High Levels of 18F-FDG Uptake in Aortic Aneurysm Wall are Associated with High Wall Stress


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Abstract
Background: Functional imaging using positron emission tomography (PET) showed increased metabolic activities in the aneurysm wall prior to rupture, whereas separate studies using finite element analysis techniques found the presence of high wall stresses in aneurysms that subsequently ruptured. This case series aimed to evaluate the association between wall stress and levels of metabolic activities in aneurysms of the descending thoracic and abdominal aorta.

Methods: Five patients with aneurysms in the descending thoracic aorta or abdominal aorta were examined using positron emission tomography—computed tomography (PET-CT). Patient-specific models of the aortic aneurysms were reconstructed from CT scans, and wall tensile stresses at peak blood pressure were calculated using the finite element method. Predicted wall stresses were qualitatively compared with measured levels of 18F-fluoro-2-deoxyglucose (18F-FDG) uptakes in the aneurysm wall.

Results: The distribution of wall stress in the aneurysm wall was highly non-uniform depending on the individual geometry. Predicted high wall stress regions co-localised with areas of positive 18F-FDG uptake in all five patients examined. In the two ruptured cases, the locations of rupture corresponded well with regions of elevated metabolic activity and high wall stress.

Conclusions: These preliminary observations point to a potential link between high wall stress and accelerated metabolism in aortic aneurysm wall and warrant further large population-based studies.

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Abdominal aortic aneurysm (AAA) is an important cause of deaths in Western society, especially among elderly patients. Rupture of AAA is responsible for approximately 1.3% of all deaths in men.1 The fact that not all AAA would eventually rupture has created a dilemma for surgeons with regard to treatment choice: Is it necessary to operate on all patients, or should we reserve prophylactic surgery only for a subgroup where factors indicative of a probable rupture could be identified? Diameter of the aneurysm is the most important factor in the decision to repair an aneurysm, but rate of enlargement is usually taken into account where watchful surveillance is employed for sub-surgical cases.2

On the one hand, although the size of the aneurysm still remains the most widely accepted predictor of rupture, small AAAs may also rupture. In their preliminary study, Sakalilhasan et al.3 by means of combined positron emission tomography and computed tomography (PET-CT) examination, observed positive correlation between clinically unstable AAA and positive uptake of 18F-fluoro-2-deoxyglucose (FDG) in the aneurysm wall. Elevated FDG uptake was also related to the presence of a high density of inflammatory cells (e.g. macrophages and lymphocytes) in the aneurysmal aortic wall.4 These observations have been confirmed by recent clinical and fundamental studies on in vivo demonstration of inflammatory cells using PET-CT.5,6

On the other hand, recent biomechanics studies using finite element analysis and patient-specific geometries of AAAs derived from CT scans have demonstrated that peak wall stress could be a better indicator of rupture than diameter.7,8,9,10

The role of biomechanical forces in the formation, propagation and ultimate rupture of aortic aneurysms has received some attention and is beginning to be better understood. Certain key mechanisms can be outlined. The initial change in the formation of an aneurysm is structural and results from a degenerative process in the vessel wall. As the morphology changes, related changes occur in the blood flow pattern, with consequential modification of fluid stresses and their interaction with the mechanical stresses within the arterial wall. The objective of this study was to investigate the role of increased metabolism in aneurysm rupture and whether this is linked with mechanical forces experienced by the affected aorta, by a combination of function imaging using PET and finite element stress analysis based on patient-specific data.

Materials and Methods

Patients

Since the first pilot study by Sakalilihasan et al.3 PET-CT examination has been performed routinely on almost all patients referred to the Department of Cardiovascular Surgery at the University Hospital of Liege, with known aortic aneurysms diagnosed initially by CT scans. Among 131 patients, the first three patients with thoracic aortic aneurysms (TAA) in the descending aorta and two patients with abdominal aortic aneurysms (AAAs) with high FDG uptakes were included in this study. All patients had the first PET-CT examination within 2 weeks from the initial diagnostic contrast-enhanced CT scan. Thereafter, they were monitored by follow-up CT or PET-CT examinations or underwent surgical repair. The study protocol was approved by the University Hospital of Liege local ethics review board and a written informed consent and authorisation to use the images for research were obtained from the patients or their relatives.

