INCREMENTAL SHUTTLE WALKING IS ASSOCIATED WITH ACTIVATION OF
HAEMOSTATIC AND HAEMORHEOLOGIC MARKERS IN PATIENTS WITH
CORONARY ARTERY DISEASE

The Birmingham Rehabilitation Uptake Maximisation Study (BRUM)

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Abstract

**Background:** Short-term physical exertion induces coagulation activation in patients with coronary artery disease (CAD). We hypothesised that an incremental shuttle walk test (ISWT) on plasma indices of endothelial damage/dysfunction (von Willebrand factor, vWF), platelet activation (soluble P-selectin, sPsel), thrombogenesis (D-Dimer), fibrinogen and plasma viscosity (PV) produces more profound changes in 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 CAD patients (48 male, 59±10yrs) and in 19 matched healthy controls (16 male, 61±10yrs). Data were analysed before and after ISWT.

**Results:** Despite no significant difference in total distance walked between patients and controls, levels of vWF, fibrinogen, PV and D-Dimer (all p<0.05), but not sPsel, were significantly increased post-ISWT in CAD patients - even after correction for plasma volume change. Only fibrinogen and PV (both p<0.01) increased amongst 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<0.01) and peak heart rate (r= 0.28, p<0.05). The increment of PV rise also significantly correlated with total distance walked (r=0.66, p<0.001).

**Conclusions:** ISWT in patients with CAD appears to elevate fibrinogen, vWF and D-Dimer, when compared with healthy individuals.

**Keywords:** incremental shuttle walk, haemostatic markers, fibrinogen, soluble P-selectin, von Willebrand factor, coronary artery disease, exercise.
Introduction

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 persons 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 mean 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 characterized 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’, i.e. walking.

The aim of the present study was to test the hypothesis that ISWT adversely affects plasma indices of endothelial damage/dysfunction (von Willebrand factor, vWF), platelet activation (soluble P-selectin, sPsel), thrombogenesis (fibrin D-Dimer), fibrinogen and plasma viscosity (PV), 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 result to those from a cohort of age and sex matched controls free of overt CAD.

METHODS

Study population

This was a substudy of the Birmingham Rehabilitation Uptake Maximisation (BRUM) Study – a prospective randomised controlled trial of home-based versus hospital-based cardiac rehabilitation in patients following MI, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The home programme is nurse-facilitated (with home visits and telephone contact), using 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 attended the hospital’s cardiac rehabilitation department: all had recently completed a full course of cardiac rehabilitation, and had been stabilised on established secondary preventive therapy. 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 persons, defined by careful history, examination and basic blood tests, were recruited from members of the hospital staff and from those relatives attending the hospital cardiac rehabilitation with the stable CAD patients. All subjects were asked to abstain from alcoholic and caffeine-containing beverages during the evening before ISWT.

Exclusion criteria was age over 75, unstable angina, atrial fibrillation, prior history of exercise induce tachyarrhythmias or hypotension, uncontrolled systemic hypertension, known history of intermittent claudication, significant valvular 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, prior history of deep vein thrombosis or pulmonary embolism. Patients with medical conditions or on medications (eg. steroids and other immunosuppressants, hormone replacement therapy, warfarin, etc) 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 (Figure 1). The walking speed was externally paced and controlled by a series of beeps played on a CD originally generated from a microcomputer. The CD 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 was increased by a small increment every minute (0.17 m/s). During the test, patient’s heart rate was continuously monitored by a Polar heart rate monitor and was recorded at the end of each minute. The test was terminated either by the patient if he/she felt too breathless or fatigued, for any other reason(s) to maintain the required speed, or by the operators if the patient failed to complete a 10m length (shuttle) in the time allowed (being more than 0.5 meter 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 was 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 commencement of the practice walk and immediately after completion of the second ISWT. First, a sample for haemoglobin and haematocrit measurement was drawn, and thereafter samples for coagulation assays, 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/1000g for 15 minutes at 4°C. Plasma was separated and stored in multiple aliquots at -70 °C until analysis.

vWF and sPsel were measured by ELISA (R&D Systems, Abingdon, UK and Dako-Patts, Ely, UK), fibrinogen (g/L) by the Clauss technique on a Pacific Hemostasis coagulometer, with bovine thrombin from Alpha Laboratories and fibrin D-Dimer with an ELISA from Agen. Samples from the same subjects obtained before and after ISWT were tested simultaneously in one single run. Intra-assay and inter-assay coefficients of variation for all ELISAs were <5% and <10%, respectively. An EDTA sample was analyzed in the routine haematology autoanalyzers for plasma viscosity (Coulter viscometer) levels.

