CARDIOVASCULAR MEDICINE

Incremental shuttle walking is associated with activation of haemostatic and haemorheological markers in patients with coronary artery disease: the Birmingham rehabilitation uptake maximisation study (BRUM)

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Objective: To test the hypothesis that an incremental shuttle walk test (ISWT) affects plasma indices of endothelial damage and dysfunction (von Willebrand factor (vWf)), platelet activation (soluble P-selectin), thrombogenesis (D-dimer), fibrinogen, and plasma viscosity more adversely in coronary artery disease (CAD) than in health. ISWT is a standardised walking test that provokes maximal performance and correlates strongly with maximum oxygen uptake.

Methods: Research indices were measured before a practice ISWT and immediately after the second ISWT in 53 patients with CAD (48 men, mean (SD) age 59 (10) years) and in 19 matched healthy controls (16 men, 61 (10) years). Data were analysed before and after ISWT.

Results: Despite no significant difference in total distance walked between patients and controls, vWf (162 (45) before v 170 (48) U/ml after) and fibrinogen (2.9 (0.7) v 3.1 (0.7) g/l) concentrations, plasma viscosity (1.63 (0.12) v 1.71 (0.14) mPa·s), and D-dimer (0.20 (interquartile range 0.10–0.30) v 0.21 (0.12–0.31 mg/l; all $p < 0.05$), but not soluble P-selectin, were significantly increased after ISWT in patients with CAD, even after correction for plasma volume change. Only fibrinogen (2.5 (0.7) v 2.7 (0.7) g/l) and plasma viscosity (1.60 (0.08) v 1.64 (0.08) mPa·s; both $p < 0.01$) increased among controls. The increment of fibrinogen was significantly higher in patients than in controls ($p = 0.035$) and correlated with total walking distance ($r = 0.46$, $p < 0.001$) and peak heart rate ($r = 0.28$, $p = 0.02$). The increment of plasma viscosity rise also significantly correlated with total distance walked ($r = 0.66$, $p < 0.001$).

Conclusions: ISWT in patients with CAD appears to increase fibrinogen, vWf, and D-dimer compared with healthy controls.

The pathogenesis of acute coronary and thrombotic disease involves activated platelets, coagulation proteins, abnormal rheology, and loss of the anticoagulant nature of the endothelium. Activation of the coagulation cascades after acute, short term physical exertion has been reported in several studies in both healthy people and patients with coronary artery disease (CAD) (as reviewed by Lee and Lip^{1,2}). However, most of these previous studies have used either a bicycle ergometer or treadmill exercise protocol, processes not widely available to most patients. Moreover, most patients choose regular walking as a means of exercise. Furthermore, the effect of this manner of “acute” exercise on vascular function is unknown. The incremental shuttle walk test (ISWT) is a standardised incremental field walking test that is characterised by a progressive increase in the workload and is a symptom limited test that provokes maximal performance. The distance walked has been shown to correlate strongly with maximum oxygen uptake (peak VO_2).^{3–6} ISWT therefore provides an accurate and reproducible yet simple measure of exercise capacity and, furthermore, it is more relevant to most patients usual exercise patterns—that is, walking.

The objective of the present study was to test the hypothesis that ISWT adversely affects plasma indices of endothelial damage and dysfunction (von Willebrand factor (vWf)), platelet activation (soluble P-selectin (sP-sel)),

thrombogenesis (fibrin D-dimer), fibrinogen, and plasma viscosity, thereby indicating a possible mechanism for an acute coronary event. We tested our hypothesis in patients with stable CAD in a cardiac rehabilitation population and compared their result with those from a cohort of age and sex matched controls free of overt CAD.

