ELSEVIER

Journal of Cystic Fibrosis 12 (2013) 125 – 129

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Dynamic vascular changes following intravenous antibiotics in patients with cystic fibrosis

James H. Hull [a,*], Rachel Garrod [b], Timothy B. Ho [c], Ronald K. Knight [c], John R. Cockcroft [d], Dennis J. Shale [d,e], Charlotte E. Bolton [f]

[a] Centre for Clinical Pharmacology, Division of Biomedical Sciences, St George's, University of London, Cranmer Terrace, London. SW17 0RE, UK
[b] Dept. of Physiotherapy, Kings College Hospital NHS Foundation Trust, Dulwich Hospital, London, UK
[c] Frimley Park Hospital NHS Foundation Trust, Frimley, Surrey, GU16 7UJ, UK
[d] Dept. of Cardiology, Wales Heart Research Institute, School of Medicine, Cardiff University, Heath Park, Cardiff, CF14 4XW, UK
[e] Dept. of Respiratory Medicine, School of Medicine, Cardiff University, Academic Centre, University Hospital Llandough, Penarth, Vale of Glamorgan, CF64 2XX, UK
[f] NIHR Nottingham Respiratory Biomedical Research Unit, School of Clinical Sciences, University of Nottingham, City Hospital, Nottingham, UK. NG5 1PB, UK

Received 27 February 2012; received in revised form 9 June 2012; accepted 5 July 2012
Available online 1 August 2012

Abstract

Background: Adults with cystic fibrosis (CF) have altered large artery haemodynamics which is associated with a persisting systemic inflammatory state. We hypothesized that a short-term intervention favorably influencing the inflammatory status may modify their haemodynamic state.
Methods: Adult patients with CF were studied immediately preceding and following 2 weeks of intravenous antibiotics. Large artery haemodynamics, principally heart rate-adjusted augmentation index (AIx) were obtained. Blood pressure (BP), spirometry and CRP were also measured.
Results: Complete data was available for 15 patients; mean (SD) age 28 (6) years. CRP was reduced while FEV_1% predicted improved. Following treatment AIx was lower: 10.9 (10.9)% to 8.1 (10.9)% ($p<0.05$) while BP was similar and a trend toward lower heart rate ($p=0.06$). Change in AIx was related to baseline FEV_1% predicted ($r=0.77$) and BMI ($r=0.71$) (both $P<0.01$).
Conclusion: The abnormal central haemodynamics evident in adults with CF is modulated with a short intervention of intravenous antibiotics.

Keywords: Arterial; Stiffness; Inflammation; Cystic fibrosis; Blood pressure; Vascular

1. Introduction

Adult patients with cystic fibrosis (CF) have evidence of haemodynamic alterations within the systemic circulation as depicted by an increase in the vascular parameter, augmentation index (AIx) [1,2]. These alterations are evident at clinical stability [1], appear exaggerated during light exercise [3] and may have deleterious consequences for myocardial work and perfusion of target organs, such as the brain and kidney [4].

The mechanisms underlying increased AIx, a marker of loading or 'stress' on the central systemic vasculature, in the CF population are currently unclear. A predictive relationship between circulating C-reactive protein (CRP) and AIx, suggests that systemic inflammation may be relevant [1], although not demonstrating causation. A similar relationship is apparent in cross-sectional studies in both healthy individuals [5] and patients with chronic inflammatory disorders [6–9]. In the general population the nature of this relationship is furthered by the finding that an acute pro-inflammatory stimulus such as vaccination is associated with heightened vessel stiffness [10], whereas, anti-inflammatory therapy can favorably alter large artery haemodynamics. More specifically, anti-tumor necrosis factor alpha (TNFα) is associated with reductions in both AIx and aortic pulse wave velocity (APWV) in rheumatoid arthritis [6,11,12].

* Corresponding author at: Department of Clinical Pharmacology, Division of Biomedical Sciences, St George's Hospital, Tooting, London, SW17 0RE, UK. Tel.: +44 208 725 5394; fax: +44 208 725 3369.
E-mail address: jiminio@doctors.org.uk (J.H. Hull).

1569-1993/$ -see front matter
doi:10.1016/j.jcf.2012.07.004

In keeping with rheumatoid arthritis, the adult stage of CF is characterized by the presence of persistent systemic inflammation that may increase periodically at times of 'exacerbation', i.e. in association with clinical deterioration. In CF, intervention with intravenous (*iv*) antibiotics is recognized to attenuate circulating markers of inflammation and result in parallel improvements in clinical characteristics; including pulmonary function, body mass [13–15] as well as reduction in energy expenditure, circulating catecholamine levels and catabolic metabolism [14–16].

