Increased Augmentation Index in Patients with Cystic Fibrosis.

James H. Hull¹, Rachel Garrod¹, Timothy B. Ho², Ronald K. Knight², John R. Cockcroft³, Dennis J. Shale³,⁴, Charlotte E. Bolton³,⁴.

1) Faculty of Health and Social Care Sciences, Kingston University and St George’s, London, SW17 0RE, United Kingdom.
2) Knight Centre for Cystic Fibrosis, Frimley Park Hospital, Frimley, Surrey, GU16 7UJ, United Kingdom.
3) Dept of Cardiology, School of Medicine, Cardiff University, Wales Heart Research Institute, University Hospital of Wales, Cardiff, CF14 4XW, United Kingdom.
4) Dept of Respiratory Medicine, School of Medicine, Cardiff University, Academic Centre, Llandough Hospital, Penarth, Vale of Glamorgan, CF64 2XX, United Kingdom.

Corresponding author: Dr J.H. Hull, Faculty of Health and Social Care Sciences, 2nd floor Grosvenor Wing, St George’s Hospital, London, SW17 0RE, United Kingdom.
Tel: 0044 208 266 6187 Fax: 0044 208 725 2248 E-mail: jiminio@doctors.org.uk

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ABSTRACT

Increased large artery stiffness occurs in a range of inflammatory conditions indicating an ageing of the vasculature and additionally being an independent risk factor for cardiovascular events. We determined large artery parameters in adults with cystic fibrosis (CF).

Clinically stable adult patients with CF, n=50, mean (SD) age 28.0 (8.2) years, and 26 age, gender and BMI matched controls were studied. Central aortic blood pressure, augmentation index (AIx) and aortic pulse wave velocity (PWV) were determined using applanation tonometry. Lung function, diabetic status and CRP were also determined.

Mean (SD) AIx was greater in patients, 8.5 (11.1) %, than controls, -1.8 (13.1) % (P<0.001), while PWV was similar. Although AIx was greatest in the sub-group with CF related diabetes (CFRD), it was also increased in the non-CFRD sub-group when compared with controls. In patients, AIx was related to log10CRP (r=0.33) and forced vital capacity (r=-0.34), both P<0.05, and CRP remained predictive in multiple regression.

AIx is increased in adults with CF, in the presence of a normal blood pressure and independent of diabetic status. AIx was related to the systemic inflammatory status. These findings have implications for management and require further exploration so that cardiovascular health is maintained.

Abstract word count: 198

Key Words: Cystic Fibrosis, arterial stiffness, diabetes mellitus, inflammation.
INTRODUCTION

As survival in cystic fibrosis (CF) increases, there is a need to focus on extra-pulmonary co-morbidities that affect the length and quality of life in the adult stage of the disease [1]. Many of the co-morbidities, including low skeletal muscle mass and function [2] and osteoporosis [3] would be expected to occur in a comparatively older population as part of physiological ageing, yet are evident in patients with CF in their second and third decade. Similar co-morbidities are a feature of other disorders with a chronic systemic inflammatory component such as rheumatoid arthritis and chronic obstructive pulmonary disease (COPD), where there is again, apparent dissociation of physiological and chronological ageing [4-6].

COPD and rheumatoid arthritis are both associated with increased arterial stiffness, an independent predictor and risk factor for cardiovascular disease in the general population [4, 7-9]. The elastic aorta does not just act as a conduit for blood flow from the heart to the peripheries but acts as a buffer to cushion the potentially deleterious effects of pulsatile energy on the microcirculation. When arteries stiffen there is a progressive change in large artery haemodynamics leading to an increase in pulse wave propagation as well as amplitude and timing of peripheral arterial wave reflections. These changes increase left ventricular afterload, reduce coronary perfusion in diastole and adversely affect perfusion of distal organs such as the renal parenchyma, although these secondary events are often occult initially. Overall such alterations in haemodynamics are most concisely summarised in young individuals by the determination of augmentation index (AIx), a composite vascular parameter of both arterial stiffness and global peripheral wave reflection [10].
This accelerated vascular ageing has recently been demonstrated in untreated patients with HIV, a condition characterized by chronic systemic inflammation and catabolic intermediary metabolism [11]. Similarly in CF, both chronic systemic inflammation and catabolic intermediary metabolism occur [12], and therefore raises the possibility that premature ageing of the vasculature may occur, where its impact is likely to affect adult patients.

