Increased arterial stiffness in children with cystic fibrosis

To the Editors:

The survival of patients with cystic fibrosis (CF) is increasing and, therefore, there is a need to focus on extrapulmonary comorbidities that could affect their length and quality of life [1]. Diseases with a systemic inflammatory state are associated with increased arterial stiffness, an independent risk factor for cardiovascular diseases [2, 3]. This premature ageing of the vasculature has been demonstrated in CF adults, but it is not known whether it begins in childhood [4]. We hypothesised that arterial stiffness is increased in CF children compared with healthy controls and that it is related to the degree of systemic inflammation.

Digital volume pulse (DVP) analysis, with the computation of the stiffness index (SI_{DVP}) and pulse wave velocity between the carotid and femoral arteries (PWV_{cf}) were determined in 31 CF children (13 females; median age 12.2 yrs, interquartile range (IQR) 9.3–14.8 yrs) and in 48 healthy controls, matched for sex and age (19 female; median age 10.9 yrs, IQR 9.7–13.4 yrs). Office blood pressure was taken as the mean of three measurements obtained from the supine child after 10 min of rest with a validated oscillometric device (Dinamap XL; Criticon Inc., Tampa, FL, USA). The Pulse Trace PWV unit (Micro Medical Ltd, Rochester, UK) recorded PWV_{cf} by measuring the time lag between the arrival of the arterial pulse at the carotid and femoral arteries (Δt_{cf}) [5]. PWV_{cf} was calculated by dividing the distance between carotid and femoral arteries by Δt_{cf}. The same device was used to record DVP by photoplethysmography [5]. The timing of the diastolic component relative to the systolic component (Δt_{DVP}) depends upon the PWV_{cf} of the pressure waves within large arteries. The SI_{DVP} is obtained from subject height divided by Δt_{DVP}. Body composition and hydration state were assessed with a whole-body bioimpedance spectroscopy device (BCM; Fresenius Medical Care, Bad Homburg, Germany). Hydration status, lean tissue index (LTI) and fat tissue index (FTI) were calculated based on a physiological tissue model. Forced expiratory volume in 1 s (FEV_1) was measured according to current recommendations (Masterlab; Jaeger, Würzburg, Germany) [6]. Lung clearance index (LCI) (Exhalyzer D; Eco Medics AG, Duernten, Switzerland) [7], current colonisation with *Pseudomonas aeruginosa* or *Stenotrophomonas maltophilia*, C-reactive protein (CRP), immunoglobulin (Ig)G and presence of CF-related diabetes mellitus (CFRD) [8] at the time of investigation were documented.

Data are expressed as median (IQR). Relationships among variables were assessed by using a best-fit linear regression analysis. Unpaired t-tests or Mann–Whitney U-tests were used to compare groups, as appropriate. Significance was assigned at $p<0.05$.

Table 1 summarises the characteristics of the study children. Height standard deviation score was lower and diastolic blood pressure (corrected for sex, height and age) [9] was higher in the CF group compared with control children. Puberty stage (Tanner stages) was comparable between the two groups of children. In CF children, median (IQR) FEV_1 was 92 (74–102)% predicted, LCI was 7.0 (6.1–8.8), and LTI was 13.6 (12.4–14.8) $kg \cdot m^{-2}$ and FTI 2.9 (1.9–5.0) $kg \cdot m^{-2}$. 20% of the CF children showed a reduced lean mass (below the 10th centile corrected for age); however, the fat mass distribution was within the normal range. Hydration status, expressed as a percentage of body weight was 0.0 (-0.8–1.1)%. Median IgG and CRP were 9.3 (7.0–12.2) $g \cdot L^{-1}$ and 8.0 (3.5–18.5) $mg \cdot L^{-1}$, respectively.

SI_{DVP} was significantly higher and PWV_{cf} showed a trend towards higher values in CF children compared with the control group (table 1). PWV_{cf} was significantly increased in CF children colonised with *P. aeruginosa* or *S. maltophilia* (n=12) compared with uninfected children (6.4 (6.0–7.1) *versus* 5.6 (5.3–5.9) $m \cdot s^{-1}$; p=0.003). CF children with CFRD (n=10) did not display higher PWV_{cf} or SI_{DVP} compared with the CF children not affected by CFRD (PWV_{cf} 6.4 (5.7–7.5) *versus* 5.8 (5.3–6.2) $m \cdot s^{-1}$; nonsignificant). PWV_{cf} was related to IgG ($r^2=0.50$, p=0.02) and LTI ($r^2=0.16$, p=0.04). Neither PWV_{cf} nor SI_{DVP} was related to hydration status, height, weight, body mass index, blood pressure, FEV_1, LCI or CRP.