METHODS

Study population

This was a substudy of the BRUM (Birmingham rehabilitation uptake maximisation) study—a prospective randomised controlled trial of home based versus hospital based cardiac rehabilitation of patients after a myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting. The home programme is nurse facilitated (with home visits and telephone contact) based on the Heart Manual (West Lothian Health Care Trust). The BRUM study protocol has been reported in detail.⁷

For this substudy, patients with clinically stable CAD were recruited from those attending the hospital's cardiac rehabilitation department: all had recently completed a full course

Abbreviations: BRUM, Birmingham rehabilitation uptake maximisation; CAD, coronary artery disease; ELISA, enzyme linked immunosorbent assay; ISWT, incremental shuttle walk test; sP-sel, soluble P-selectin; VO_2 , oxygen uptake; vWf, von Willebrand factor

of cardiac rehabilitation and had been stabilised with established secondary prevention. Hence, patients included in this substudy were relatively well trained and clinically stable as required by the study protocol inclusion and exclusion criteria. We also recruited age and sex matched non-smoking healthy controls. These participants, defined by careful history, examination and basic blood tests, were recruited from members of the hospital staff and from relatives attending the hospital cardiac rehabilitation with the patients with stable CAD. All participants were asked to abstain from alcoholic and caffeine containing beverages during the evening before ISWT.

Exclusion criteria were age over 75, unstable angina, atrial fibrillation, prior history of exercise induce tachyarrhythmias or hypotension, uncontrolled systemic hypertension, known history of intermittent claudication, significant valve disease, congestive heart failure, permanent pacemaker, orthopaedic limitations to exercise, pulmonary disease such as asthma, neoplastic, infectious, or inflammatory diseases, renal or hepatic failure, connective tissue diseases, or history of deep vein thrombosis or pulmonary embolism. Patients with medical conditions or who were taking medications (for example, steroids and other immunosuppressants, hormone replacement therapy, or warfarin) that may potentially influence the levels of our choice of research indices and plasma haemostatic markers were also excluded from our present study. All medications were continued as routine. The study was approved by the west Birmingham ethics committee and all patients gave written informed consent.

ISWT protocol

The ISWT was performed in the hospital's cardiac rehabilitation department as described by Singh *et al.*^{3,4} In brief, the test required patients to walk at a gradually increasing speed, up and down a 10 m course identified by two marker cones, until they reach a symptom limited maximum (fig 1). The walking speed was externally paced and controlled by a series of beeps played on a compact disk originally generated from a microcomputer. The compact disk gave a standardised explanation of instructions for patients at the start. There were 12 progressive levels in total, beginning with 0.5 m/s and increasing by a small increment every minute (0.17 m/s). During the test, the patient's heart rate was continuously monitored by a Polar heart rate monitor (Polar USA, Lake

Success, New York, USA) and was recorded at the end of each minute. The test was terminated either by the patient, if he or she felt too breathless or fatigued or for any other reason(s) to maintain the required speed, or by the operators, if the patient failed to complete a 10 m length (shuttle) in the time allowed (being more than 0.5 m away from the cone when the beep sounded). After the test, the number of completed shuttles was recorded and the total distance walked was calculated. Peak rate of perceived exertion (by modified Borg scale), peak blood pressures and heart rate, and the main reason for test termination were recorded. All patients were first familiarised with the ISWT with one practice walk. The test was then repeated 30 minutes after the practice walk and the result of the second ISWT was used for analysis.^{3,4}

Blood samples and laboratory analyses

Venous blood samples were taken at two time points: before the start of the practice walk and immediately after completion of the second ISWT. First, a sample for haemoglobin and packed cell volume measurement and thereafter samples for coagulation assays were drawn into tubes containing 0.13 mol/l trisodium citrate (9:1 blood/citrate, vol/vol). Samples were put in ice immediately and citrated plasma was obtained from venous blood by centrifugation at 3000 rpm (1000 *g*) for 15 minutes at 4°C. Plasma was separated and stored in multiple aliquots at -70°C until analysis.

vWF and sP-sel were measured by enzyme linked immunosorbent assay (ELISA) (R&D Systems, Abingdon, UK and Dakopatts, Ely, UK), fibrinogen (g/l) by the Clauss technique on a Pacific Hemostasis coagulometer (Huntersville, North Carolina, USA), with bovine thrombin from Alpha Laboratories (Eastleigh, Hampshire, UK) and fibrin D-dimer with an ELISA from Agen (Brisbane, Australia). Samples from the same participants obtained before and after ISWT were tested simultaneously in one single run. Intra-assay and interassay coefficients of variation for all ELISAs were < 5% and < 10%, respectively. An EDTA sample was analysed in the routine haematology autoanalysers for plasma viscosity (viscometer; Coulter Instruments, Luton, UK).