In addition, in the non-CF population, diabetes mellitus is associated with increased arterial stiffness, appearing to advance vascular age by approximately 8-9 years [13]. The course of CF in adults is often complicated by the development of abnormalities in glucose metabolism and by CF related diabetes mellitus (CFRD) [14]. In these patients with CFRD, we currently scrutinize for microvascular abnormalities but not macrovascular risk. Other factors associated with presence of increased arterial stiffness such as hypoxia, loss of lung function [15] and renal impairment [16] are also relevant to the CF population.

We hypothesized that adults with CF would have increased Alx, compared with controls which would be related to the presence of systemic inflammation and greatest in the sub-group with diabetes. We therefore evaluated large arterial haemodynamics in a group of adult patients with CF, both with and without CFRD and compared them with cohort matched non-CF control subjects.
METHODS

Subjects
Adult patients with confirmed CF (clinical features and positive sweat test and/or an accepted CF genotype) and healthy age, gender and body mass index (BMI) cohort matched controls were recruited. All subjects provided written informed consent and the study was approved by the Local Research Ethics Committee.

Study Design
Assessments occurred when the patient was clinically stable with no exacerbation (new or change in respiratory symptoms associated with a >10% fall in FEV₁ from their usual value) in the month prior to study. No patient had received iv antibiotics for 4 weeks prior to the assessment. Liver cirrhosis, chronic renal failure, known cardiovascular disease and transplantation were exclusion criteria (n=16). Additionally, long-term oxygen therapy, non-invasive ventilation, Burkholderia cepacia pulmonary infection or maintenance prednisolone (or equivalent) >5mg/day were exclusion criteria (n=8). Controls had similar exclusion criteria and were free from respiratory and metabolic disease.

All subjects were studied in the morning, following an overnight fast and abstinence from caffeinated beverages, tobacco and inhaled short acting β-2 agonists.

Anthropometry, lung function, and physical activity
Height, weight, hip and waist circumference were measured and from these, BMI (kg/m²) and waist to hip ratio (WHR) were calculated. Fat free mass (FFM) and its height squared index (FFMI) were determined by bio-electrical impedance (BodyStat, UK).

Forced expiratory volume in one second (FEV₁), forced vital capacity (FVC) [17] and resting percutaneous oxygen saturation (SpO₂) were measured. Habitual physical activity (expressed in METS; 1 MET=energy expended at rest) was determined by recall questionnaire relating to typical activity in the preceding month [18].

**Haemodynamic measures**

Haemodynamic measurements were taken prior to any invasive or physiologically stressful measurement. Peripheral blood pressure (BP), the mean of three consecutive brachial artery readings, was measured seated (OMRON Corporation, Japan). Radial artery waveforms were recorded using a high fidelity micromanometer (Millar instruments, Texas, USA). Pulse wave analysis (Sphygmocor; AtCor Medical, Sydney, Australia) was then used to generate a corresponding central arterial waveform and with the integral software calculate augmentation index (Alx). Alx is defined as the difference between the second and first systolic peaks expressed as a percentage of the pulse pressure (PP) and was corrected for a heart rate of 75. All results for Alx are presented as heart rate adjusted. Pulse wave velocity (PWV) was determined supine by sequentially recording ECG gated carotid, radial and femoral artery waveforms to obtain pulse wave transit time and then dividing by the distance between two recording sites to give aortic (carotid-femoral) and brachial (carotid-radial) PWV [4, 10]. Values were taken
as the mean of duplicate reproducible readings from traces reviewed by an independent operator, blinded to the individual’s status.