Currently there is little detail available regarding the haemodynamic response to treatment with *iv* antibiotics in the CF population. Studies detail a reduction in heart rate (HR) [15,17,18], however there are no data available concerning alterations in blood pressure or large artery haemodynamics. This latter is important given the implications of altered large artery haemodynamics for cardiovascular health and more specifically for myocardial work and perfusion of the distal organs.

The aim of this study therefore was to evaluate the effect of a two-week course of *iv* antibiotics on large artery haemodynamics in a cohort of adults with CF. We hypothesized that in addition to the improvement in standard clinical parameters, there would be an associated improvement in large artery haemodynamics following *iv* antibiotic treatment.

2. Methods

2.1. Participants

Adult patients with CF (clinical features and positive sweat test and/or an accepted CF genotype) were recruited from consecutive patients attending Frimley Park Hospital at a time of initiation of *iv* antibiotic treatment for an exacerbation in respiratory symptoms. Decision to initiate antibiotic treatment and thus definition of 'exacerbation' as well as selection of antibiotic therapy were made by the physician in charge and independent to the study investigator.

Initiation of oral corticosteroid therapy was an exclusion factor given its potential to confound vascular and inflammatory measures, however those patients on a regular daily dose were not excluded provided the dose was unaltered throughout the study period.

2.2. Ethical statement

The study was approved by the Surrey Research Ethics Committee, National Research Ethics Service, Education Centre, Royal Surrey County Hospital (Surrey, UK—07/Q1909/82). All subjects provided written informed consent.

2.3. Study design

Subjects were required to attend on two occasions; at onset of symptoms and prior to initiation of *iv* antibiotics (visit 1) and following 2 weeks of treatment (visit 2). At each visit, subjects were requested to abstain from caffeinated beverages and tobacco prior to assessment. Patients were also requested to abstain from inhaled short acting ß-2 agonists prior to visit on the day of assessment. Patients were advised to administer other medications according to their usual routine but to adhere to the same medication regime (i.e. timing and dose) for both visits.

Study assessments were planned to take place at the same time of day and with similar timing of dietary intake prior to assessment with no food to be consumed in the 2 h prior to assessment. All patients classified as having CF related diabetes (CFRD) [19] were on treatment with regular subcutaneous insulin therapy and were advised to administer subcutaneous insulin in accordance with their usual regime but not within 2 h of haemodynamic measurement.

2.4. Visit assessment

Height and weight were measured and BMI (kg/m^2) was calculated. Peripheral oxygen saturation (SpO_2) and temperature were measured. Subjects then underwent haemodynamic measurements following 10 min of supine rest. Forced expiratory volume in 1 s (FEV_1) and vital capacity (FVC) were determined by spirometry [20] and venous blood was collected.

2.5. Haemodynamic assessment

Measurements were taken, in a quiet temperature controlled laboratory. Peripheral blood pressure (BP), the mean of three consecutive brachial artery readings, was measured (OMRON Corporation, Japan). Radial artery waveforms were recorded using a high fidelity micromanometer (Millar instruments, Texas, USA) as described previously [1]. In brief, radial artery waveforms were recorded and analyzed using pulse wave analysis (SphygmoCor, AtCor Medical, Sydney, Australia) to generate a corresponding central arterial waveform and calculate AIx, normalized to a HR of 75 beats per minute. Brachial and APWV were determined by sequentially recording ECG gated radial, carotid and femoral artery waveforms [21].

2.6. Laboratory analyses

Venous blood was collected for determination of high sensitivity C-reactive protein (CRP), serum creatinine and sodium (Na^+) by standard methods in an accredited laboratory (ADVIA 2400, Siemens Medical solutions). Estimated glomerular filtration rate (GFR) was determined [22].

2.7. Statistical analysis

Data is reported as arithmetic mean (SD), unless otherwise stated. Positively skewed data (CRP) was $\log_{10}$ transformed and reported as geometric mean (SD). A two-sided paired *t*-test was used to evaluate differences in continuous normally distributed variables between the visits with relationships assessed using Pearson's correlation coefficient. Continuous variables that did not conform to a normal distribution (SpO_2) were evaluated using non-parametric tests (Wilcoxon signed ranks test and Spearman's correlation coefficient). Analysis was performed using SPSS v 15 (SPSS Inc., Chicago, USA) and GraphPad (Prism v. 5, GraphPad Software Inc, USA) with a p-value of <0.05 considered