Changes in plasma volume were estimated from values before and after ISWT haematocrit and haemoglobin data, according to the method of Dill and Costill (8). The values for haemostatic markers except plasma viscosity were corrected for changes of plasma volume occurring during exercise by the following factor: (100 + ΔPV)/100, where ΔPV is the change of plasma volume given in percent (9).
The pre-exercise analytical values were expressed without a correction for plasma volume changes. With the plasma volume correction, all post-exercise values of vWF, fibrinogen, sP-sel and D-Dimer were, on average, 4% lower. Data were analysed and the post-ISWT values were expressed, in concentrations before and after correction for plasma volume changes. Post-ISWT plasma viscosity values were 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. In order to achieve this at p<0.05 and 1-beta = 0.8, good samples from 50 subjects are required. We therefore recruited to slightly in excess of this number. At the same time we sought reference and comparator data from healthy controls expected to have lower levels 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.

**Statistical analysis**

Data expressed as mean ± SD or as medians with inter-quartile ranges (IQR). Categorical variables were compared by using the Chi-2 test. For continuous variables, data were compared within groups using paired Student's t or Wilcoxon tests and between groups using unpaired Student's t or Mann-Whitney U tests, as appropriate. A two-way (group x time [before and after ISWT]) analysis of variance (ANOVA) with repeated measures was used to evaluate whether the mean responses of ISWT differed between patients and controls on exercise data and haemostatic markers levels before and after ISWT. Non-parametric data were logarithmic transformed before ANOVA analyses. Correlations were performed with Spearman's rank correlation method. The significance level was set at P<0.05. All statistical analyses were performed using SPSS software, version 11 (SPSS Inc., Chicago, Illinois, USA).

**Results**

Table 1 summarises the demographic and clinical characteristics of all CAD patients and controls. None of the subjects 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 CAD patients and healthy controls in shuttle walking indices before and after ISWT. Plasma volumes were significantly changed after ISWT in both CHD patients and controls (both p<0.01). However, there were no significant differences between patients and controls in total distance walked, rate of perceived exertion and change in plasma volume after ISWT, and before and immediately after ISWT mean heart rate, systolic and diastolic blood pressures. There were no significant differences in the Group vs Exercise effects between diabetic (n=11) and non-diabetic CAD patients (data not shown).

Table 3a shows the comparisons between CAD patients and healthy controls in haemostatic indices before and after ISWT (corrected for plasma volume change). As expected, at rest, patients had significantly higher levels of vWF, fibrinogen and sP-sel compared to controls. Immediately after ISWT, vWF, fibrinogen, D-Dimer and plasma viscosity levels were significantly increased whilst sP-sel levels were not significantly changed in CAD patients.
Only fibrinogen and plasma viscosity levels were significantly increased in healthy controls immediately after ISWT. The ISWT-induced increment in fibrinogen levels was significantly higher in patients compared to healthy controls. The correction applied for change in plasma volume (i.e. haemoconcentration after ISWT) significantly affected these results (when comparing Tables 3a and Table 3b).

