Eur Respir J 2009; 34: 1322–1328
DOI: 10.1183/09031936.00044009

Increased augmentation index in patients with cystic fibrosis

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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).

50 clinically stable adult patients with CF (mean±SD age 28.0±8.2 yrs) and 26 controls matched for age, sex and body mass index 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 C-reactive protein (CRP) were also determined.

Mean±SD AIx was greater in patients than controls, 8.5±11.1% and -1.8±13.1%, respectively ($p<0.001$), 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 log_{10} CRP ($r=0.33$) 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 can be maintained.

KEYWORDS: Arterial stiffness, cystic fibrosis, diabetes mellitus, inflammation

As survival in cystic fibrosis (CF) increases, there is a need to focus on extra-pulmonary comorbidities that affect the length and quality of life in the adult stage of the disease [1]. Many of the comorbidities, 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 of life. Similar comorbidities 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 characterised 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

For editorial comments see page 1217.

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Received:
March 17 2009
Accepted after revision:
July 07 2009
First published online:
July 16 2009

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

stiffness, appearing to increase vascular age by ~8–9 yrs [13]. The course of CF in adults is often complicated by the development of abnormalities in glucose metabolism and by CF-related diabetes (CFRD) [14]. In patients with CFRD, we currently scrutinise 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 hypothesised that adults with CF would have increased AIx, compared with controls which would be related to the presence of systemic inflammation and greatest in the subgroup with diabetes. Therefore, we 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, sex 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 (Guildford, UK).

Study design

Assessments occurred when the patient was clinically stable with no exacerbation (new respiratory symptoms or a change in respiratory symptoms associated with a >10% fall in forced expiratory volume in 1 s (FEV_1) from their usual value) in the month prior to study. No patient had received intravenous 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, noninvasive ventilation, *Burkholderia cepacia* pulmonary infection or maintenance prednisolone (or equivalent) >5 $mg \cdot day^{-1}$ 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 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, Douglas, Isle of Mann, UK).

FEV_1, forced vital capacity (FVC) [17] and resting arterial oxygen saturation measured by pulse oximetry (S_{P,O_2}) were measured. Habitual physical activity (expressed in metabolic equivalent of task (METS), where 1 MET=energy expended at rest) was determined by a 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 when the patient was seated (OMRON Corporation, Kyoto, Japan). Radial artery waveforms were recorded using a high fidelity micromanometer (Millar instruments, Houston, TX, USA). Pulse wave analysis (Sphygmocor; AtCor Medical, Sydney, Australia) was then used to generate a corresponding central arterial waveform and with the integral software to calculate AIx. AIx is defined as the difference between the second and first systolic peaks and expressed as a percentage of the pulse pressure (PP). All results for AIx are presented as heart rate (HR), corrected for a HR of 75 $beats \cdot min^{-1}$. Pulse wave velocity (PWV) was determined in the supine position 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 and triglyceride (TG)) (Advia 2400; Siemens Medical Solutions, Erlangen, Germany) were determined. Estimated glomerular filtration rate (GFR) was calculated from the equation of COCKCROFT and GAULT [19]. Patients without a previous diagnosis of 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

A questionnaire and/or an interview were used to evaluate medication, smoking and family cardiovascular history.

Statistical analysis

Data is reported as arithmetic mean±SD, unless otherwise stated. Positively skewed data (CRP and glucose) were $\log_{10}$ transformed and results are shown as geometric mean±SD. Continuous variables with normal distribution were evaluated using unpaired t-tests, Pearson's correlation coefficient and one-way ANOVA with Tukey's *post hoc* test. Categorical data were analysed using the Chi-squared test. Multiple stepwise regressions were used to determine predictors of AIx in patients. Analysis was performed using SPSS 15 (SPSS Inc., Chicago, IL, USA) and a p-value <0.05 was considered significant.

RESULTS

Subject's characteristics

50 patients and 26 controls 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 was 3 (2–20) pack-yrs in patients and 3 (2–5) pack-yrs in controls. There was a family history of cardiovascular disease, in first degree relatives aged <60 yrs in two patients but no controls. The BMI and FFMI (48 patients, 26 controls) were similar whilst WHR was greater in patients.

