardized uptake value [SUV<sub>max</sub>]) in symptomatic disease. Histological analysis of the sites with maximal FDG signal showed that the higher FDG signal in the 3 symptomatic patients in this study was associated with medial inflammatory cell infiltration and reduced vascular smooth muscle cell and collagen content. Elastin fibers were severely reduced in all samples.<sup>13</sup> In another study in 18 subjects undergoing

open aneurysm repair, an FDG signal could be detected in 8 subjects. In patients with FDG uptake in AAA, expression of markers of inflammation was higher in areas of high FDG signal compared with FDG-negative areas. In addition, subjects with positive FDG signal demonstrated higher markers of inflammation even in aortic areas without FDG signal when compared with subjects without any FDG uptake in AAA. This suggests more generalized inflammation in subjects who have focal FDG signal.<sup>17</sup>

These findings, often in subjects with large or high risk AAA, are in apparent contradiction with other studies of FDG-PET in AAA. In a group of 34 consecutive subjects with AAA (mean maximal AAA diameter, 5.0 cm) undergoing routine ultrasound surveillance, the predictive value of <sup>18</sup>F-FDG-PET imaging for a 12-month period was addressed in 25 patients who completed the study. The authors reported a negative correlation between average SUV<sub>max</sub> of transaxial images of aneurysm and future expansion determined by ultrasound but no correlation between maximal SUV<sub>max</sub> or target/background ratio and AAA expansion, highlighting the importance of the methodology of image analysis and quantification.<sup>19</sup> Interestingly, a recent retrospective examination of FDG-PET/CT studies performed primarily for oncological indications in a cohort of 151 patients with AAA (median diameter, 5.0 cm) and 159 matched controls found no major difference in visual and quantitative evaluation of infrarenal aortic FDG uptake between the 2 groups (Figure 5).<sup>24</sup>

Several factors may have contributed to the apparent discrepancy of these results. The study populations are heterogeneous. In addition, image acquisition, analysis, and quantification methodology vary greatly between different studies (Table).<sup>5</sup> Interestingly, many of the studies reporting a positive value of FDG-PET imaging in AAA include subjects with advanced disease. As such, many questions and uncertainties on the role of FDG-PET in AAA persist. Given the poor specificity of FDG in inflammation imaging and many potential confounding factors, the positive association between FDG uptake and poor AAA outcome could be weak or nonexistent, at least for small AAA under routine surveillance.



**Figure 5.** **A** and **B**, Axial and coronal computed tomographic (CT) and <sup>18</sup>F-fluorodeoxyglucose (FDG)-positron emission tomographic (PET) images in a patient with an abdominal aortic aneurysm (AAA) 6.6 cm (arrows) that ruptured 6 weeks after the study, showing diffuse increased activity (SUV<sub>max</sub>, 1.9). **C** and **D**, Axial and coronal CT and FDG-PET images in a subject with nonaneurysmal aorta, showing a similar tracer uptake. **E**, Quantification of FDG signal in patients with AAA and controls (mean±2SD), *P*=0.02 for infrarenal SUV<sub>max</sub> and nonsignificant for other comparisons. SUV indicates standardized uptake value; and TBR, target/background ratio. Reprinted from Barwick et al<sup>24</sup> with permission of the publisher. Copyright © 2014, Springer.

