Atherosclerosis 233 (2014) 510–517

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

CT signal heterogeneity of abdominal aortic aneurysm as a possible predictive biomarker for expansion

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ARTICLE INFO

Article history:
Received 7 May 2013
Received in revised form
18 December 2013
Accepted 3 January 2014
Available online 18 January 2014

Keywords:
Abdominal aortic aneurysm
Computed tomography texture analysis
CT signal heterogeneity
Positron-emission tomography
Risk stratification

ABSTRACT

Objective: There is a need for prognostic biomarkers for risk assessment of small abdominal aortic aneurysm (AAA). Since CT textural analysis of tissue is a recognized feature of adverse biology and patient outcome in other diseases, we investigated it as a possible biomarker in small AAA.
Methods: Fifty consecutive patients (46-men, 4-woman, median-age 75y, range 56–85) with small AAA (3–5.5 cm) under surveillance undergoing serial ultrasound were prospectively recruited and assessed at baseline with CT texture analysis (CTTA) and ^{18}F-Fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET). We followed forty patients (36-men, 4-woman, median-age = 74 y, range 60–85, participation rate = 80% for 1 year. For each axial image, CTTA using the filtration-histogram technique was carried out using a software algorithm that selectively extracts texture features of different coarseness (fine, medium and coarse) and intensity variation. Standard-deviation (SD) and kurtosis (K) at each feature-scale were measured. The maximum standardized uptake value (SUV_{max}) of ^{18}F-FDG in each axial image of the AAA was also measured with corrections for blood pool ^{18}F-FDG activity to assess AAA metabolic activity. Specificity, sensitivity, and c-statistics were calculated with 95% confidence intervals for prediction of significant AAA expansion (≥2 mm) by CTTA measures before and after adjusting for clinical variables.
Results: The median aneurysm expansion at 12 months was 2.0 mm, (IQR 0.0–4.0). Coarse texture SD correlated inversely with AAA SUV_{max} ($r_s = -0.456$, $P = 0.003$). Medium coarse texture K correlated significantly with future AAA expansion adjusted for baseline size ($r_s = 0.343$, $P = 0.030$). AAA SUV_{max} correlated inversely with AAA expansion corrected for baseline size ($r_s = -0.383$, $P = 0.015$). Medium texture K was a strong predictor of significant AAA expansion (area under the Receiver-operating-characteristic (ROC) curve was 0.813) after adjusting for clinical variables.
Conclusion: We have shown evidence that CT signal heterogeneity measurements in small aortic aneurysm may be considered as a risk stratification tool in future prospective studies to identify aneurysms at risk of significant expansion. CT textural data appears to reflect AAA metabolism measured by PET.

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1. Introduction

Abdominal aortic aneurysm (AAA) continues to pose a substantial health and economical burden, and is present in up to 10% of men between the ages of 65 and 79 years [1]. Aneurysm rupture is associated with 80% mortality for patients reaching emergency hospital services and 50% for those deemed fit for emergency intervention [1]. Dilatation greater than 50% compared with the expected normal diameter of the artery in question [2] or maximum diameter of the infrarenal aorta greater than 3.0 cm [3], is considered aneurysmal.

There is a need for risk stratification of small AAA (maximum diameter between 3.0 and 5.5 cm) [2]. In a large observational study, Thompson et al. reported that an adjusted annual AAA growth rate of at least 2 mm was significantly associated with clinical events such as intervention or rupture [4]. Currently, patients with slow growing small AAA, reaching the threshold of 5.5 cm, are offered intervention. However, some aneurysms rupture at a smaller size [5–7], and many larger aneurysms grow to a considerable size without rupture [8]. Furthermore, patients who

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http://dx.doi.org/10.1016/j.atherosclerosis.2014.01.001

are in need of more frequent screening and early intervention need to be identified, and strategies for testing new medical therapies are required [9–12]. Apart from baseline AAA size, it is critical to develop non-invasive imaging techniques to detect characteristics predicting significant aneurysm growth.

Other than measuring AAA anterior posterior (AP) diameter on CT or ultrasound, other imaging methods have been used to improve risk stratification in AAA. An area of interest has been the use of ^{18}F-FDG PET/CT, which has shown promise in semi-quantitative assessment of metabolic activity in AAA walls [13], the extent of which might predict future expansion [14]. Macrophages play an active role in all stages of vascular inflammation and the atherosclerotic plaque formation. Increased radioactivity using ^{18}F-FDG-PET can be used to assess macrophage activity because these cells have a high basal metabolic rate that is GLUT (Glucose transporter) dependent [15–17].

Up until now the CT component of the PET/CT scan has been used mainly for PET co-registration. CT can be exploited to quantify signal heterogeneity of tissues via texture analysis by assessing image grey-level distribution and degree of coarseness. In vascular disease, CT textural analysis (CTTA) has been used to investigate intraluminal thrombus in AAA after intervention [18] and carotid atherosclerosis [19]. An approach to quantify CT signal heterogeneity via CTTA is to use the filtration-histogram approach to enhance features at fine, medium and coarse texture-scales. Histogram characteristics such as the standard deviation (SD) that relates the degree of variation from the mean pixel value; and kurtosis (K) that reflects the pointedness of the histogram could then be quantified.

