International Journal of Cardiology xxx (2011) xxx–xxx

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Editor

Large and small artery endothelial dysfunction in chronic fatigue syndrome☆

David J. Newton [a,*], Gwen Kennedy [a], Kenneth K.F. Chan [a], Chim C. Lang [b], Jill J.F. Belch [a], Faisel Khan [a]

[a] Vascular and Inflammatory Diseases Research Unit, Institute of Cardiovascular Research, University of Dundee, Dundee, UK
[b] Department of Clinical Pharmacology, Institute of Cardiovascular Research, University of Dundee, Dundee, UK

ARTICLE INFO

Article history:
Received 12 October 2011
Accepted 18 October 2011

Keywords:
Chronic fatigue syndrome
Endothelium
Microcirculation
Cardiovascular diseases

There is accumulating evidence that myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is associated with cardiovascular symptoms including autonomic dysfunction [1], impaired blood pressure regulation [2] and loss of beat-to-beat heart rate control [3]. A number of recent studies reporting raised levels of oxidative stress [4], low-grade inflammation [5] and increased arterial stiffness contribute to a picture of increased cardiovascular risk in ME/CFS. One potential site of oxidative injury is the vascular endothelium, and such damage would be expected to lead to endothelial cell dysfunction and diminished vasodilator capacity. The primary aim of the current study was to investigate large-vessel endothelial function in ME/CFS using flow-mediated dilatation (FMD), and to assess microvascular endothelial function using post-occlusive reactive hyperaemia, both of which have been shown to be related to cardiovascular risk and outcome [6,7].

FMD and haematological markers were measured in 30 patients who fulfilled Centers for Disease Control and Prevention criteria for CFS, and in 27 healthy control subjects. All participants gave informed consent to their involvement in the study, which was approved by the Tayside Committee on Medical Research Ethics. The brachial artery was imaged in longitudinal section using an Acuson Sequoia C512 ultrasound system (Siemens Medical Solutions USA Inc., Malvern, USA) with a 5 to 8 MHz linear array transducer placed 5 to 10 cm above the antecubital fossa. Images were recorded for 1 minute at baseline, and then for a further 2½ minutes following deflation of a sphygmomanometer cuff that had been inflated suprasystolically around the forearm for 5 minutes. The media-to-media diameter of a user-defined section of artery was determined for each image, and the percentage change in diameter after cuff release was calculated with respect to baseline (FMD). After resting for 15 minutes, the change in brachial artery diameter was similarly measured in response to sublingual administration of 0.4 mg of the endothelium-independent vasodilator glyceryl trinitrate (GTN, Lipha Pharmaceuticals Ltd, West Drayton, UK). A 30-mL venous blood sample was taken for the assessment of plasma glucose, and serum levels of cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, interleukin-8 and high-sensitivity C-reactive protein (hs-CRP).

Endothelial function in the cutaneous microcirculation was assessed by measuring post-occlusive reactive hyperaemia in 9 ME/CFS patients and 9 healthy controls. Forearm skin blood flow was measured using laser Doppler flowmetry (MBF3, Moor Instruments, Axminster, UK) for a baseline period of 1 minute, and then for a further 2 minutes following deflation of a sphygmomanometer cuff that had been inflated suprasystolically around the forearm for 5 minutes. Peak blood flow after cuff release was recorded, and the response was also expressed as the area under the response curve over 2 minutes with respect to baseline flow.

FMD was significantly lower in ME/CFS patients than in age- and gender-matched control subjects (median [interquartile range]: 5.99 [3.65] versus 9.24 [3.47]%, $p<0.001$). In contrast, there was no significant group difference in the response to GTN (18.00 [9.82] versus 14.90 [5.26]%, $p=0.213$). ME/CFS patients had a significantly lower hyperaemic response in forearm skin microvessels than did control subjects, when expressed as the peak response (38.33 [14.95] versus 69.80 [35.66] AU, $p=0.002$) or as the area under the response curve over 2 minutes with respect to baseline (19.76 [15.46] versus 38.70 [18.14] AU·min, $p=0.012$). The patient group also had significantly higher levels of serum hs-CRP (1.32 [1.54] versus 0.36 [0.60] mg/L, $p=0.016$) and triglycerides (1.62 [1.74] versus 0.98 [0.92] mmol/L, $p=0.034$), and lower levels of serum HDL cholesterol (1.24 [0.72] versus 1.45 [0.48] mmol/L, $p=0.041$).

The central finding of this study is that adult patients with ME/CFS have reduced FMD in the brachial artery and reduced post-occlusive reactive hyperemia in the forearm skin microcirculation. These responses are both endothelium-mediated via an increase in shear stress [8,9], and the results therefore lend further support to the hypothesis that endothelial function is impaired in ME/CFS, both in large vessels and in the microcirculation. We believe this is the first time that vascular endothelial dysfunction has been measured

☆ Grant support: The study was funded by a grant from ME Research UK. Jill Belch and Gwen Kennedy receive support from the Sir John Fisher Foundation.
* Corresponding author at: Vascular and Inflammatory Diseases Research Unit, Institute of Cardiovascular Research, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK. Tel.: +44 1382 632435; fax: +44 1382 632333.
E-mail address: d.j.newton@dundee.ac.uk (D.J. Newton).

0167-5273/$ – see front matter
doi:10.1016/j.ijcard.2011.10.030

directly in ME/CFS patients, and these findings build on previous work reporting indirect markers of endothelial dysfunction, such as increased oxidative stress [4,10], inflammation [5,11] and arterial stiffness [5]. This evidence collectively points to increased cardiovascular risk in ME/CFS patients, which is borne out epidemiologically by their high mortality due to heart disease [12].

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Please cite this article as: Newton DJ, et al, Large and small artery endothelial dysfunction in chronic fatigue syndrome, Int J Cardiol (2011), doi:10.1016/j.ijcard.2011.10.030