**Table. Selected Studies Evaluating FDG-PET Imaging in AAA Patients**

	Clinical Characteristics			FDG-PET Imaging		Correlation With Outcome Measures
	Study Population	AAA Size, cm	AAA Expansion	Time, min	Image Analysis	
Sakalihan et al <sup>12</sup>	15 asymptomatic 11 symptomatic	5.9±2.8 (4.5–7.0) 6.7±3.2 (5.1–7.8)	6/26 (rapid expansion)	60	5/15 increased uptake 5/11 increased uptake	Half of patients with increased uptake required urgent repair vs none in the low-uptake group
Reeps et al <sup>13</sup>	15 asymptomatic 3 symptomatic 24 age-matched controls	5.9±1.2 (5.0–7.2) 5.4±0.8 (4.5–7.2) n/a	4/7 (>0.6 cm/y) n/a	60	SUV <sub>max</sub> : 3.5±0.6 SUV <sub>max</sub> : 7.5±0.3 SUV <sub>max</sub> : 3.0±0.5	Higher uptake in symptomatic vs asymptomatic patients; uptake correlated with inflammation but no correlation with AAA size and growth
Kotze et al <sup>15</sup>	14 (1 symptomatic)	5.4±0.8 (4.4–6.7)	2/14 (recent expansion)	180	12/14 SUV <sub>max</sub> >2.5	No correlation with AAA size and growth
Kotze et al <sup>19</sup>	25 (3 symptomatic)	5.0 (IQR, 4.0–5.4)	4/25 (≥0.6 cm/y)	180	SUV <sub>max</sub> : 2.2 (IQR, 1.9–2.7)	No correlation with AAA size Negative correlation with AAA growth
Marini et al <sup>20</sup>	12 (asymptomatic) 12 age- and sex-matched controls	4.8±0.4 (4.5–5.3) n/a	12/12 (≥1.0 cm/6 mo) n/a	60	SUV <sub>max</sub> : 0.9±0.2 SUV <sub>max</sub> : 1.5±0.4	No visible uptake in abdominal aorta Correlation with cell density
Palombo et al <sup>21</sup>	40 asymptomatic 44 age-matched controls	4.9 (4.8–5.4) n/a	18/40 (>1 cm/6 mo) n/a	≥60	SUV <sub>max</sub> : 0.9±0.3 vs 1.1±0.3, no AAA SUV <sub>max</sub> : 1.0±0.2	No visible uptake in abdominal aorta
Tegler et al <sup>22</sup>	12 asymptomatic 13 age- and sex-matched controls	5.2 (3.4–6.6) n/a	0/12 (>0.5 mm/6 mo or >10 mm/y) n/a	60	SUV <sub>max</sub> : 2.7 (2.4–3.4) SUV <sub>max</sub> : 1.8 (1.2–2.3)	No increased uptake despite vessel wall inflammation
Reeps et al <sup>16</sup>	26 asymptomatic 5 symptomatic	5.6±0.7 (4.7–7.0) 6.6±1.3 (4.7–8.2)	n/a	90	SUV <sub>max</sub> : 2.7±0.9 SUV <sub>max</sub> : 5.2±2.7	Increased uptake in symptomatic compared with asymptomatic patients
Courtois et al <sup>17</sup>	18 (1 symptomatic)	5.9±0.9 (4.0–8.0)	4/18 (≥0.8 cm/y)	60	8/18 increased uptake	Correlation with markers of inflammation and remodeling
Nchimi et al <sup>18</sup>	47 AAA and 6 TAA	4.9 (groups: 4.2±0.7 to 6.5±1.3)	4/53 (>1 cm/y)	69 (59–100)	Increased uptake in 38% of examinations	Modest correlation with wall stress Higher rate of clinical events in patients with increased uptake, no correlation with aneurysm size
Kotze et al <sup>23</sup>	40 (2 symptomatic)	5.1 (IQR, 4.1–5.6)	25/40 (≥0.2 cm/y; range 0–0.9)	180	SUV <sub>max</sub> : 1.8 (IQR, 1.5–2.4)	Higher uptake in small AAA Negative correlation with AAA growth
Barwick et al <sup>24</sup>	151 (asymptomatic) 159 age-, sex-, and risk factor-matched controls	5.0 (3.2–10.4) n/a	n/a n/a	90	36/151 increased uptake (SUV <sub>max</sub> : 1.8±0.4) 30/159 increased uptake (SUV <sub>max</sub> : 1.9±0.3)	No difference between AAA and control subjects No correlation with AAA size
Morel et al <sup>25</sup>	39 asymptomatic	4.8±0.4	9/39 (≥0.25 cm/9 mo)	90	SUV <sub>max</sub> : 2.2±0.7	Higher uptake in small AAA Negative relationship between uptake and growth

AAA indicates abdominal aortic aneurysm; FDG, <sup>18</sup>F-fluorodeoxyglucose; IQR, interquartile range; n/a, not available; PET, positron emission tomography; SUV, standardized uptake value; and TAA, thoracic aortic aneurysm.