Changes in plasma volume were estimated from packed cell volume and haemoglobin data before and after ISWT according to the method of Dill and Costill.⁸ The values for haemostatic markers except plasma viscosity were corrected for plasma volume changes during exercise by the following factor: $(100 + \Delta PV)/100$, where ΔPV is the change of plasma volume given as a percentage.⁹

The pre-exercise analytical values were expressed without a correction for plasma volume changes. With the plasma volume correction, all post-exercise concentrations of vWf, fibrinogen, sP-sel, and D-dimer were, on average, 4% lower. Data were analysed and the post-ISWT values were expressed as concentrations before and after correction for plasma volume changes. Post-ISWT plasma viscosity was analysed and given without correction for plasma volume change.

Power calculations

It was our hypothesis that the ISWT would be associated with an increase of 0.30 of a standard deviation in markers of thrombosis and haemostasis in patients with CAD. To achieve this at $p < 0.05$ and $1 - \beta = 0.8$, good samples from 50 patients were required. We therefore recruited slightly more than this number. At the same time we sought reference and comparator data from healthy controls expected to have lower concentrations of the plasma markers. A sample size of 19 brings the $1 - \beta$ power of 0.8 to define a difference of 0.5 of a standard deviation at $p < 0.05$.

Figure 1 Incremental shuttle walk test protocol.

Table 1 Clinical and demographic characteristics of patients with coronary artery disease (CAD) and controls

	CAD (n = 53)	Controls (n = 19)	p Value
Age (years)	59 (10)	61 (10)	0.34
Men	48 (91%)	16 (84%)	0.43
BMI (kg/m ²)	28 (3)	28 (5)	0.89
Cholesterol (mmol/l)	3.8 (0.7)	5.3 (0.8)	<0.001
HDL cholesterol (mmol/l)	1.22 (0.3)	1.48 (0.5)	0.06
TC:HDL ratio	3.2 (0.8)	3.9 (1.2)	0.032
Creatinine (μmol/l)	94 (16)	86 (11)	0.073
Known risk factors			
Prior MI	31 (59%)	NA	
Prior PCI	26 (49%)	NA	
Prior CABG	7 (13%)	NA	
Hypertension	15 (28%)	NA	
Diabetes mellitus	11 (21%)	NA	
Active smoker	13 (25%)	NA	
Medications			
Aspirin	47 (89%)	NA	
β Blocker	42 (79%)	NA	
ACE inhibitor	30 (57%)	NA	
Statin	47 (89%)	NA	
ARB	5 (9%)	NA	
CCBs	5 (9%)	NA	
Nitrates	9 (17%)	NA	
Clopidogrel	7 (13%)	NA	
Nicorandil	4 (8%)	NA	
Hypoglycaemic	7 (13%)	NA	
Insulin	2 (4%)	NA	

Data are mean (SD) or number (%).

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CCBs, calcium channel blockers; HDL, high density lipoprotein; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention; TC, total cholesterol.

Statistical analysis

Data are expressed as mean (SD) or as medians with interquartile ranges. Categorical variables were compared by using the χ^2 test. For continuous variables, data were compared within groups by the paired Student's *t* or Wilcoxon test and between groups by unpaired Student's *t* or Mann-Whitney *U* test, as appropriate. A two way (group $\times$ time (before and after ISWT)) analysis of variance with repeated measures was used to evaluate whether the mean responses of ISWT differed between patients and controls on exercise data and haemostatic marker concentrations before and after ISWT. Non-parametric data were logarithm transformed before analyses of variance. Correlations were determined with Spearman's rank correlation method. The significance level was set at $p < 0.05$. All statistical analyses were performed with SPSS software, version 11 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Table 1 summarises the demographic and clinical characteristics of all patients with CAD and of controls. None of the patients experienced anginal chest pain and complications during the maximal, symptom limited exercise test, but stopped due to leg fatigue or failure to complete the shuttle in the time allowed.