TABLE 1 Subject characteristics

	Controls	Patients		
		All	Non-CFRD	CFRD
Subjects n	26	50	37	13
Age yrs	28.4±5.7	28.0±8.2	26.5±7.9	32.2±8.1¶
Sex male/female n	14/12	33/17	24/13	9/4
Height m	1.74±0.1	1.70±0.1	1.71±0.1	1.68±0.1
BMI kg·m^{-2}	22.2±1.7	22.2±3.1	21.9±3.0	22.9±3.5
Total FFMI$^{\#}$ kg·m^{-2}	18.2±1.8	18.1±2.6	18.0±2.6	18.3±2.6
WHR	0.80±0.06	0.85±0.08*	0.86±0.06*	0.83±0.13
FEV$_1$ % pred	97.4±8.5	65.1±21.2**	69.4±22.0**	52.9±12.6**,¶¶
FVC % pred	97.5±10.4	79.6±18.6**	83.9±18.9**	67.2±10.6**,¶¶
Physical activity MET	39 (33–62)	42 (29–77)	42 (29–77)	40 (30–63)
Biochemical measurements				
Total cholesterol mmol·L^{-1}	4.5±0.7	3.7±0.7**	3.7±0.7**	3.9±1.0
Cholesterol ratio TC/HDL	3.1±0.7	3.0±0.7	2.9±0.8	3.0±0.7
Triglyceride mmol·L^{-1}	0.7±0.3	0.9±0.3*	0.9±0.3	0.9±0.3
Fasting glucose mmol·L^{-1}	5.1±1.1	5.4±1.3	4.8±1.1	7.5±1.5**,¶¶
CRP mg·L^{-1}	0.4±3.9	2.7±4.8**	1.9±4.7**	7.4±3.3**,¶¶
GFR mL·min^{-1}	109.7±15.4	95.5±18.7**	95.9±18.5**	94.3±19.9*

Data presented as mean±SD or median (range), unless otherwise stated. Fasting glucose and C-reactive protein (CRP) are presented as geometric mean±SD. CFRD: cystic fibrosis-related diabetes; BMI: body mass index; FFMI: fat-free mass index; WHR: waist-to-hip ratio; FEV$_1$: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; MET: metabolic equivalent of task; TC: total cholesterol; HDL: high density lipoprotein; GFR: glomerular filtration rate. $^{\#}$: in 48 patients. *: $p<0.05$, and **: $p<0.01$ difference from controls; ¶: $p<0.05$, and ¶¶: $p<0.01$ difference from non-diabetic patients.

Of the patients, 25 (50%) were homozygous for δF508 mutation, 42 (84%) had pancreatic insufficiency and 28 (56%) had respiratory isolates for *Pseudomonas aeuriginosa*. Current therapy for patients included long-term oral and inhaled antibiotics (98% of patients), with patients receiving oral azithromycin (86%), vitamin 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 groups. In patients, $\log_{10}$ CRP was inversely related to FEV1 % predicted ($r= -0.42$, $p<0.01$), FVC % pred ($r= -0.48$, $p<0.001$) 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/high-density lipoprotein) was similar between groups by virtue of reduced high-density lipoprotein in patients ($p<0.05$). No patient had a TC >5.4 mmol·L^{-1} or TG level >1.8 mmol·L^{-1}. Estimated GFR was lower in patients than controls ($p<0.001$).

Haemodynamic results

Both peripheral and central BP parameters (systolic, diastolic, mean arterial pressure (MAP) and PP) were similar in patients and controls although patients had greater HR than controls ($p<0.001$) (table 2).

Mean±SD AIx was greater in patients than controls, 8.5±11.1% and -1.8±13.1%, respectively ($p<0.001$), and remained greater after adjustment for known potential confounders: age, sex, 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-yr age bands for the overlapping age range, *i.e.* 20–39 yrs (fig. 1). The AIx was greater in females than males in both groups ($p<0.01$) 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 with non-CFRD (6.9±12.3%) and controls (-1.8±13.1%) ($p<0.001$, ANOVA and Tukey's *post hoc* analysis) (table 2, fig. 2). This difference remained after adjustment for previous confounders including age ($p<0.05$). Importantly, AIx remained greater in the non-CFRD patients than the controls ($p<0.05$, ANOVA and Tukey's *post hoc* analysis).