### Phagocytic Activity

Magnetic resonance imaging (MRI) with ultrasmall superparamagnetic particles of iron oxide (USPIO) is an alternative technique for imaging vessel wall inflammation in human aneurysm

and other vascular pathologies.<sup>26–28</sup> The underlying principles for this approach are the uptake of these particles by phagocytic cells, including macrophages and the signal void generated by iron particles on specific MR sequences (T2 and T2\*). Similar

to FDG, the availability of approved USPIO formulations for clinical use in other applications has facilitated the evaluation of this technique in human AAA. The long circulation time of USPIO mandates imaging at relatively late time points after tracer administration. As such, pilot studies of USPIO imaging in human AAA have relied on differences in T2- and T2\*-weighted MR images acquired before and 36 hours after USPIO administration.<sup>27,28</sup> In a pilot study of USPIO MRI in patients with AAA of 4.0 to 6.6 cm, the pattern of USPIO signal (distinct areas of focal USPIO uptake beyond the periluminal area) could identify patients with faster AAA growth rate (Figure 6).<sup>28</sup> On histological analysis of aneurysm tissue of a subset of patients who had open AAA repair, USPIO particles colocalized with CD68-positive cells (macrophages). Relative to PET, MRI has the advantage of providing high-resolution anatomic images, which may also be used for biomechanical analysis of AAA. However, there are many biological and technical pitfalls in acquiring and interpreting USPIO-based MR images.<sup>5,29</sup> Indeed, the promising pilot data discussed here are based on qualitative rather than quantitative analyses of the processed images. Nevertheless, the deficiencies of the current approach to AAA risk stratification and the promising pilot data have led to the MA<sup>3</sup>RS (MRI Using USPIO in Patients Under Surveillance for AAAs to Predict Rupture or Surgical Repair) study, an ongoing prospective multicenter clinical trial of USPIO MRI in predicting AAA outcome.<sup>30</sup> The results of this study are expected in 2017.

#### Translocator Protein Expression

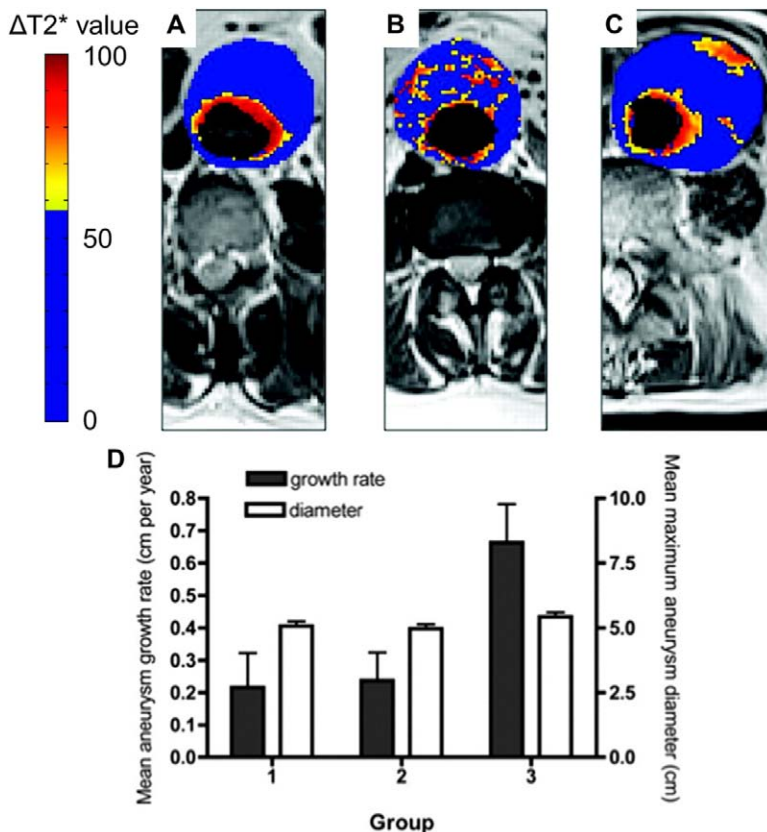
Translocator protein is a widely expressed mitochondrial protein involved in cholesterol transport and immunomodulation. Translocator protein ligands, including <sup>11</sup>C-PK11195,