This study demonstrates increased stiffness of the large arteries in CF children with a median age of 12 yrs, especially in those colonised by *P. aeruginosa* or *S. maltophilia*. These novel results indicate that altered arterial compliance in CF is already manifest in childhood. The increase in arterial stiffness seems to be related

TABLE 1 Characteristics of the children

	CF	Controls	p-value
Subjects n	31	48	
Females/males n	13/18	19/29	1.00
Age yrs	12. 2 (9.3–14.8)	10.9 (9.7–13.4)	0.30
Height cm	143.0 (129.0–159.0)	147.2 (135.8–155.3)	0.50
Height SDS	-0.9 (-1.4–0.1)	-0.1 (-0.7–0.5)	0.0008
BMI $kg \cdot m^{-2}$	16.5 (15.3–19.3)	17.5 (15.5–20.3)	0.60
BMI SDS	-0.4 (-1.0–0.13)	-0.0 (-0.7–0.5)	0.16
SBP mmHg	110.0 (99.0–118.0)	105.0 (100.0–115.0)	0.56
SBP SDS	0.1 (-0.4–1.0)	0.2 (-0.4–0.9)	0.80
DBP mmHg	65.0 (60.0–71.0)	59.0 (55.0–64.0)	0.002
DBP SDS	0.5 (-0.2–0.8)	-0.2 (-0.5–0.2)	0.0008
PWV_{cf} $m \cdot s^{-1}$	5.9 (5.4–6.4)	5.5 (5.2–6.0)	0.06
SI_{DVP}	6.9 (6.1–8.1)	5.7 (5.4–6.1)	<0.0001

Data are presented as median (interquartile range), unless otherwise stated. CF: cystic fibrosis; SDS: standard deviation score; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PWV_{cf}: pulse wave velocity between the carotid and femoral arteries; SI_{DVP}: stiffness index measured by digital volume pulse.

to systemic inflammation, as expressed by increased IgG and resulting from colonisation with pathogens and irrespective of blood pressure or diabetes status. Conversely, in adult CF patients, CFRD seems to influence arterial stiffness [4]. This discrepancy between adults and children may indicate that the changes in the arterial wall architecture appear only after decades of hyperglycaemic burden.

The present study did not examine whether an intervention, such as intravenous antibiotics, is able to reduce the increase in arterial stiffness; however, a recent study published in abstract form seems to reveal benefits of interventions aiming to reduce inflammation on the cardiovascular system in adult CF patients [10]. It remains unclear whether these interventions completely normalise the increase in arterial stiffness or the vascular changes remain permanently altered. The results of the present exploratory study, together with the results of other studies [4, 10], suggest that aggressive and early anti-inflammatory therapies are indicated in CF patients not only to stabilise lung function but also to avoid extrapulmonary complications and to reduce the accelerated vascular ageing process.

A strength of this study is the homogenous and young CF population without other cardiovascular risk factors likely to be encountered in adulthood. Limitations include the lack of other biochemical inflammatory or metabolic markers for cardiovascular risk such as triglycerides and cholesterol.

In conclusion, this study demonstrates haemodynamic alterations in the presence of persisting systemic inflammation already in children suffering from CF. With increasing survival, awareness of these vascular changes is required in order to maintain cardiovascular health in CF patients.

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Monitoring of tobramycin levels in patients with cystic fibrosis by finger-prick sampling

To the Editors:

Chronic pulmonary infection is the major cause of morbidity and premature mortality in patients with cystic fibrosis (CF). The major pathogen for patients with CF is *Pseudomonas aeruginosa*. Tobramycin, an aminoglycoside antibiotic, is widely used against Gram-negative bacterial infections and is particularly useful for the treatment of *P. aeruginosa* in patients with CF [1]. Intravenous tobramycin has a narrow therapeutic range and monitoring of the drug is required to reduce serious side-effects, such as nephrotoxicity and ototoxicity [2]. Dosage alterations based on the results of drug monitoring can improve efficacy and minimise toxicity. Monitoring currently requires venesection and patients may find finger-prick samples less painful and more acceptable.

Finger-prick blood sampling is routinely performed by patients with diabetes mellitus, is an easy technique to teach and uses