Furthermore, in oncology, CTTA parameters (SD and K) have been used to evaluate heterogeneity of various tumour types, with histological validation of the signals (representing hypoxia and neovascularisation) [20,21], that have been associated with overall and progression-free survival in lymphoma, oesophageal and colorectal cancers [21–23]. The biological basis for such findings is unclear, but may reflect areas of hypoxia/metabolic mismatch. AAA is associated with atherosclerosis [24] and is characterized by structural enzymatic degradation of elastic media, inflammatory infiltrate and neovascularisation [25]. Increased CT signal heterogeneity of vasculature may suggest structural changes with increased vascularity [26–28].

To our knowledge this is the first study to investigate small AAA using CTTA that attempts to link these parameters with prospective aneurysm growth. For these reasons we assessed the potential role of CTTA as a risk stratification tool for expansion in patients with small AAAs under surveillance. We also assessed correlation of CT features of heterogeneity with the FDG signal derived from PET.

2. Methods

2.1. Patients

During the period between February 2008 and June 2011, patients enrolled under AAA surveillance at one of our institutions (University College London Hospital, London or Royal Sussex County Hospital, Brighton) were invited to participate in this prospective CTTA and ^{18}F-FDG-PET/CT study. Fifty consecutive patients (44-men, 6-woman, median-age 75 years, range 56–85) with small aortic aneurysms (median diameter 48.5 mm, IQR 43.0–53.0) under routine surveillance were recruited for CTTA and ^{18}F-FDG-PET/CT. All patients had an asymptomatic infrarenal abdominal aortic aneurysm. One patient also had an iliac aneurysm. Patients with thoracic, inflammatory and or symptomatic AAA were excluded. The baseline demographics are presented in Table 1. Institutional Review Board permission and patient consent were obtained.

Table 1
Summary of the medical details of the patient population.

History or symptoms	*N = 40* (%)
Age (median, range)	74 (60–85) y
Male	90
Female	10
Ischaemic heart disease	33
Raised lipids	75
Statin use	70
Diabetes	10
Hypertension	78
Current or previous smoker	55
Median maximal AAA diameter	49.5 (IQR 43.0–53.0) mm[a] 51.0 (IQR 41.0–55.8) mm[b]

[a] Baseline median maximal AAA diameter as measured on duplex ultrasound.
[b] Baseline median maximal AAA diameter as measured on CT.

2.2. PET/CT image acquisition

We used a combined PET/64-detector CT instrument (GE Healthcare Technology, Waukesha, WI) to obtain images. Patients fasted for 6 h prior to scans. PET/CT images were acquired 3 h after injecting 200 MBq of ^{18}F-FDG, according to recognized protocol [29–32]. CT was performed using 64 × 3.75 mm detectors, a pitch of 1.5 and 5 mm collimation (140 kVp and 80 mA in 0.8 s) over the patient's abdominal aorta. For technical information on PET/CT image acquisition please refer to the Appendix.

2.3. CT texture analysis

Image heterogeneity of the AAA via CTTA using a filtration-histogram technique was assessed using TexRAD (TexRAD Ltd, Somerset, UK), a proprietary software algorithm developed by Ganeshan et al. [33]. CTTA of AAA was derived by filtering each CT image; to obtain fine texture scale i.e. filter value 1.0, approximately 2 mm in width (radius); medium texture scale i.e. filter value 1.5–2.0, approximately 3–5 mm in width (radius); and coarse texture scale i.e. filter value 2.5, approximately 6 mm in width (radius) was used. The filtered images were quantified using histogram-based parameters. These texture parameters include standard-deviation (SD) that relates the degree of variation from the mean pixel value (SD, width of the histogram) and kurtosis (K) that reflects pointedness of the histogram. SD increases approximately in proportion to the square-root of the number of features highlighted and their mean intensity difference compared to background (i.e. dark and bright features are both positive). Kurtosis is related inversely to the number of features highlighted (whether bright or dark) and increases by intensity variations in highlighted features. By quantifying these different image features (size, concentration and density-variation of the features highlighted by the filter) within a tissue (representing the different aspects of tissue heterogeneity), computed image texture analysis algorithms have the potential to provide additional morphological information relating to tissue heterogeneity [34]. A detailed description of the above image filtration and quantification is described in the Appendix. CTTA was performed by an experienced reader (C.W.) under supervision from a researcher (B.G.) with 7 years' experience in texture analysis of radiographic images who aided in inter-observer variability measurements. Both were blinded to the results of FDG-PET analysis and aneurysm growth rates. Interclass correlation coefficient (ICC) to assess inter-observer variability was performed by C.W and B.G. For each patient, a whole vessel analysis of the imaged AAA was performed. CTTA was measured over the whole volume of each AAA considering all the individual axial slices. A region of interest (ROI) was placed to include the aneurysm wall

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