**Correlations**
In the overall group, the increment of fibrinogen level post-ISWT was significantly correlated with total distance ambulated (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 ambulated ($r=0.66$, $p<0.001$). 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 methodology 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 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 in patients post-coronary bypass grafting and in patients waiting for cardiac transplantation. Importantly, the distance walked in ISWT correlates with peak VO\textsubscript{2}\text{max} and percent achieved of age- and sex-predicted peak VO\textsubscript{2}\text{max} better than distance in 6-minute walk test in patients with heart failure (4-6). ISWT can also predict adverse cardiac events in heart failure patients (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/dysfunction (vWf), platelet activation (sPsel), thrombolysis (D-Dimer), fibrinogen and plasma viscosity. We show that plasma vWf, fibrinogen, D-Dimer and plasma viscosity levels were significantly increased in CAD patients whereas only fibrinogen and plasma viscosity were increased in healthy controls immediately after maximal ISWT. However, the increment of fibrinogen was significantly higher in patients than in healthy controls. sPsel levels 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, D-Dimer and plasma viscosity levels in CAD patients, and fibrinogen and plasma viscosity in healthy controls after maximal ISWT are of clinical significance or pathologic relevance. Nonetheless, the established close association between sudden physical exertion and increased risk of MI and sudden cardiac death, particularly in sedentary subject with pre-existing atherosclerosis may be related to increased blood thrombogenicity that reflected by an abnormal/increased level of plasma haemostatic markers after acute exertion. Furthermore, most cases of acute coronary syndromes are associated with intra-coronary thrombus formation, and that close relationships between haemostatic factors such as vWf (11), fibrinogen (12), plasma viscosity (13;14) or D-Dimer (15) and increased risk of adverse cardiovascular events have been reported in prospective populational studies.

Our study is limited by measuring only one arm of the haemostatic balance and its relevance to clinically stable CAD patients. We recognise that there are a wide variety of indices that can be measured eg flow cytometry, inflammation, fibrinolysis – the list is actually endless. We did not wish to be repetitive of previous work (eg. flow cytometry and fibrinolysis – as reviewed by us (1,2)) but felt that in this paper we have addressed a defined set of parameters in relation to a specific exercise stimulus (the Shuttle walk test) and a specific patient population (CAD patients following cardiac rehabilitation), as a substudy of the Birmingham
Rehabilitation Uptake Maximisation Study (BRUM)(7). Several studies have consistently reported that acute, short-term exercise enhances fibrinolytic capacity in both healthy and CHD subjects 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 while 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 susceptible sedentary individuals 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 higher post exercise increment of vWF, fibrinogen and D-Dimer in patients than healthy controls suggest that the blood of these patients was of greater ‘thrombogenic’ potential compared to 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 individuals with intact endothelium and normal haemostasis.

A possible limitation is that coronary angiographic data were not collected, as the hypothesis and study design was related to a cardiac rehabilitation population, after a clinical diagnosis of coronary artery disease, i.e. previous myocardial infarction or revascularisation. This study also limited by blood samplings only at 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 in men and in women at moderate intensity (50–55% of VO₂max) suppress 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. It also remains to be investigated if our observations have clinical implications in patients with CHD. Further studies need to be conducted to clarify the relative changes of coagulative and fibrinolytic indices after ISWT.

ACKNOWLEDGEMENTS

We acknowledge the support of the Peel Medical Research Trust and the Sandwell and West Birmingham Hospitals NHS Trust Research and Development programme for the Haemostasis Thrombosis and Vascular Biology Unit. The BRUM study is funded by the NHS Health Technology Assessment Programme.
REFERENCES


Table 1. Clinical and demographic characteristics of CAD patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>CAD (n=53)</th>
<th>Controls (n=19)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>59 ± 10</td>
<td>61 ± 10</td>
<td>0.34</td>
</tr>
<tr>
<td>Male (%)</td>
<td>48 (91)</td>
<td>16 (84)</td>
<td>0.43</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28 ± 3</td>
<td>28 ± 5</td>
<td>0.89</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>3.8 ± 0.7</td>
<td>5.3 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.22 ± 0.3</td>
<td>1.48 ± 0.5</td>
<td>0.06</td>
</tr>
<tr>
<td>TC/HDL ratio</td>
<td>3.2 ± 0.8</td>
<td>3.9 ± 1.2</td>
<td>0.032</td>
</tr>
<tr>
<td>Creatinine (umol/L)</td>
<td>94 ± 16</td>
<td>86 ± 11</td>
<td>0.073</td>
</tr>
</tbody>
</table>

