Eur J Vasc Endovasc Surg (2017) ■, 1–10

Flow Mediated Dilatation and Progression of Abdominal Aortic Aneurysms

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WHAT THIS PAPER ADDS

Abdominal aortic aneurysm (AAA) is a complex disease with multifactorial contributions towards disease progression. Biomarkers for AAA progression will be useful to better inform the surveillance interval and threshold for surgery in individual patients. This study provides novel evidence to support the potential utility of flow mediated dilatation (FMD) as a biomarker in the context of AAA disease: FMD deteriorates during the natural history of AAA growth; FMD is inversely correlated with future AAA growth, and can be improved by AAA surgery. These findings warrant further investigation.

Objective/Background: Biomarker(s) for prediction of the future progression rate of abdominal aortic aneurysms (AAA) may be useful to stratify the management of individual patients. AAAs are associated with features of systemic inflammation and endothelial dysfunction. Flow mediated dilatation (FMD) of the brachial artery is a recognised non-invasive measurement for endothelial function. We hypothesised that FMD is a potential biomarker of AAA progression and reflects the temporal changes of endothelial function during AAA progression.
Methods: In a prospectively recruited cohort of patients with AAAs (Oxford Abdominal Aortic Aneurysm Study), AAA size was recorded by antero-posterior diameter (APD) (outer to outer) on ultrasound. Annual AAA progression was calculated by (ΔAPD/APD at baseline)/(number of days lapsed/365 days). FMD was assessed at the same time as AAA size measurement. Analyses of data were performed in the overall cohort, and further in subgroups of AAA by size (small: 30–39 mm; moderate: 40–55 mm; large: $>$ 55 mm).
Results: FMD is inversely correlated with the diameter of AAAs in all patients ($n = 162$, Spearman's $r = -.28$, $p < .001$). FMD is inversely correlated with AAA diameter progression in the future 12 months (Spearman's $r = -.35$, $p = .001$), particularly in the moderate size group. Furthermore, FMD deteriorates during the course of AAA surveillance (from a median of 2.0% at baseline to 1.2% at follow-up; $p = .004$), while surgical repair of AAAs ($n = 50$ [open repair $n = 22$, endovascular repair $n = 28$)] leads to an improvement in FMD (from 1.1% pre-operatively to 3.8% post-operatively; $p < .001$), irrespective of the type of surgery.
Conclusion: FMD is inversely correlated with future AAA progression in humans. FMD deteriorates during the natural history of AAA, and is improved by surgery. The utility of FMD as a potential biomarker in the context of AAA warrants further investigation.

Article history: Received 16 December 2016, Accepted 1 March 2017, Available online XXX
Keywords: Abdominal aortic aneurysm, Biomarkers, Flow mediated dilatation, AAA Progression

INTRODUCTION

Abdominal aortic aneurysms (AAAs) can result in rupture and death if left untreated. Existing international guidelines recommend a threshold of 55 mm for elective surgical repair in men. In clinical practice, patients with AAAs $<$ 55 mm are typically kept under surveillance by regular ultrasound until the AAA expands above the threshold.[1] However, the landmark clinical trials that led to the establishment of these guidelines also demonstrated the progression rate of AAAs vary between individuals, and the majority of patients ($\sim$70%) with an initial AAA diameter $<$ 55 mm will progress and require surgery within 5 years.[2,3] Biomarkers of future AAA progression can improve clinical management. Those with AAAs that will be fast growing may benefit from surgery earlier than the existing 55 mm threshold. However, such a biomarker is, as yet, not available.

AAAs are associated with features of systemic inflammation and endothelial dysfunction.[4–6] Endothelial dependent vasomotion has been widely used as a surrogate marker of endothelial function. Flow mediated dilatation (FMD) was first reported by Celermajer *et al.* to be a

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http://dx.doi.org/10.1016/j.ejvs.2017.03.001

Please cite this article in press as: Lee R, et al., Flow Mediated Dilatation and Progression of Abdominal Aortic Aneurysms, European Journal of Vascular and Endovascular Surgery (2017), http://dx.doi.org/10.1016/j.ejvs.2017.03.001

repeatable, non-invasive physiological assessment for the quantification of systemic endothelial function.[7] It has since become a widely recognised and applied method for the assessment of endothelial function.[8]

FMD is measured following the generation of a vasodilatory stimulus of a distal vascular bed, most commonly the forearm.[8] In practice this involves the application of a blood pressure cuff on the forearm, which is then inflated to supra-peak systolic pressure to generate a short period of blood flow occlusion. The brachial artery is imaged continuously using ultrasound to detect any changes in arterial diameter induced by shear stress from changes in blood flow. This test is frequently coupled with the pharmacological supplementation of nitroglycerin to assess the endothelium independent vasodilatory response, which serves as a comparator for FMD mediated through the endogenous release of nitric oxide.[9]