Aortic PWV was greater in the CFRD subgroup of patients than both the non-CFRD patient and controls (both $p<0.05$), 7.3±2.1, 6.1±1.1 and 6.1±0.8 m·s^{-1}, respectively, 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 AIx and FEV1 % pred ($r= -0.34$, $p<0.01$) and FVC % pred ($r= -0.33$,

TABLE 2 Haemodynamic data

	Controls	Patients		
		All	Non-CFRD	CFRD
Subjects n	26	50	37	13
***f*C beats·min^{-1}**	62.9±7.3	73.2±11.6**	71.9±11.6**	76.8±11.2**
Peripheral systolic BP mmHg	124.8±13.1	128.3±12.2	128.0±11.7	129.2±13.9
Peripheral diastolic BP mmHg	75.1±8.2	76.9±8.3	77.2±7.2	76.0±11.0
Peripheral PP mmHg	49.7±11.3	51.7±11.2	51.2±11.4	53.2±10.9
Peripheral MAP mmHg	91.7±8.6	94.0±8.2	94.1±7.2	93.7±10.9
AIx %	-1.8±13.1	8.5±11.1**	6.9±12.3*	13.1±4.3**
Brachial PWV m·s^{-1}	8.2±0.9	8.3±1.4	8.1±1.3	8.7±1.6
Aortic PWV m·s^{-1}	6.1±0.8	6.4±1.5	6.1±1.1	7.3±2.1*,#
Central systolic BP mmHg	106.7±10.0	111.2±11.3	111.1±11.7	111.6±10.6
Central diastolic BP mmHg	76.3±8.2	79.2±8.7	78.9±7.8	79.9±11.3
Central PP mmHg	30.4±6.0	33.2±7.7	32.8±8.2	34.3±6.0

Data presented as mean±SD, unless otherwise stated. CFRD: cystic fibrosis-related diabetes; *f*C: cardiac frequency; BP: blood pressure; PP: pulse pressure; MAP: mean arterial pressure; AIx: augmentation index; PWV: pulse wave velocity. *: $p<0.05$, and **: $p<0.01$ difference from controls; #: $p<0.05$ difference from non-diabetic patients.

$p<0.01$). Whilst in patients alone, AIx was inversely related to FVC % pred (r= -0.34, $p<0.05$) but not FEV_1 % pred. No patients had an S_{p,O_2} of <92% and there was no association between AIx and S_{p,O_2}.

Laboratory data

The AIx 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, AIx was inversely related to estimated GFR (r= -0.55, $p<0.001$). In patients and controls there was no relationship between TC, cholesterol ratio or TG level and AIx.

Other clinical characteristics

There was no difference in AIx between the patients homozygous for δF508 and other genotypes or between patients who were pancreatic sufficient and insufficient. There was an inverse relationship of AIx 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 AIx (table 3). Known previously reported confounders of AIx (age, height and peripheral MAP) together with markers used to evaluate disease severity (BMI, FVC % pred 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 AIx. In a second model, diabetic status was added but did not affect the results.

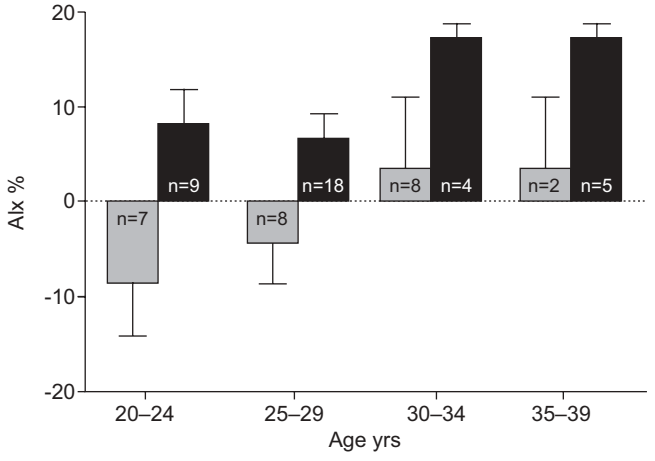

FIGURE 1. Augmentation index (AIx) in patients (■) and controls (■) stratified according to 5-yr age groupings. The error bars represent +1SEM.

DISCUSSION

Adult patients with CF have increased AIx compared with age- and sex-matched healthy controls, which is related to systemic inflammatory status. These findings suggest early vascular abnormalities in the setting of a normal peripheral BP. These alterations occur in patients with or without CFRD, and with mild to moderate 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 [11, 13, 21–26]. Indeed, AIx is the most relevant measure of stiffness in subjects aged >50 yrs and our finding of increased AIx rather than PWV is in keeping with the literature [27]. 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 [28]. As such, AIx increases markedly and progressively up to 50 yrs of age, whilst aortic PWV increases only modestly in parallel with

