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Large and small artery endothelial dysfunction in chronic fatigue syndrome ☆

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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 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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Winning the *war*, *far*, *in* developing countries. Novel anticoagulants as a new weapon against stroke

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I have just returned from an African mission in Zimbabwe. I am now in the university hospital in Bologna where I work. In the waiting room of the anticoagulation therapy center I see a silent mass of people, mostly elderly, waiting for a blood sample to be taken. The expression on the faces of these men and women is generally sad and resigned; I know this ritual well, it can happen from two to four times a month. The queue, the nurse, the needle and the wait for the verdict – INR – that will decide the dose of the medicine to be taken in the evening, a few hours after meals. Meals that in turn are limited by the countless interferences of *warfarin*/Coumadin, the infamous rat poison that has become a life-saver for heart disease patients. This image takes me back irresistibly to Africa. Some go to Black Africa with their world-class Reflex to look for the "Big Five" on safari, some go with a portable echocardiograph to look for the many "big African hearts" in the improvized clinics between the wards where people are dying of HIV and TBC, as was my case last week. In just a few days I saw around a hundred people with heart disease, some with rheumatic valvulopathy, some with congenital heart disease; I did the follow-up on those who had already been operated on in Italy and screened those scheduled for surgery. The great majority of these patients are being treated with Coumadin due to the presence of a valvular prosthesis or atrial fibrillation. In the last year, among the young cardiopathic patients with valvular disease being followed up there were 6 deaths; in 3 of them the suspected cause was an acute malfunction of the prosthesis and in the other 3 it was stroke (both of these had chronic atrial fibrillation). In all these cases, inappropriate anticoagulant therapy seems to have been the cause of death. It is not difficult to imagine how prohibitive anticoagulant therapy can be in third world countries. The reagent is expensive and the test is inaccessible to most patients, never mind the unreliability of the test results due to laboratory errors; on top of all this lack of compliance and dietary errors complete the disastrous scenario. Finding a drug to replace warfarin would be enormously significant for a number of reasons, including its possible use in developing countries.

Dabigatran is an oral anticoagulant which acts by directly and competitively inhibiting thrombin, the "leader" of a class of drugs to which new active ingredients are being added. The RE-LY study (The Randomized Evaluation of Long-Term Anticoagulation Therapy) is a multicentre, prospective, randomized trial that enrolled 18,113 patients with atrial fibrillation (AF) and at least one additional cardiovascular risk factor for stroke. The primary endpoint was the incidence of stroke or thromboembolism [1,2]. Other outcomes included mortality myocardial infarct rates. In patients with AF, dabigatran administered at the dose of 110 mg was associated with stroke and systemic embolism rates similar to those observed with warfarin (1.53% dabigatran vs 1.69% warfarin) with a lower rate of severe hemorrhage (2.71% vs 3.36% per year). Dabigatran administered at the dose of 150 mg showed lower rates of stroke and systemic embolism compared to warfarin (1.11% vs 1.69%), with similar rates of major hemorrhage (3.11% dabigatran vs 3.36% warfarin). The rates of major hemorrhage (reduction of hemoglobin by at least 2 g/dl, transfusion of at least 2 packs of blood units or symptomatic bleeding in at least one organ) per year were 3.36% for warfarin, 2.71% for dabigatran 110 mg ($p = 0.003$) and 3.11% for dabigatran 150 mg ($p = 0.31$) [3].

The RE-LY study demonstrates that dabigatran represents a valid and important alternative to warfarin: at the lower dose, dabigatran proved to be as safe as warfarin but more effective; at the higher dose it was as effective but safer than warfarin. Controversial aspects remain, however, such as the lack of an antidote to dabigatran.

A study on rivaroxaban, an oral factor Xa inhibitor, in patients with nonvalvular atrial fibrillation has just been published [4]. The study showed that rivaroxaban is not inferior to warfarin for the prevention of stroke or systemic embolism. There was no significant

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