bind to activated macrophages and are used for imaging inflammation, including vasculitis associated with systemic inflammatory disorders.<sup>31</sup> The potential of <sup>11</sup>C-PK11195 for detection of vessel wall inflammation in asymptomatic, mostly large, AAA was investigated in a small study, which yielded negative results,<sup>32</sup> possibly highlighting the difference in the severity of inflammation between systemic vasculitis and AAA.

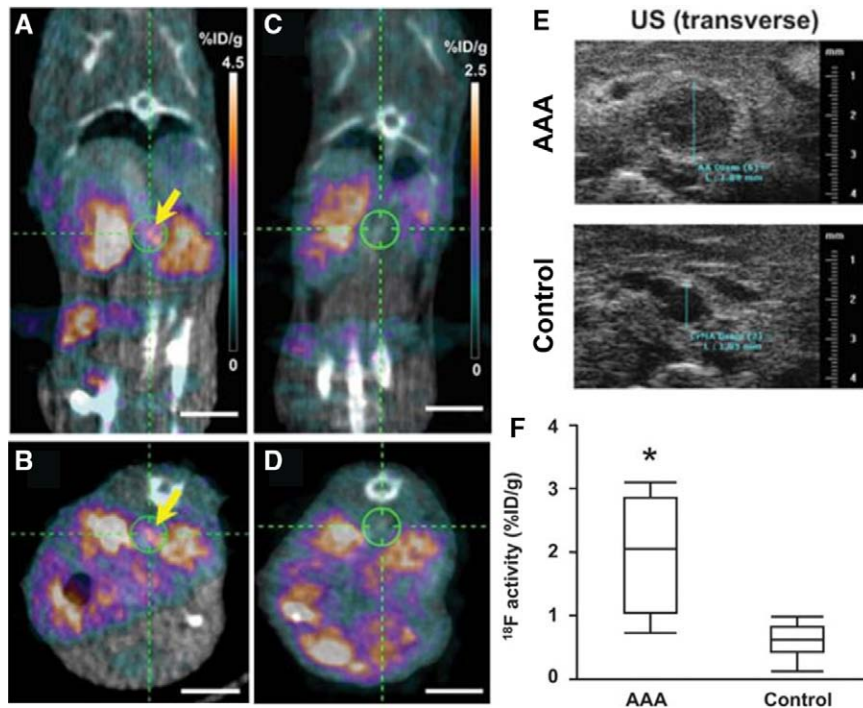
#### Preclinical Tracers and Targets

##### Integrin $\alpha_v\beta_3$

The integrin  $\alpha_v\beta_3$  is upregulated and activated in proliferating endothelial cells, vascular smooth muscle cells, and macrophages. Labeled arginine-glycine-aspartate (RGD) peptides and peptidomimetics (which bind to  $\alpha_v$  integrins) are used for imaging angiogenesis, as well as vessel wall inflammation and remodeling.<sup>33–36</sup> The feasibility of integrin-targeted imaging for detection of vessel wall biology has been shown in several animal models of aneurysm. In a murine model of calcium chloride-induced carotid aneurysm, NC100692, a <sup>99m</sup>Tc-cyclic RGD tracer, micro-single-photon emission computed tomography (microSPECT)/CT imaging showed significantly higher uptake of the tracer in the aneurysmal carotid artery compared with contralateral control vessel, with a correlation with the degree of inflammation.<sup>35</sup> Similarly, an <sup>18</sup>F-labeled RGD-based compound has been used to detect vascular changes in angiotensin II (AngII)-induced murine AAA (Figure 7).<sup>36</sup> In this study, RGD tracer uptake on PET images correlated with both the degree of vascular inflammation and neovessel counts (but