**Laboratory analyses**

Electrolytes, high sensitivity C-reactive protein (CRP), fasting glucose and lipid profile (total cholesterol (TC), high and low density lipoprotein (HDL & LDL), and triglyceride (TG)) (Advia 2400, Siemens Medical Solutions) were determined. Estimated glomerular filtration rate (GFR) was calculated from the Cockcroft-Gault equation [19]. Patients without a previous diagnosis of CF related diabetes (CFRD) underwent an oral glucose tolerance test (OGTT). Subsequently, patients were classified as CFRD (previous diagnosis or fulfilling OGTT criteria) or non-CFRD [20].

**Other measurements**

Questionnaire and/or interview was used to evaluate medication, smoking and family cardiovascular history.

**Statistics**

Data is reported as arithmetic mean (SD), unless otherwise stated. Positively skewed data (CRP and glucose) were log$_{10}$ transformed and results shown as geometric mean (SD). Continuous variables with normal distribution were evaluated using independent t-tests, Pearson’s correlation coefficient and one-way ANOVA with Tukey’s post hoc test. Categorical data was analyzed using chi-squared. Multiple stepwise regressions were used to determine predictors of AIx in patients. Analysis was performed using SPSS 15 with a p-value of <0.05 considered significant.
RESULTS

Subject’s characteristics

Patients (n=50) and controls (n=26) were similar for mean age (Table 1). A similar proportion of patients (n=2) and controls (n=3) were ex-smokers, however three patients were current smokers. In this minority who had smoked, median (range) smoking pack years was 3 (2-20) in patients and 3 (2-5) in controls. There was a family history of cardiovascular disease, in first degree relatives less than 60 years old in two patients but no controls. The BMI and FFMI (48 patients, 26 controls) were similar whilst WHR was greater in patients.

Of the patients, 25 (50%) were homozygous for δF508 mutation, 42 (84%) were pancreatic insufficient and 28 (56%) had respiratory isolates for Pseudomonas aeuriginosa. Current therapy for patients (% of patients) included long-term oral and inhaled antibiotics (98%), 86% being on oral azithromycin, vitamin (90%) supplements (90%), pancreatic enzyme supplements (84%), nebulised DNAse (76%) and inhaled corticosteroid (66%). No patients were on oral diabetic, anti-hypertensive or cholesterol lowering medication.

Laboratory data

Circulating CRP was greater in patients than controls (P<0.01) but similar between males and females in both patient and control groups. In patients, log_{10} CRP was inversely related to FEV\textsubscript{1} % predicted (r=-0.42, P<0.01), FVC % predicted (r=-0.48, P<0.001) and FFMI (r=-0.32, P<0.05). Patients had lower total cholesterol and greater triglyceride levels than controls (Table 1) however cholesterol ratio (TC/HDL) was similar
between groups by virtue of reduced HDL in patients (P<0.05). No patient had a total cholesterol greater than 5.4mmol/L or triglyceride level greater than 1.8mmol/L. Calculated GFR was lower in patients than controls, P<0.001.

**Haemodynamic results**

Both peripheral and central blood pressure parameters (systolic, diastolic, mean arterial pressure (MAP) and pulse pressure (PP)) were similar in patients and controls although patients had greater heart rate (HR) than controls (P<0.001), (Table 2).

Mean (SD) AIx was greater in patients, 8.5 (11.1) %, than controls, -1.8 (13.1) % (P<0.001) and remained greater after adjustment for known potential confounders: age, gender, height and peripheral MAP. Neither aortic nor brachial PWV were different between patients and controls.

The AIx was related to age in all subjects (r=0.41, P<0.001) and patients (r=0.54, P<0.001), and was greater in patients than controls in each of the 5-year age banding for the overlapping age range, i.e. 20-39 years old (Figure 1). The AIx was greater in females than males in both the patients and controls (P<0.01) but the difference in both study groups was lost when adjusted for height.