Known risk factors (%):
- Prior MI: 31 (59)
- Prior PCI: 26 (49)
- Prior CABG: 7 (13)
- Hypertension: 15 (28)
- Diabetes Mellitus: 11 (21)
- Active smoker: 13 (25)

Medications (%):
- Aspirin: 47 (89)
- Beta blocker: 42 (79)
- ACE inhibitor: 30 (57)
- Statin: 47 (89)
- ARB: 5 (9)
- CCBs: 5 (9)
- Nitrates: 9 (17)
- Clopidogrel: 7 (13)
- Nicorandil: 4 (8)
- Hypoglycemic: 7 (13)
- Insulin: 2 (4)

BMI, body mass index; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCBs, calcium channel blockers.
Table 2. Comparisons between CAD patients and healthy controls on ISWT indices

<table>
<thead>
<tr>
<th></th>
<th>Overall CAD (n=53)</th>
<th>Controls (n=19)</th>
<th>Inter-Group(^1)</th>
<th>Group x Exercise effects(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total distance (m)</td>
<td>430 (350 – 540)</td>
<td>440 (360 – 520)</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>RPE</td>
<td>12 (11 – 13)</td>
<td>12 (11 – 13)</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>∆Plasma volume (%)</td>
<td>-4.1 (-7.4 – -2.1)</td>
<td>-3.2 (-8.1 – -0.69)</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>HR before (bpm)</td>
<td>66 ± 13</td>
<td>64 ± 9</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>HR after</td>
<td>104 ± 13</td>
<td>108 ± 12</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>SBP before (mmHg)</td>
<td>133 ± 17</td>
<td>132 ± 7</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>SBP after</td>
<td>158 ± 16</td>
<td>160 ± 9</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>DBP before (mmHg)</td>
<td>78 ± 10</td>
<td>78 ± 7</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>DBP after</td>
<td>88 ± 9</td>
<td>92 ± 4</td>
<td>0.026</td>
</tr>
</tbody>
</table>

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

\(^1\)Unpaired Student's t or Mann-Whitney U tests
\(^2\)Two-way ANOVA with repeated measures of the exercise effect. Group x Exercise indicates Group-by-Exercise interactions.
Table 3. Comparisons between CAD patients and healthy controls on haemostatic indices

(a) *after* applying correction for contraction of plasma volume:

<table>
<thead>
<tr>
<th></th>
<th>Overall CAD (n=53)</th>
<th>Controls (n=19)</th>
<th>1^Inter-Group Before P-value</th>
<th>2^CAD Before - After P-value</th>
<th>2^Controls Before - After P-value</th>
<th>3^Group x Exercise effects F(1, 70)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>vWF before (iu/dL)</td>
<td>162 ± 45</td>
<td>122 ± 17</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vWF after</td>
<td>170 ± 48</td>
<td>124 ± 17</td>
<td></td>
<td>0.018</td>
<td>0.23</td>
<td>16.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Fibrinogen before (g/L)</td>
<td>2.9 ± 0.7</td>
<td>2.5 ± 0.7</td>
<td>0.041</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen after</td>
<td>3.1 ± 0.7</td>
<td>2.7 ± 0.7</td>
<td></td>
<td>&lt;0.001</td>
<td>0.008</td>
<td>4.6</td>
<td>0.035</td>
</tr>
<tr>
<td>D-Dimer before (mg/L)</td>
<td>0.20 (0.10 – 0.30)</td>
<td>0.20 (0.10 – 0.30)</td>
<td>0.90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-Dimer after</td>
<td>0.21 (0.12 – 0.31)</td>
<td>0.20 (0.10 – 0.35)</td>
<td>0.006</td>
<td>0.62</td>
<td>0.10</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>sP-sel before (ng/mL)</td>
<td>78 (68 – 88)</td>
<td>67 (59 – 85)</td>
<td>0.033</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sP-sel after</td>
<td>75 (66 – 92)</td>
<td>69 (62 – 76)</td>
<td></td>
<td>0.50</td>
<td>0.96</td>
<td>4.0</td>
<td>0.049</td>
</tr>
<tr>
<td>PV before (mPa.s)</td>
<td>1.63 ± 0.12</td>
<td>1.60 ± 0.08</td>
<td>0.29</td>
<td></td>
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<tr>
<td>PV after</td>
<td>1.71 ± 0.14</td>
<td>1.64 ± 0.08</td>
<td></td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>2.9</td>
<td>0.09</td>
</tr>
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</table>

CHD, coronary heart disease; PV, plasma viscosity; vWF, von Willebrand factor; sP-Sel, soluble P-selectin.