**Figure 6.** A–C, Color maps representing the magnitude of the change in  $T2^*$  values in abdominal aortic aneurysm (AAA; with blue reflecting changes below the threshold attributable to ultrasmall superparamagnetic particles of iron oxide [USPIO] accumulation and red reflecting large change) showing 3 patterns of USPIO uptake. Group 1 (A) shows a large periluminal change in  $T2^*$  value, representing nonspecific uptake; groups 2 and 3 (B and C) show diffuse patchy changes in  $T2^*$  throughout the intraluminal thrombus and distinct focal area of USPIO uptake affecting the aortic wall, respectively. D, Relationship of diameter (open bars) and growth rate (solid bars) with patient group showing a similar diameter but higher AAA growth rate in patients in group 3 compared with those in groups 1 and 2.  $P=0.020$ . Reprinted from Richards et al<sup>28</sup> with permission of the publisher. Copyright © 2011, Springer.



**Figure 7.** Integrin-targeted ( $^{18}\text{F}$ -labeled RGD-based compound [ $^{18}\text{F}$ -FPPRGD<sub>2</sub>]) positron emission tomographic (PET) imaging of murine abdominal aortic aneurysm (AAA). **A–D**, Examples of PET/computed tomographic images in angiotensin II-induced AAA (**A** and **B**) and normal control aorta (**C** and **D**), showing focal increase in the  $^{18}\text{F}$ -FPPRGD<sub>2</sub> signal in AAA (yellow arrows). **E**, Examples of in vivo ultrasound measurement of aortic diameter. **F**, Quantification of aortic signal showing a higher uptake in AAAs compared with control aortae (\* $P=0.003$  vs control). %ID/g indicates injected dose per gram; and US, ultrasound. Reprinted from Kitagawa et al<sup>36</sup> with permission of the publisher. Copyright © 2013, Springer.

not with AAA diameter).<sup>36</sup> Several RGD-based tracers are currently under clinical investigation for imaging angiogenesis in cancer and vessel wall inflammation and may prove to be useful for imaging human AAA.