PET-CT imaging

The PET-CT examination was performed by following the procedure described by Burger et al.11 After a minimum of 6-h fasting, 3.7 mBq F18-FDG per kilogram body weight was injected through a peripheral vein catheter. The patient was placed in a quiet room and instructed not to move. One hour after injection of the tracer, static whole-body examination was performed with a PET-CT scanner (Discovery LS, GE Healthcare). The CT component of this scanner can acquire eight slices per X-ray tube rotation. After scout views, continuous CT was performed from the skull base to the femoral necks with the following parameters: 5 mm collimation, 50 × 50 cm field-of-view (FOV), 140 mA and 140 kVp, pitch of 1:5:1 and gantry rotation cycle of 0.8 s. The patients were asked to breath slowly during CT data acquisition.

Emission and transmission images were recorded 60 min after the F18-FDG injection, at each couch position for 4–5 and 2–3 min, respectively. PET data were acquired as six consecutive coronal 4.25-mm-slice-thickness 2D scans in all patients, overlapping from 15–30% PET raw data, were reconstructed by means of ordered subset expectation maximisation (pixel matrix of 128 × 128 and FOV of 50 cm), with 5.86 mm full width at half maximum (FWHM) post filter and 3.91 mm FWHM loop filter model-based scatter correction (convolution subtraction) and normalisation correction. Additional attenuation correction was performed on PET data, using the CT raw data.11 Attenuation-corrected PET and reformatted CT data were fused on a dedicated workstation (Advantage Windows, release 4.4.07, GE Healthcare). Both uncorrected and attenuation-corrected images were assessed to identify potential artifacts. The FDG uptake was defined as high when the maximum Standardised Uptake Value (SUV max) was greater than 2.5.

3D geometry reconstruction

The contrast-enhanced CT images were processed using our in-house MATLAB-based image processing toolkit, which has been tested extensively for accuracy and reproducibility.12,13 The lumen boundary was segmented semi-automatically by using the region growing method (RGM),14 which traces the perimeter of the lumen by seeking pixels of a selected range of intensities. Before applying the RGM, images were pre-processed by using a Gaussian filter to reduce the noise and improve image clarity. The segmented lumen contours were then assembled in 3D, and the lumenal surface was constructed by using cubic B splines. Similar procedures were followed for the segmentation and reconstruction of the outer wall surface. Since all patients included in this study presented intra-luminal thrombus (ILT) in their aneurysms, ILT was also reconstructed and
included in the finite element stress analysis model. Owing to the low contrast between arterial wall and ILT in CT images, it was not possible to distinguish the wall from thrombus; therefore, the inner wall boundary was generated by shrinking the outer wall boundary by a constant thickness, which was determined using an average value of 12 measurements made at sections where wall thickness was clearly defined (usually in the region where the thrombus was not present).

**Finite element stress analysis**

Stress analysis was performed for all the reconstructed aneurysm models by using a finite element method code ADINA 8.2 (Automatic Dynamic Incremental Nonlinear Analysis, Watertown, MA, USA). Since arterial walls exhibit non-linear behaviour and undergo large strains, a finite strain constitutive equation was employed. This was based on the two-parameter hyper-elastic constitutive model derived by Raghavan and Vorp, specifically suited for aortic aneurysms with corresponding material properties obtained from uniaxial tensile testing carried out on aneurysm tissue specimens. Each aneurysm model consisted of the arterial wall domain, including both wall and thrombus, where present. The thrombus was treated in a similar way to the aortic wall but with different material properties, as reported by Wang et al. A uniform load (corresponding to the peak systolic pressure) was applied on the inner surface of the aneurysm models in the direction normal to the surface. Suitable boundary conditions were applied at the two ends, where rotations and translations were constrained to simulate the tethering to the rest of the aorta. For the wall–thrombus boundary, the same number of elements was used; therefore the displacement was continuous across the two domains.