1. Unpaired Student's t or Mann-Whitney U tests. Paired Student's t or Wilcoxon tests
2. Two-way ANOVA with repeated measures of the exercise effect. Group x Exercise indicates Group-by-Exercise interactions
Table 3. Comparisons between CAD patients and healthy controls on haemostatic indices

(b) *Before* applying correction for contraction of plasma volume

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<td></td>
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</tr>
<tr>
<td>vWF after</td>
<td>178 ± 49</td>
<td>126 ± 17</td>
<td>&lt;0.001</td>
<td>0.016</td>
<td>18.2</td>
<td>0.001</td>
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</tr>
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<td>Fibrinogen before (g/L)</td>
<td>2.9 ± 0.7</td>
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<td>0.041</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen after</td>
<td>3.2 ± 0.7</td>
<td>2.7 ± 0.7</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>5.8</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>D-Dimer before (mg/L)</td>
<td>0.20 (0.10 – 0.30)</td>
<td>0.20 (0.10 – 0.30)</td>
<td>0.90</td>
<td></td>
<td></td>
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<td>D-Dimer after</td>
<td>0.21 (0.12 – 0.31)</td>
<td>0.20 (0.10 – 0.35)</td>
<td>&lt;0.001</td>
<td>0.43</td>
<td>0.16</td>
<td>0.70</td>
<td></td>
</tr>
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<td>sP-sel before (ng/mL)</td>
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<td>0.033</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sP-sel after</td>
<td>79 (68 – 93)</td>
<td>72 (63 – 78)</td>
<td>0.19</td>
<td>0.24</td>
<td>1.5</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>PV before (mPa.s)</td>
<td>1.63 ± 0.12</td>
<td>1.60 ± 0.08</td>
<td>0.29</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV after</td>
<td>1.71 ± 0.14</td>
<td>1.64 ± 0.08</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>2.9</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

CHD, coronary artery disease; PV, plasma viscosity; vWF, von Willebrand factor; sP-Sel, soluble P-selectin.

1. Unpaired Student's t or Mann-Whitney U tests
2. Paired Student's t or Wilcoxon tests
3. Two-way ANOVA with repeated measures of the exercise effect. Group x Exercise indicates Group-by-Exercise interactions
**Figure 1**

![Figure 1](image)

**The incremental shuttle walk test protocol**

<table>
<thead>
<tr>
<th>Level</th>
<th>Speed (m/s)</th>
<th>Number of shuttles per level</th>
<th>Distance ambulated at the end of each level (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.50</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>0.67</td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>0.84</td>
<td>5</td>
<td>120</td>
</tr>
<tr>
<td>4</td>
<td>1.01</td>
<td>6</td>
<td>180</td>
</tr>
<tr>
<td>5</td>
<td>1.18</td>
<td>7</td>
<td>250</td>
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<tr>
<td>6</td>
<td>1.35</td>
<td>8</td>
<td>330</td>
</tr>
<tr>
<td>7</td>
<td>1.52</td>
<td>9</td>
<td>420</td>
</tr>
<tr>
<td>8</td>
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<td>520</td>
</tr>
<tr>
<td>9</td>
<td>1.86</td>
<td>11</td>
<td>630</td>
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<td>11</td>
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<tr>
<td>12</td>
<td>2.37</td>
<td>14</td>
<td>1020</td>
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</table>
Incremental shuttle walking is associated with activation of haemostatic and haemorheologic markers in patients with coronary artery disease: the Birmingham Rehabilitation Uptake Maximisation Study (BRUM)

Kaeng Lee, Andrew Blann, Jackie Ingram, Kate Jolly and Gregory Y H Lip

Heart published online March 17, 2005

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