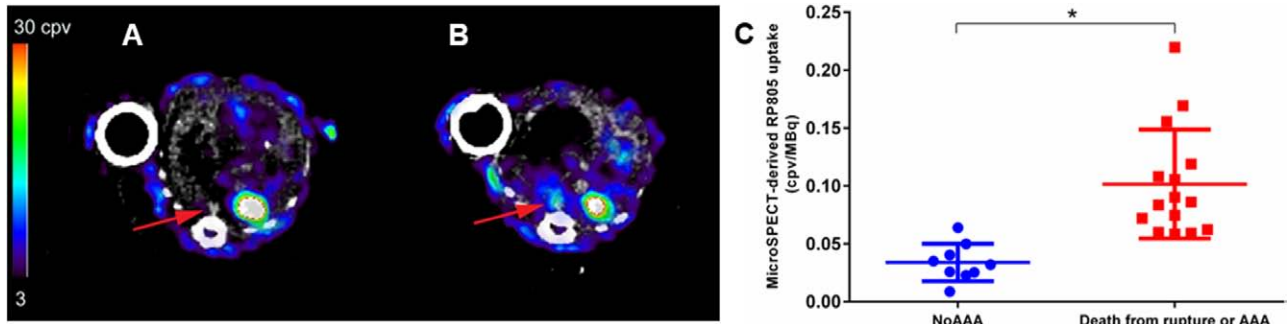
### Matrix Remodeling

Collagen and elastin are critical to vessel wall integrity, and imaging their turnover may be useful for AAA risk stratification. MRI using gadolinium-based micellar nanoparticles functionalized with CAN-35, a collagen-binding protein, was used to detect vessel wall collagen in a murine model of AAA induced using a combination of AngII infusion and transforming growth factor- $\beta$  neutralization.<sup>37</sup> Vessel wall enhancement was detectable in AAA on delayed imaging (at 32 hours post injection) and the nanoparticles colocalized with collagen fibers on histological analysis. Importantly, in mice undergoing imaging at 5 and 15 days post AngII infusion, signal enhancement was higher in stable AAA than those that ruptured.<sup>37</sup> Recently, a gadolinium-based elastin-specific MRI agent was used to detect changes in elastin (and tropoelastin) expression associated with AAA development in AngII-infused mice.<sup>38</sup> Vessel wall enhancement by this agent facilitated the identification of AAA rupture sites and provided insight into the compensatory proelastin synthesis encountered in this model of AAA.<sup>38</sup> In this regard, a molecular probe that differentiates between mature elastin in elastic laminae and tropoelastin may prove to be useful for AAA risk stratification.

Several proteases, including members of the MMP family, degrade the pillars of vessel wall integrity, particularly elastin

and collagen fibers, and as such, are key mediators of aneurysm expansion and rupture. Both MRI and nuclear imaging-based techniques have been used for in vivo AAA imaging in preclinical studies. P947, a gadolinium-based MR contrast agent with modest affinities for MMPs and several other zinc-dependent metalloproteinases, showed modest vessel wall enhancement on MR images in a rat model of elastase-induced AAA, but the correlates of the signal were not defined.<sup>39</sup> The applicability of this approach to imaging in humans remains to be determined.

Given their high sensitivity, nuclear imaging techniques may be more effective than MRI for imaging vessel wall biology in aneurysm. The feasibility of MMP-targeted nuclear imaging has been demonstrated in several models of vascular disease.<sup>40–42</sup> An  $^{111}\text{In}$ -labeled macrocyclic pan-MMP inhibitor (RP782) that binds with high affinity to activated MMPs was shown to detect MMP activation by microSPECT/CT imaging in murine calcium chloride-induced carotid aneurysm.<sup>41</sup> Tracer uptake in the aneurysmal artery paralleled vessel wall inflammation assessed by CD68 expression. In addition, MMP signal on images obtained at an early time point correlated with aneurysm size at a later time point.<sup>41</sup> These data were confirmed using a  $^{99\text{m}}\text{Tc}$ -labeled homolog, RP805, in a study of murine AngII-induced AAA.<sup>42</sup> In this study, suprarenal aortic RP805 uptake on microSPECT/CT images obtained at 1 week of AngII administration predicted future AAA expansion and spontaneous rupture (Figure 8).<sup>42</sup> It remains to be determined whether targeting MMP activation in general or a specific member of MMP family (eg, MMP-12) is more effective for predicting outcome in AAA. Although promising, the



**Figure 8.** Predictive value of matrix metalloproteinase (MMP)-targeted RP805 imaging in murine abdominal aortic aneurysm (AAA). Examples of RP805 (MMP-targeted)-fused single-photon emission computed tomographic (SPECT)/CT images at 1 week after angiotensin II (Ang II) infusion in mice that did not (A) and did (B) develop aneurysm at 4 weeks, demonstrating aortic MMP signal in the former mouse. Arrows point to suprarenal abdominal aorta. C, Quantification of suprarenal aorta RP805 uptake in images obtained at 1 week in mice that did not develop AAA at 4 weeks and those that had AAA or died of AAA rupture. \* $P < 0.0001$ . cpv indicates counts per voxel. Reprinted from Golestani et al<sup>42</sup> with permission of the publisher. Copyright © 2015, Springer.

validity of these observations needs to be established in large animal models and human AAA.