Since the first report by Knipp *et al.*, which showed impaired FMD in patients with AAA compared with healthy volunteers or those with peripheral occlusive arterial disease,[6] two other small case series ($n \leq 66$) further reported the inverse association between FMD and the diameter of AAAs.[4,5] Further, it has been shown that vascular intervention for occlusive arterial disease, either in the form of endovascular intervention or surgical bypass,[10,11] can lead to significant improvements in brachial artery FMD. In the broader literature for cardiovascular disease, endothelial dysfunction has also been shown to correlate with the severity of atherosclerotic arterial disease, and is a potentially reversible risk factor.[12] However, no study has yet examined the changes of FMD during the course of AAA progression, or the effect of operative intervention on FMD.

We investigated the role of FMD as a potential biomarker of AAA by assessments of FMD during the natural history in individuals with AAAs.

METHODS

Participant cohort

The Oxford Abdominal Aortic Aneurysm (OxAAA) study is designed to investigate longitudinally the natural history of AAAs. The study received full regulatory and ethics approval from the Oxford University and Oxford University Hospitals (OUH) National Health Service (NHS) Foundation Trust (Ethics Ref: 13/SC/0250). Every participant provided written consent. Participants were recruited at the John Radcliffe Hospital, which is part of the OUH NHS Foundation Trust.

We recruited patients with infrarenal AAAs (aortic diameter $\geq$ 30 mm) under surveillance and those that had an incidentally diagnosed AAA requiring surgery. To capture a study cohort that reflects the characteristics of modern day patients with AAA, we only excluded patients with active neoplasms, renal failure on dialysis, or where long-term participation in the study would not be reasonable (e.g., unwillingness to return to OUH for follow-up assessments, or the inability to tolerate the FMD protocol). Participants in the surveillance group were approached after being identified through the OUH regional vascular unit surveillance database by the clinical team, followed by an invitation to take part in the study. If patients chose to participate, their study visits were synchronised with their regularly scheduled surveillance appointments in order to minimise their inconvenience.

Participants in the operative stream were typically assessed at the time of pre-operative assessment or during their hospital admission for surgery. This stream also included patients who were part of the surveillance programme and progressed through to the surgical threshold. After surgery, patients routinely returned for a post-operative assessment in the outpatient clinic between 8 and 12 weeks, when the research assessment was also repeated.

For each study assessment, the participant was required to fast for 6 hours before the study (except their regular medications) and to refrain from caffeinated beverages and cigarette smoking for 24 hours prior to their visits. Demographic data were collected at the first research appointment and changes in medications and comorbidities were recorded at each subsequent appointment. Clinical blood tests were performed by the OUH biochemistry laboratory.

AAA size and subgroups

For each participant, AAA size was obtained as the clinical test by the NHS AAA surveillance, performed by a certified vascular technologist in the vascular laboratory. AAA size was defined by the maximum antero-posterior (AP) diameter (outer to outer). For this study, an AAA was defined by AP diameter $>$ 30 mm. Further subgroups were defined according to the AP diameter (APD) into small (30–39 mm), moderate (40–55 mm), and large ($>$ 55 cm) AAAs. The annual growth rate of AAA during surveillance was calculated by: (ΔAPD/APD at baseline)/(number of days lapsed/365 days).

For the analyses pertaining to future growth rate, we focused on those with AAAs $<$ 55 mm at the time of recruitment. We reasoned that beyond this point, biomarkers of future AAA progression should have little impact on existing clinical practice: those with large AAAs ($>$ 55 mm) should have been referred for surgery promptly, and those who do not undergo surgery beyond this size are likely to be affected by other confounding factors. The distinction was set between the subgroup of small and moderate size AAAs, as the previous clinical trials on early surgery versus surveillance for AAAs used 40–55 mm as the size criteria for inclusion.[13] On the other hand, patients with small AAAs (30–39 mm) are unlikely to be offered surgery, even in a clinical trial setting.

Ultrasound image acquisition and analyses

The research appointments for each patient took place on the same visit as the NHS AAA surveillance scan, during daytime hours. Ultrasound imaging of the brachial artery was then performed (CX50, L12-3 probe; Phillips, Eindhoven, The Netherlands) to record flow mediated and nitroglycerin mediated responses according to an established protocol.[9] For detailed descriptions of the FMD procedure and analysis please see Appendix S1 (Supplementary Material).

Please cite this article in press as: Lee R, et al., Flow Mediated Dilatation and Progression of Abdominal Aortic Aneurysms, European Journal of Vascular and Endovascular Surgery (2017), http://dx.doi.org/10.1016/j.ejvs.2017.03.001