- Diabetic status

There was no difference in peripheral BP between CFRD, non-CFRD and controls. However, AIx was greatest in patients with CFRD, 13.1 (4.3) % compared to non-CFRD, 6.9 (12.3) % and controls, - 1.8 (13.1) %, (P<0.001, ANOVA and Tukey's post hoc
analysis) (Table 2 and Figure 2). This difference remained after adjustment for previous confounders including age, P<0.05. Importantly, Alx remained greater in the non-CFRD patients than the controls (ANOVA and Tukey’s post hoc analysis, P<0.05).

Aortic PWV was greater in the CFRD subgroup of patients: 7.3 m/sec (2.1), than both the non-CFRD patients: 6.1 m/sec (1.1) and controls: 6.1 m/sec (0.8), both P<0.05 and remained so after adjustment for age (ANOVA).

- Pulmonary function

Pulmonary function results are shown in Table 1. In all subjects, there was an inverse relationship between Alx and FEV$_1$ % predicted (r=-0.34, P<0.01) and FVC % predicted (r=-0.33, P<0.01). Whilst in patients alone, Alx was inversely related to FVC % predicted (r=-0.34, P<0.05) but not FEV$_1$ % predicted. No patients had a SpO$_2$ of less than 92% and there was no association between Alx and SpO$_2$.

- Laboratory Data

The Alx was related to Log$_{10}$CRP in all subjects (r=0.41, P<0.001) and in patients alone (r=0.33, P<0.05). In patients, Alx was inversely related to estimated GFR (r=-0.55, P<0.001). In patients and controls there was no relationship between total cholesterol, cholesterol ratio or triglyceride level and Alx.

- Other clinical characteristics

There was no difference in Alx between the patients homozygous for δF508 and other genotypes or between patients who were pancreatic sufficient and insufficient. There
was an inverse relationship of Alx to FFMI in all subjects ($r=-0.38$, $P<0.001$) and to a similar degree in patients ($r=-0.33$, $P<0.05$).

- Multiple Regression

Multiple stepwise regression analysis was performed to evaluate potential variables in patients that may influence Alx (Table 3). Known, previously reported confounders of Alx (age, height and peripheral MAP) together with markers used to evaluate disease severity (BMI, FVC % predicted and log$_{10}$CRP) were entered into the model. In patients, age, height and log$_{10}$CRP were predictive and accounted for 50% in total of the variance in Alx. In a second model, diabetic status was added but did not affect the results.
DISCUSSION

Adult patients with CF have increased augmentation index compared with age and gender matched healthy controls, which is related to systemic inflammatory status. These findings suggest early vascular abnormalities in the setting of a normal peripheral blood pressure. These alterations occur in patients with or without CFRD, and with mild to moderate severity lung disease. Such findings, present in early adulthood, have an immediate cardiovascular functional relevance and may have important clinical implications for future cardiovascular health, especially as longevity increases in CF.

Determination of pulse wave reflection has been used to demonstrate arterial stiffness, delineate arterial ageing and predict cardiovascular risk in both healthy individuals and subjects with chronic disease states [13, 21-27]. Indeed, AIx is the most relevant measure of stiffness in subjects under 50 years and our finding of increased AIx rather than PWV is in keeping with the literature [28]. Throughout life there is ageing of the large vasculature however aortic PWV and AIx characterise this vascular ageing differently due to their relationship with the physical qualities of the aorta and the relative contribution of peripheral wave reflection [29]. As such, AIx increases markedly and progressively up to 50 years of age, whilst aortic PWV increases only modestly in parallel with systolic and diastolic BP in the same age range. A UK population study (ACCT) reported that, in this age range, a 9% increase in AIx corresponded to the effect of ageing by ten years [28]. We found this magnitude of difference between patients and controls, inferring that the large artery haemodynamics of the patients are behaving approximately a decade in advance of that expected for their chronological age. This premature vascular ageing in our patients was not explained by increased blood
pressure, physical activity, smoking history or other accepted cardiovascular risk factors, such as plasma lipids, as our patients and control subjects were well matched in these respects. These findings are consistent with both our own group and others’ reports of vascular ageing in different chronic inflammatory conditions [4, 7-9, 13, 30-32].