Table 2 shows the comparisons between patients with CAD and healthy controls in shuttle walking indices before and after ISWT. Plasma volumes were significantly changed after ISWT in both patients with CAD and controls (both $p < 0.01$). However, there were no significant differences between patients and controls in total distance walked, rate of perceived exertion, change in plasma volume after ISWT, and before and immediately after ISWT mean heart rate, and systolic and diastolic blood pressures. There were no significant differences in the group versus exercise effects

between diabetic ($n = 11$) and non-diabetic patients with CAD (data not shown).

Table 3 shows the comparisons between patients with CAD and healthy controls in haemostatic indices before and after ISWT (corrected for plasma volume change). At rest, as expected, patients had significantly higher concentrations of vWf, fibrinogen, and sP-sel than did controls. Immediately after ISWT, vWf, fibrinogen, and D-dimer concentrations and plasma viscosity were significantly increased, whereas sP-sel concentrations were not significantly changed in patients with CAD. Only fibrinogen concentration and plasma viscosity were significantly increased in healthy controls immediately after ISWT. The ISWT induced increment in fibrinogen concentrations was significantly higher in patients than in healthy controls. The correction applied for change in plasma volume (that is, haemoconcentration after ISWT) significantly affected these results (when comparing before versus after applying correction for contraction of plasma volume; table 3).

Correlations

In the overall group, the increment of fibrinogen concentration after ISWT was significantly correlated with total distance walked (Spearman's $r = 0.46$, $p < 0.001$) and peak heart rate ($r = 0.28$, $p = 0.02$). The increment of plasma viscosity also significantly correlated with total distance walked ($r = 0.66$, $p < 0.001$). The correction applied for change in plasma volume after ISWT did not significantly affect the outcome of the correlations results.

DISCUSSION

Many studies have reported a positive effect towards an antithrombotic state and improving fibrinolytic capacity by long term regular exercise of low to moderate intensity. Conversely, the available evidence suggests that acute, short term exercise activates both the coagulative and fibrinolytic cascades.¹ Indeed, it has been known for many years that blood taken immediately after exercise is prothrombotic, as indicated by shortening of the whole blood clotting times and activated partial thromboplastin time, which measures the activity of the intrinsic and common pathways in the coagulation cascade.¹ However, data on the effect of acute, short term exercise on coagulation factors, including platelet reactivity, are conflicting. This is most likely due to variations in methods including subject health, training status, exercise protocol, and laboratory methods with or without correction for plasma volume change after exercise.¹ As an example, many of the previous studies have used bicycle ergometer or treadmill exercise.

The ISWT is a simple and safe method to assess a patient's functional capacity and is reproducible after just one practice walk.³⁻⁶ Indeed, the ISWT has also been increasingly used in functional capacity assessment of patients post-coronary bypass grafting and in patients waiting for cardiac transplantation. Importantly, for patients with heart failure the distance walked in ISWT correlates with peak $\dot{V}O_2$ and percentage achieved of age and sex predicted peak $\dot{V}O_2$ better than does distance in a six minute walk test.⁴⁻⁶ ISWT can also predict adverse cardiac events in patients with heart failure.¹⁰ In the present study, we have applied the ISWT to patients with CAD to assess the effect of acute, short term walking on plasma indices of endothelial damage and dysfunction (vWf), platelet activation (sP-sel), thrombolysis (D-dimer), fibrinogen, and plasma viscosity. We showed that plasma vWf, fibrinogen, and D-dimer concentration and plasma viscosity were significantly increased in patients with CAD, whereas only fibrinogen and plasma viscosity were increased in healthy controls immediately after maximal ISWT. However, the increment of fibrinogen was significantly

Table 2 Comparisons between patients with CAD and healthy controls on incremental shuttle walk test (ISWT) indices