#### Other Potential Targets

CD105 (endoglin) is a membrane glycoprotein and part of the receptor complex interacting with transforming growth factor- $\beta$ , a key mediator of aneurysm development.<sup>43</sup> It is highly expressed on endothelial cells of neovessels and monocyte-macrophages. A copper-64-labeled CD105 Fab antibody fragment was evaluated for PET imaging of murine calcium-induced AAA.<sup>44</sup> High uptake of the tracer was noted in the abdomen in the AAA area on 6-hour postinjection images, and blocking experiments supported the specificity of the signal. The biological significance of this signal remains to be determined, especially as it is difficult to conclusively attribute the *in vivo* signal to AAA in the absence of hybrid imaging with CT. The high-residual blood pool activity ( $\approx 8\%$  injected dose per gram at 24 hours), often observed with Fab-based molecular probes, is a major limitation for clinical translation of this tracer.

Radiolabeled nanoparticles in conjunction with nuclear imaging may be used to detect the phagocytic activity of the cells in the vessel wall. Fluorine-18-labeled dextran-coated iron oxide nanoparticles were evaluated for PET/CT imaging of vessel wall inflammation in murine AngII-induced AAA.<sup>45</sup> PET imaging 10 to 12 hours after nanoparticle administration showed higher uptake in aneurysm compared with nonaneurysmal aorta. Furthermore, the high uptake of the tracer on early images (1 week of AngII treatment) was associated with future aneurysm growth and rupture.<sup>45</sup> Although useful as a research tool, the long circulation time of nanoparticles that mandates delayed imaging to clear blood pool activity maybe a barrier to clinical translation of this approach. Smaller nanoparticles that are cleared rapidly from bloodstream may address this limitation of nanoparticle-based imaging.

A variety of other molecular probes targeting relevant molecular markers or processes implicated in AAA have been evaluated in various pathological conditions (eg, atherosclerosis) and could be useful for AAA imaging.<sup>46</sup> Considering AAA pathophysiology, the most promising agents are likely those targeting inflammation and matrix remodeling.

### Molecular Imaging as Companion to Medical Therapy

In the absence of an effective medical therapy to slow down AAA progression, watchful waiting remains the mainstay of clinical approach to nonsurgical AAA. To address this limitation, many drugs are under development and, if found effective, may transform our approach to AAA management. In addition to antihypertensive agents that may ameliorate aneurysm biomechanics, emerging classes of pathophysiology-based AAA drugs include anti-inflammatory agents (cyclosporine A [ClinicalTrials.gov, NCT02225756] and canakinumab, [NCT02007252]), MMP inhibitors (doxycycline, NCT01756833), and antithrombotic agents (ticagrelor, NCT02070653). Along with their potential role in AAA risk stratification and guiding the timing of invasive interventions, molecular imaging techniques aimed at detecting inflammation, MMP activation, and thrombosis may facilitate AAA drug development by providing surrogate end points for *in vivo* assessment of drug effects. In addition, as companion to emerging medical therapies, they can help improve clinical efficacy by guiding treatment intensity based on tissue biology.

### Challenges in Clinical Translation and Implementation

#### Imaging Technology and Methodology

The small size of blood vessels is a major hurdle for effective vascular molecular imaging. In the case of abdominal aorta, its relative stability facilitates nuclear imaging. However, issues, such as scatter from blood, partial volume effect, and relatively low spatial resolution of PET and SPECT, need to be overcome for quantitative nuclear molecular imaging. The small size of the artery and vessel wall, especially in the case of rodent models of AAA, mandates hybrid imaging (eg, with CT angiography or MRI) to define anatomic structure and differentiate aortic signal from uptake in surrounding structures. Although less limited by spatial resolution, molecular MRI of AAA has its own challenges, including signal quantification, poor sensitivity, the relatively high amounts (and potential toxicity) of imaging probes, and the need for delayed imaging. Imaging and quantification methodology, which make it difficult to compare and explain the discrepancies of the results,



need standardization. Those considerations are discussed in detail elsewhere.<sup>47</sup>

### Animal Models of Aneurysm

In the absence of a reliable spontaneous model of AAA, preclinical imaging studies are performed in animal models that share some but not all features of human disease. Adventitial application of an irritating agent, such as calcium chloride,<sup>48</sup> or intraluminal exposure of proteolytic enzymes (eg, elastase)<sup>49,50</sup> is often used to induce focal inflammation and dilation of the artery in rodents and large animals.<sup>51</sup> Although these are useful preclinical models for imaging studies of inflammation, and possibly vascular remodeling in aneurysm, considerable perivascular changes and the associated wound are confounding factors. These issues must be carefully dealt with, for example, by using CT angiography or MRI to identify anatomic structure. The lack of spontaneous rupture in most of these experimental models is a major limitation for prospective studies of outcome in aneurysm.