Systemic inflammation is associated with cardiovascular risk in various populations, including healthy individuals [33]. The predictive relationship between CRP and AIx, implicates systemic inflammation in the vascular ageing process we report. This is reiterated by previous studies of chronic inflammatory disorders where the relationship is demonstrated, even though concurrent overt cardiovascular health appears maintained, only manifesting as disease at a later stage [4, 7, 8, 30-32]. Inflammation affects endothelial function but may also promote arterial stiffness by direct effects on vessel architecture and vascular smooth muscle function [32]. Support for the association between systemic inflammation and arterial stiffness is further demonstrated by the attenuation in arterial stiffness following treatment with anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis [7]. Indeed the fact that therapeutic and lifestyle intervention may modulate arterial stiffness in other conditions highlights the essential importance of its identification.

There is currently little clinical or epidemiological evidence of increased cardiovascular disease in CF and it has been argued that such patients are protected against the development of atherosclerosis by virtue of a favorable lipid and peripheral blood pressure profile [34]. Recent reports of myocardial infarction [35, 36] and hypertension [37] in non-transplanted patients however challenge this; whilst our data highlights that
the traditional peripheral brachial blood pressure assessment may be normal in the presence of altered large artery haemodynamics. Although our findings need verifying in longitudinal studies to determine the longer term clinical implications of the increased AIx, it is important to identify this vascular ageing at the earliest possible stage. Certainly, in the general population, early adulthood exposure to risk has been shown to predict the later development of cardiovascular disease and determine its rate of progression [38, 39]. As such, detection of arterial stiffness may be important to ensure the improved life expectancy now enjoyed by many patients is not offset by an increase in cardiovascular events.

Additional to the increased AIx for the whole patient group and although demonstrable in the non-CFRD subgroup, AIx was greatest in patients with CFRD, a finding consistent with that in young non-CF diabetics where AIx is increased from an early age [13, 24]. Supplementing the finding of an increased AIx in this subgroup was the increased PWV. Coronary heart disease, stroke and peripheral vascular disease are at least twofold greater in patients with diabetes than in the general population. This association holds for all age groups and is particularly pronounced in the young [40]. Thus, our findings suggest that patients with CFRD may be at heightened risk of cardiovascular disease and that surveillance of this risk may be particularly important in the CFRD subgroup. Whilst we diligently screen for microvascular changes, we have been ignorant of potential macrovascular changes. In addition, the increased heart rate in the CFRD group may have prognostic importance as in non-CF diabetics and may reflect increased sympato-adrenal drive related to arterial stiffness, affecting arterial tone and structure [41-43]. Vascular changes may occur in diabetes for various reasons, including
development in elastic artery walls of advanced glycosylation end-products [44] and the effects of hyperglycemia on endothelial function [45]. In addition, systemic inflammation may act synergistically in diabetes to promote arterial stiffening, perhaps pertinent here, given our findings and the CRP results [30].

The inverse relationship between AIx and FVC in our patients is in keeping with previous reports linking arterial stiffness to FVC in the general population [15, 46] The FVC was not predictive in the multiple regression, perhaps because other factors of relevance for the patient with CF, and not measured in previous studies such as inflammatory status dominate [46] or because the spectrum of lung function impairment was limited. The inverse relationship between AIx and GFR implicates a potential interplay of renal function and the haemodynamic changes. It is increasingly recognized that arterial stiffness has implications for perfusion of the distal microvasculature. Loss of buffering of pressure pulsations leads to damage of the microcirculation of structures, such as the kidney – so called “target organ damage” [16]. Supporting this, AIx is increased in renal disease [22] and is inversely related to GFR in healthy individuals [47]. Our findings suggest similar may be relevant in CF, although the relationship may be influenced by glycaemic status or secondary to the impact of repeated exposure to aminoglycoside antibiotics.