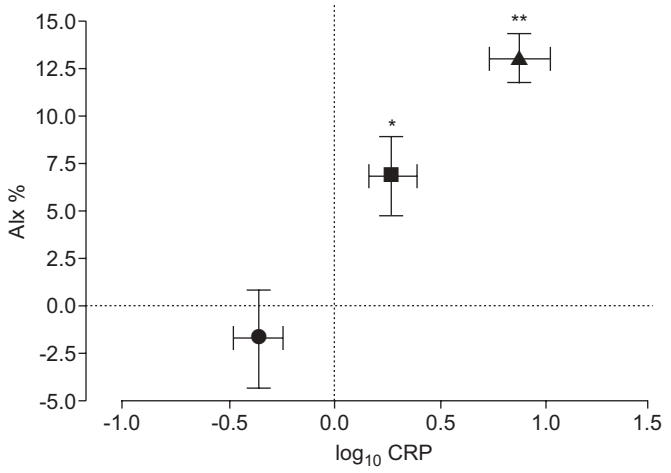

FIGURE 2. Relationship between $\log_{10}$ C-reactive protein (CRP) and augmentation index (AIx) in controls (●), non cystic fibrosis-related diabetes (CFRD) patients (■) and CFRD patients (▲). Data are presented as mean values with error bars representing ±1SEM. *: $p<0.05$, and **: $p<0.01$ difference in AIx from controls.

systolic and diastolic BP in the same age range. A UK population study (Anglo-Cardiff Collaborative Trial) reported that, in this age range, a 9% increase in AIx corresponded to the effect of ageing by 10 yrs [27]. 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 BP, 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 other reports of vascular ageing in different chronic inflammatory conditions [4, 7–9, 13, 29–31].

Systemic inflammation is associated with cardiovascular risk in various populations, including healthy individuals [32]. Likewise, our finding of a relationship between CRP and AIx in multiple regression, 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 to be maintained, only manifesting as disease at a later stage [4, 7, 8, 29–31].

TABLE 3 Multiple regression analysis with augmentation index as the dependent variable in patients

Variable	Regression coefficient	SE	R^2 change %	p-value
Age	0.61	0.14	29	<0.0001
Height	-0.46	0.11	19	<0.001
Log_{10}CRP	3.42	1.67	4	<0.05

The variables entered were: age, height, mean arterial pressure, body mass index, forced vital capacity (% predicted) and $\log_{10}$ C-reactive protein (CRP). Diabetic status was additional.

Inflammation affects endothelial function but may also promote arterial stiffness by direct effects on vessel architecture and vascular smooth muscle function [31]. Support for the association between systemic inflammation and arterial stiffness is further demonstrated by the attenuation in arterial stiffness following treatment with anti-tumour necrosis factor-α 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 favourable lipid and peripheral BP profile [33]. However, recent reports of myocardial infarction [34, 35] and hypertension [36] in non-transplanted patients challenge this; whilst our data highlights that the traditional peripheral brachial BP assessment may be normal in the presence of altered large artery haemodynamics. Although our findings need verifying in longitudinal studies to determine the long-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 [37, 38]. 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.

In addition 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, 23]. 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 two-fold greater in patients with diabetes than in the general population. This association holds true for all age groups and is particularly pronounced in the young [39]. 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. The increased HR in the CFRD group may also have prognostic importance as in non-CF diabetics, and may reflect increased sympatho-adrenal drive related to arterial stiffness, affecting arterial tone and structure [40–42]. Vascular changes may occur in diabetics for various reasons, including development of advanced glycosylation end-products in elastic artery walls [43] and the effects of hyperglycaemia on endothelial function [44]. In addition, systemic inflammation may act synergistically in diabetes to promote arterial stiffening, perhaps pertinent here given our findings and the CRP results [29].

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, 45]. The FVC was not predictive in the multiple regression, perhaps because other factors of relevance for the patient with CF, and factors not

measured in previous studies, such as inflammatory status, dominate [45], 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 recognised 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, and thus is called ''target organ damage'' [16]. Supporting this, AIx is increased in renal disease [21] and is inversely related to GFR in healthy individuals [46]. Our findings suggest similar may be evident in CF, although this 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 selected to be free from other confounders for arterial stiffness, such as hypoxaemia, post-transplantation and in need of noninvasive ventilation [4]. Application of these exclusion criteria are likely to have led to an underestimation of the true extent of central arterial changes.

Conclusion

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 BP but in the presence of a 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.

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

We would like to thank the patients together with the nursing and laboratory staff at Frimley Park Hospital (Frimley, UK), especially J. Duguid and S. Morgan. In addition, we are grateful to M. Munnery and B. McDonnell (Cardiff University, Cardiff, UK), P. Fraser (St. George's, University of London, London, UK) and P. Soan (Kingston University, London), for their expertise and assistance.

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