**Results**

**PET-CT examinations**

The characteristics and outcome of the patients are summarised in Table 1. Patient 1 with a TAA (initial diameter 46 mm) declined any surgical treatment despite having a high FDG uptake in the terminal segment of the descending thoracic aorta, which was also rapidly expanding. Six months later, he was admitted to the emergency department with back pain. A CT examination performed immediately revealed a markedly larger and ruptured terminal descending thoracic aorta, which was also rapidly expanding. CT examination performed immediately revealed a markedly larger and ruptured terminal descending thoracic aorta, despite the proposal of endovascular repair, this patient refused any treatment. Unfortunately, she presented Type B dissection diagnosed by PET-CT examination.

Patient 3 was followed up for 3 years with diffuse-moderate uptake of the FDG at the level of the descending thoracic aorta. She died from unrelated causes.

Patient 4 underwent resection of a large inflammatory abdominal aortic aneurysm (IAAA) with increased uptake of FDG at the neck of the aneurysmal sac (Fig. 2).

The last patient (patient 5) having a diffuse pattern of FDG uptake at the edge of intra-luminal thrombus on the anterior wall, and the junction between the neck and AAA sac on the posterior wall, refused any operation. Seven months later, he was admitted to the emergency department with back pain. A CT examination performed immediately confirmed the suspected clinical diagnosis of early stage AAA rupture (leaking) at the junction between the neck and AAA sac on the posterior wall (Fig. 3). Expanded retro-peritoneal haematoma was observed during surgery.

**Wall stress patterns**

Our finite element analysis of wall stress shows that the stress distribution is highly dependent on the 3D geometric features of the aneurysms, and that areas of maximum stress do not occur at the maximum diameter. In the case of patient 1 (Fig. 1A(b)), there are two concentrated regions of elevated wall stress, but the peak wall stress was found in the distal part of the aorta (marked by a black triangle). In patient 4 (Figs. 2A(c) and 2B(a)), the maximum stress is located approximately 5 mm below the renal arteries, in the anterior aspect of the aneurysm neck, but the overall stress levels are low owing to the thick thrombus. In patient 5, high wall stress can be seen in the anterior aspect of the aneurysm neck (Fig. 3(e)) and local stress concentration at the junction between the neck and aneurysm sac in the posterior side (not shown here) where fluid wall shear stress was found to be high (Fig. 3(f)).

**Comparison with PET images**

Since the finite element models were constructed from contract-enhanced CT images, matching the wall stress analysis results and the corresponding PET-CT images has to be performed carefully. This was achieved with the aid of anatomical landmarks, such as the renal arteries or the

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a Diameter at the time of the PET/CT examination.
aortic bifurcation. The vertical distance to or from the anatomical landmarks were calculated and used to find the correspondence between the two data sets. It can be seen from Figs. 1A and 1B where wall stress contours in a vertical section (1A(b)) and a horizontal section (1B(b)) of the TAA in patient 1 are compared with the corresponding PET-CT images. It is clear that there was a high level of FDG uptake in the terminal aorta. Rapid expansion of the TAA at this location was confirmed by subsequent scans and the aneurysm eventually ruptured at approximately the same location. It is interesting to note that levels of wall stress were also high in this region (shown in red). The horizontal plot further demonstrates that the location of high wall stress at this section correlates well with the site of high FDG uptake shown by the PET-CT fusion image (Fig. 1B(a)).

CT scan performed 6 months after the PET-CT examination revealed covered rupture of the TAA and a much enlarged terminal aorta (93 mm) at the same site as shown in Fig. 1B(c). And the finite element model (based on the geometry 6 months prior to rupture) predicted high levels of wall stress at the location of rupture.

Similar correspondence between areas of high wall stress and sites of elevated FDG uptake has also been found for the other patients examined. Figs. 2A and 2B show the comparison of high wall stress region in the aneurysm neck of patient 4 and the corresponding PET-CT image revealing elevated FDG uptake at the same location. This observation has significant clinical importance since the FDG uptake and high wall stress region was close to the renal arteries and the proximal suture following aneurysm resection of this patient was placed just below the renal arteries but at the top of this region. If the suture was performed lower (i.e. closer to the level of increased metabolism identified by PET-CT), the risk of recurrent AAA or false aneurysm at the level of the suture would be higher. This was reinforced by the finite element analysis, although wall stress results were not available at the time of resection.