**Study limitations**

The cross-sectional design of this study does not allow the relationship of AIx and cardiovascular outcome to be defined. A further limitation is that the group of patients we
studied were highly selected free of other confounders for arterial stiffness, such as significant hypoxaemia, post transplantation status and non-invasive ventilation [4]. Application of these exclusion criteria are likely to have led to an underestimate of the true extent of central arterial changes.

In conclusion, we have demonstrated an increase in AIx in adult patients with CF which appears to reflect premature, covert arterial damage in the presence of a normal peripheral blood pressure but in the presence of persisting systemic inflammatory state and irrespective of diabetic status. These haemodynamic alterations contribute to the extrapulmonary complications that beset the adult phase of the disease. Whilst limited survival may have overshadowed detection of significant overt cardiovascular disease, the evolving nature of the adult life course demands consideration of these vascular changes in order to predict and maintain future cardiovascular health.
ACKNOWLEDGEMENTS

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References


FOOTNOTES

Table 1
Data presented as mean (SD), unless # Geometric mean (SD) or ¶ median (range).
*p<0.05 and **p<0.01 difference from controls,
^p<0.05 and ^^p<0.01 difference from non-diabetic patients.

Definition of abbreviations: 
BMI = body mass index; FFMI = fat free mass index (in 48 patients); WHR = waist to hip ratio; 
FEV$_1$ = forced expiratory volume in one second; FVC = forced vital capacity; TC = total cholesterol; 
HDL = high density lipoprotein; CRP = C-reactive protein; GFR = glomerular filtration rate.

Table 2
Data presented as mean (SD).
*p<0.05 and **p<0.01 difference from controls,
^p<0.05 difference from non-diabetic patients.

Definition of abbreviations: BP = blood pressure; PP = pulse pressure; MAP = mean 
arterial pressure; AIx = augmentation index; PWV = pulse wave velocity.

Table 3
Variables entered were i) age, height, MAP, BMI, FVC (% predicted), log$_{10}$CRP and ii) 
diabetic status additionally.
FIGURE LEGENDS

Figure 1. Alx in the patients and controls stratified according to 5 year age groupings.

Columns represent mean in controls (gray) and patients (black). Error bars represent ± 1 SEM.

- Controls
- Patients
Figure 2. Relationship between log_{10}CRP and A lx in controls (•), non-CFRD patients (||) and CFRD patients (x). Symbols represent mean values with error bars representing +/-1 SEM. *p<0.05 and **p<0.01 difference in A lx from controls.

Figure 2.
### Table 1. Subject characteristics

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<tr>
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<th>Controls</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=26)</td>
<td>(n=50)</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>28.4 (5.7)</td>
<td>28.0 (8.2)</td>
</tr>
<tr>
<td><strong>Gender (male: female)</strong></td>
<td>14 : 12</td>
<td>33 : 17</td>
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<tr>
<td><strong>Height (m)</strong></td>
<td>1.74 (0.1)</td>
<td>1.70 (0.1)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>22.2 (1.7)</td>
<td>22.2 (3.1)</td>
</tr>
<tr>
<td><strong>Total FFMI (kg/m²)</strong></td>
<td>18.2 (1.8)</td>
<td>18.1 (2.6)</td>
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<td><strong>WHR</strong></td>
<td>0.80 (0.06)</td>
<td>0.85 (0.08)*</td>
</tr>
<tr>
<td><strong>FEV₁ (% predicted)</strong></td>
<td>97.4 (8.5)</td>
<td>65.1 (21.2)**</td>
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<tr>
<td><strong>FVC (% predicted)</strong></td>
<td>97.5 (10.4)</td>
<td>79.6 (18.6)**</td>
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<tr>
<td><strong>Physical activity (mets)</strong></td>
<td>39 (33-62)</td>
<td>42 (29-77)</td>
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<tr>
<td><strong>Biochemical measurements</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Total cholesterol (mmol/L)</strong></td>
<td>4.5 (0.7)</td>
<td>3.7 (0.7)**</td>
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<tr>
<td><strong>Cholesterol ratio (TC/HDL)</strong></td>
<td>3.1 (0.7)</td>
<td>3.0 (0.7)</td>
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<tr>
<td><strong>Triglyceride (mmol/L)</strong></td>
<td>0.7 (0.3)</td>
<td>0.9 (0.3)*</td>
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<tr>
<td><strong>Fasting glucose (mmol/L)</strong></td>
<td>5.1 (1.1)</td>
<td>5.4 (1.3)</td>
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<td><strong>CRP (mg/L)</strong></td>
<td>0.4 (3.9)</td>
<td>2.7 (4.8)**</td>
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<tr>
<td><strong>GFR (mls/min)</strong></td>
<td>109.7 (15.4)</td>
<td>95.5 (18.7)**</td>
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Table 2. Haemodynamic data