AngII infusion (possibly in conjunction with anti-transforming growth factor- $\beta$  agents) induces aneurysm along the aorta, most prominently in suprarenal aorta, in mice.<sup>52,53</sup> The response to AngII infusion is more prominent in hyperlipidemic mice. Spontaneous rupture and dissection are often seen in this mode, and there is no interference from periarterial wound healing process. As such, AngII infusion is a useful and popular model for molecular imaging studies of AAA. Differences in aortic structure between humans and the mouse, including gene expression pattern and responsiveness to various stimuli, exist.<sup>54</sup> Unlike humans, the aorta in the mouse is a muscular artery,<sup>54</sup> and the time course of aneurysm development in the mouse is different from humans. Nevertheless, these are useful models for initial preclinical molecular imaging studies that can set the stage for early phase human studies.

### Economics and Regulatory Issues

Introduction of novel imaging agents to the clinic is a costly and time-consuming process, analogous to drug development.<sup>55</sup> A full discussion of economic and regulatory issues is beyond the scope of this review. However, only those agents with a potentially broad market can realistically recoup the costs associated with research and development, and securing regulatory approvals. Although a deadly disease, one can debate whether there is a large enough market for aneurysm-specific molecular imaging agents. Ultimately, imaging agents that target pathobiological processes common in multiple disease states are best positioned to overcome economic hurdles of clinical translation in AAA.

### Closing the Gap

Bridging the translational valley of death<sup>56</sup> of molecular imaging requires a concerted effort of all stakeholders, from clinicians and scientists, to industry and regulatory agencies. Currently, several clinical trials of AAA molecular imaging are underway (eg, MA<sup>3</sup>RS,<sup>30</sup> sodium fluoride imaging, <sup>18</sup>F-NaF PET-CT, in AAAs [SoFIA3]; ClinicalTrials.gov, NCT02229006). These trials are based on tracers approved for other indications and in general seek to establish the predictive value of various molecular imaging techniques in AAA.

Ultimately, for clinical implementation, the incremental value of these and other emerging molecular imaging techniques over anatomic imaging will have to be established. On the basis of the rupture rate of small AAA, probably a large number of subjects would be required to prove such an incremental value in patients with AAA <5 cm. A reasonable intermediary step may be the evaluation of the incremental value of emerging molecular imaging techniques in subjects with large AAA (and thus at high complication risk) who because of existing comorbidities might or might not benefit from AAA repair.

### Conclusions and Future Directions

The prevalence of AAA is increasing with aging of the population. Despite considerable progress in AAA screening and management in the past 2 decades, it remains a deadly disease. The classical anatomy-based approach to AAA imaging fails to fully capture the risk of rupture and identify factors that predispose to complications of EVAR. Emerging molecular imaging techniques may address some of these issues, but their clinical implementation is challenging. In this regard, FDG-PET studies of AAA have yielded inconsistent and contradictory results, suggesting the need for novel imaging agents and techniques for AAA risk stratification as paramount. Many agents are under development for imaging inflammation and matrix remodeling. These could prove to be useful for molecular imaging of AAA. Despite their limitations, preclinical models are important for evaluation of novel tracers and better characterization of the targeting properties of existing approved tracers, but there is also value in early testing of novel agents in humans. For clinical translation, image acquisition, processing, and quantification methodology need standardization. Ultimately, large-scale clinical trials are necessary to establish the added value of these emerging imaging approaches in AAA.

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## Novel Molecular Imaging Approaches to Abdominal Aortic Aneurysm Risk Stratification

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