	Overall CAD (n = 53)	Controls (n = 19)	Intergroup p value*	Group × exercise effects†	
				F(1, 70)	p Value
Total distance (m)	−430 (350–540)	−440 (360–520)	−0.94	NA	NA
RPE	12 (11–13)	12 (11–13)	0.85	NA	NA
ΔPlasma volume (%)	−4.1 (−7.4 to −2.1)	−3.2 (−8.1 to −0.69)	0.38	NA	NA
HR _{before} (beats/min)	66 (13)	64 (9)	0.56		
HR _{after}	104 (13)	108 (12)	0.29	0.08	0.78
SBP _{before} (mm Hg)	133 (17)	132 (7)	0.91		
SBP _{after}	158 (16)	160 (9)	0.72	0.02	0.89
DBP _{before} (mm Hg)	78 (10)	78 (7)	0.89		
DBP _{after}	88 (9)	92 (4)	0.026	1.55	0.22

Data are mean (SD) or median (interquartile range).

*Unpaired Student's *t* or Mann-Whitney U test; †two way analysis of variance with repeated measures of the exercise effect in group by exercise interactions.

Δ indicates changes after ISWT; DBP, diastolic blood pressure; HR, heart rate; RPE, rate of perceive exertion; SBP, systolic blood pressure.

higher in patients than in healthy controls. sP-sel concentrations were not significantly changed in both patients and healthy controls after correction for plasma volume change.

It is unknown whether the magnitude of increments in vWf, fibrinogen, and D-dimer concentrations and plasma viscosity in patients with CAD, and fibrinogen and plasma viscosity in healthy controls after maximal ISWT are of clinical significance or pathological relevance. Nonetheless, the established close association between sudden physical exertion and increased risk of myocardial infarction and sudden cardiac death, particularly in sedentary subjects with pre-existing atherosclerosis, may be related to increased blood thrombogenicity that is reflected by an abnormal or increased concentration of plasma haemostatic markers after acute exertion. Furthermore, most cases of acute coronary syndromes are associated with intracoronary thrombus formation. Close relations between haemostatic factors such as vWf,¹¹ fibrinogen,¹² plasma viscosity,^{13–14} or D-dimer¹⁵ and increased risk of adverse cardiovascular events have been reported in prospective population studies.

Our study is limited by measuring only one arm of the haemostatic balance and its relevance to *clinically stable* patients with CAD. We recognise that a wide variety of indices can be measured such as flow cytometry, inflammation, fibrinolysis—the list is actually endless. We did not wish to repeat previous work (for example, flow cytometry and fibrinolysis, as we reviewed^{1–2}) but felt that in this study we addressed a defined set of parameters in relation to a *specific exercise stimulus* (the shuttle walk test) and a *specific patient population* (patients with CAD after cardiac rehabilitation) as a substudy of the BRUM study.⁷ Several studies have consistently reported that acute, short term exercise enhances fibrinolytic capacity in both healthy people and patients with CAD in a wide range of exercise protocols incorporating various exercise intensities and durations.¹ However, the increased level of fibrinolytic activity falls sharply during the recovery period, whereas activation of the coagulation cascade is persistent.^{16–17} Such a temporal unbalance between the coagulative and fibrinolytic systems has been thought to precipitate acute coronary thrombosis in

Table 3 Comparisons between patients with CAD and healthy controls on haemostatic indices