In patient 5, maximum wall stress (Fig. 3(e)) was found to correlate with one of the regions showing positive FDG uptake on initial PET-CT scan (Fig. 3(a)). A suspected early rupture of AAA on the posterior wall was confirmed on subsequent CT examinations performed 6 months after the initial PET-CT scan. As shown in Figs. 3(b) and (c), the AAA started leaking (early sign of rupture) at the junction between its neck and sac where both wall stress concentration and fluid shear stress (shown in Fig. 3(f)) were relatively high. The AAA neck was found to have expanded from 40 mm to 42 mm during the 6-month period.

**Discussion**

Inflammation and media cell death are important biological activities involved in aneurysm growth. PET can help locate and measure metabolic activity of cells: PET is a technique that can produce image maps of functional processes in the body. It is based on the use of a short-lived radioactive tracer isotope, which has been chemically incorporated into a metabolically active molecule and injected into a living subject through the blood circulation. The
radioactive tracer decays by emitting a positron; the most commonly used molecule for this purpose is fluorodeoxyglucose (FDG). This technique is usually used for the detection of tumours, since FDG uptake into malignant cells is enhanced by an increased expression of glucose transport molecules on the tumour cell surface. However, FDG uptake is not specific for tumours. FDG-PET can also be positive in inflammatory disease and atherosclerotic lesions, as part of FDG is taken by macrophages and other blood cells. The macrophage glycolysis generates the signal that reaches the scanner.

In a previous study, we investigated the clinical use of PET for detecting increased metabolic activity in the aneurysm wall and concluded that PET imaging has the capacity to assess increased metabolic activity within the aneurysm wall. A subset of aneurysms showed increased 18-FDG uptakes, suggestive of a focally accelerated metabolism. This FDG uptake in the aneurysm wall probably reflects the presence of a high density of inflammatory cells (e.g. macrophages and lymphocytes) in the adventitia, as previously described. The activated inflammatory cells might correspond to the increased metabolic activity seen on PET imaging. These preliminary observations have been confirmed recently by a study performed by Reeps et al. In their study, increased FDG uptake was found in patients with a very high macrophage activity and symptomatic AAA. However, in agreement with the reports of Sakalihasan and Truijers et al., these authors failed to find a correlation
between maximum standard uptake value (SUV) and maximum cross-sectional infrarenal AAA diameter, which may predispose to rapid growth and/or imminent rupture. In the present study, five patients with expanding aneurysms were detected by PET-CT, and the expansion was found at the level of the aorta where elevated metabolic activity of the aortic wall was present. The corresponding CT images were processed separately and blindly to construct patient-specific models for finite element wall stress analyses. Our computational results showed highly non-uniform distribution of stress in the aneurysm walls due to their complex geometry. Moreover, the predicted high wall stress zones co-localised with the sites of positive FDG uptake in all five patients examined, and the location of rupture (for patient 1 and 5), and dissection (for patient 3). This observation reinforced our hypothesis that there exists a possible correlation between 18-FDG uptake by the aneurysm wall and the triggering processes leading to aortic aneurysm rupture. PET imaging, combined with biomechanical analysis, could potentially help us make more reliable decisions on the need for surgical repair of aortic aneurysms.

Conclusion

The main conclusions that can be drawn from our investigation on a small number of patients are as follows: (1) there is a potential link between accelerated metabolism in aortic aneurysm wall and high mechanical stresses experienced by the wall; and (2) PET imaging combined with wall stress analysis could potentially give more reliable predictions of the risk of aneurysm rupture. Moreover, PET-CT scan and finite element analysis are able to monitor the development and evolution of AAA. However, further large population-based studies are needed to confirm our preliminary findings.

Conflict of Interest

The authors have no conflict of interest.

Acknowledgements

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References


Figure 3 PET-CT images of the AAA in patient 5 (a) and (d) acquired at initial examination, and contrast-enhanced CT images acquired 6 months later showing early stage of rupture (white arrow) at the junction between the neck and AAA sac on the posterior wall (b), and at a distal section (c) showing peritoneal haematoma (white arrow). Predicted wall stress based on initial CT images is shown in (e) for a transverse section corresponding to the same location as (a), and predicted wall shear stress contours (f).