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<td>(n=26)</td>
<td>(n=50)</td>
<td>(n=37)</td>
<td>(n=13)</td>
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<td>Heart rate (bpm)</td>
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<td></td>
<td>62.9 (7.3)</td>
<td>73.2 (11.6)**</td>
<td>71.9 (11.6)**</td>
<td>76.8 (11.2)**</td>
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<td>Peripheral systolic BP (mmHg)</td>
<td>124.8 (13.1)</td>
<td>128.3 (12.2)</td>
<td>128.0 (11.7)</td>
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<td>Peripheral diastolic BP (mmHg)</td>
<td>75.1 (8.2)</td>
<td>76.9 (8.3)</td>
<td>77.2 (7.2)</td>
<td>76.0 (11.0)</td>
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<td>Peripheral PP (mmHg)</td>
<td>49.7 (11.3)</td>
<td>51.7 (11.2)</td>
<td>51.2 (11.4)</td>
<td>53.2 (10.9)</td>
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<tr>
<td>Peripheral MAP (mmHg)</td>
<td>91.7 (8.6)</td>
<td>94.0 (8.2)</td>
<td>94.1 (7.2)</td>
<td>93.7 (10.9)</td>
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<tr>
<td>Alx (%)</td>
<td>-1.8 (13.1)</td>
<td>8.5 (11.1)**</td>
<td>6.9 (12.3)*</td>
<td>13.1 (4.3)**</td>
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<tr>
<td>Brachial PWV (m/sec)</td>
<td>8.2 (0.9)</td>
<td>8.3 (1.4)</td>
<td>8.1 (1.3)</td>
<td>8.7 (1.6)</td>
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<td>Aortic PWV (m/sec)</td>
<td>6.1 (0.8)</td>
<td>6.4 (1.5)</td>
<td>6.1 (1.1)</td>
<td>7.3 (2.1)**</td>
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<td>Central systolic BP (mmHg)</td>
<td>106.7 (10.0)</td>
<td>111.2 (11.3)</td>
<td>111.1 (11.7)</td>
<td>111.6 (10.6)</td>
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<td>Central diastolic BP (mmHg)</td>
<td>76.3 (8.2)</td>
<td>79.2 (8.7)</td>
<td>78.9 (7.8)</td>
<td>79.9 (11.3)</td>
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<td>Central PP (mmHg)</td>
<td>30.4 (6.0)</td>
<td>33.2 (7.7)</td>
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<td>34.3 (6.0)</td>
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Table 3. Multiple regression analysis with Alx as the dependent variable in patients.

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<th>Regression coefficient</th>
<th>SE</th>
<th>R² change (%)</th>
<th>P value</th>
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<tr>
<td>Age</td>
<td>0.61</td>
<td>0.14</td>
<td>29 %</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Height</td>
<td>-0.46</td>
<td>0.11</td>
<td>19 %</td>
<td>&lt;0.001</td>
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<tr>
<td>Log₁₀CRP</td>
<td>3.42</td>
<td>1.67</td>
<td>4 %</td>
<td>&lt;0.05</td>
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