	Overall CAD (n = 53)	Controls (n = 19)	Intergroup p value*	CAD _{Before} – After p value†	Controls _{Before} – After p value†	Group × exercise effects‡	
						F(1, 70)	p Value
After applying correction for contraction of plasma volume							
vWf _{before} (IU/dl)	162 (45)	122 (17)	<0.001				
vWf _{after} (IU/dl)	170 (48)	124 (17)		0.018	0.23	16.4	0.001
Fibrinogen _{before} (g/l)	2.9 (0.7)	2.5 (0.7)	0.041				
Fibrinogen _{after} (g/l)	3.1 (0.7)	2.7 (0.7)		<0.001	0.008	4.6	0.035
D-dimer _{before} (mg/l)	0.20 (0.10–0.30)	0.20 (0.10–0.30)	0.90				
D-dimer _{after} (mg/l)	0.21 (0.12–0.31)	0.20 (0.10–0.35)		0.006	0.62	0.10	0.75
sP-sel _{before} (ng/ml)	78 (68–88)	67 (59–85)	0.033				
sP-sel _{after} (ng/ml)	75 (66–92)	69 (62–76)		0.50	0.96	4.0	0.049
PV _{before} (mPa·s)	1.63 (0.12)	1.60 (0.08)	0.29				
PV _{after} (mPa·s)	1.71 (0.14)	1.64 (0.08)		<0.001	0.001	2.9	0.09
Before applying correction for contraction of plasma volume							
vWf _{before} (IU/dl)	162 (45)	122 (17)	<0.001				
vWf _{after} (IU/dl)	178 (49)	126 (17)		<0.001	0.016	18.2	0.001
Fibrinogen _{before} (g/l)	2.9 (0.7)	2.5 (0.7)	0.041				
Fibrinogen _{after} (g/l)	3.2 (0.7)	2.7 (0.7)		<0.001	0.001	5.8	0.019
D-dimer _{before} (mg/l)	0.20 (0.10–0.30)	0.20 (0.10–0.30)	0.90				
D-dimer _{after} (mg/l)	0.21 (0.12–0.31)	0.20 (0.10–0.35)		<0.001	0.43	0.16	0.70
sP-sel _{before} (ng/ml)	78 (68–88)	67 (59–85)	0.033				
sP-sel _{after} (ng/ml)	79 (68–93)	72 (63–78)		0.19	0.24	1.5	0.29
PV _{before} (mPa·s)	1.63 (0.12)	1.60 (0.08)	0.29				
PV _{after} (mPa·s)	1.71 (0.14)	1.64 (0.08)		<0.001	0.001	2.9	0.09

Data are mean (SD) or median (interquartile range).

*Unpaired Student's *t* or Mann-Whitney U test; †paired Student's *t* or Wilcoxon test; ‡two way analysis of variance with repeated measures of the exercise effect in group by exercise interactions.

PV, plasma viscosity; sP-sel, soluble P-selectin; vWf, von Willebrand factor.

susceptible sedentary people or in patients with a diseased vascular system who may not sustain their fibrinolytic capacity (perhaps due to some endothelial dysfunction) when they are exposed to unaccustomed strenuous physical exertion. Our findings of a higher postexercise increment of vWF, fibrinogen, and D-dimer in patients than in healthy controls suggest that the blood of these patients had greater thrombogenic potential compared with matched healthy subjects after acute walking, despite similar levels of exertion. It is plausible that healthy controls with relatively intact endothelium may have higher counterbalancing enhanced fibrinolytic potential. Indeed, exercise induced activation of coagulation in combination with endothelial dysfunction and reduced fibrinolytic capacity may present an increased risk of cardiovascular events in patients with CAD compared with healthy people with intact endothelium and normal haemostasis.

A possible limitation of our study is that we did not collect coronary angiographic data, as the hypothesis and study design were related to a cardiac rehabilitation population after a clinical diagnosis of CAD—that is, previous myocardial infarction or revascularisation. This study was also limited by blood samplings at only two time points, before the practice walk and immediately after completion of the second ISWT. Furthermore, our patients were likely to have been preconditioned, as all patients had completed a course of phase III cardiac rehabilitation before being followed up for ISWT. For example, endurance physical training by men and women at moderate intensity (50–55% of peak $\dot{V}O_2$) suppresses platelet adhesiveness and aggregation both at rest and after acute strenuous exercise. However, the effects reverse back to the pretraining state after a period of deconditioning.^{18, 19}

Interestingly, the outcomes of the post-ISWT results in the present study were obviously different after correction for contraction of plasma volume. Therefore, changes in plasma volume in response to exercise should be taken into account when interpreting exercise effects on plasma concentrations of haemostatic indices. Whether our observations have clinical implications for patients with CAD also remains to be investigated. Further studies need to be conducted to clarify the relative changes of coagulative and fibrinolytic indices after ISWT.

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