CARDIOVASCULAR MEDICINE

Plasma haemostatic markers, endothelial function and ambulatory blood pressure changes with home versus hospital cardiac rehabilitation: the Birmingham Rehabilitation Uptake Maximisation Study

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Background: Cardiac rehabilitation is an accepted therapeutic intervention in patients after myocardial infarction or coronary revascularisation. The effects of cardiac rehabilitation programmes, whether home based or hospital based, on haemostatic indices (as reflected by fibrinogen, plasma viscosity, fibrin D-dimer (an index of thrombogenesis), von Willebrand factor (vWf, an index of endothelial damage/dysfunction), soluble P-selectin (an index of platelet activation)), vasomotor function (using flow-mediated dilatation (FMD)) and ambulatory blood pressure (ABP) in patients with coronary heart disease are unknown.

Methods: 81 patients (66 men, mean (SD) 59 (11) years) after myocardial infarction or coronary revascularisation were randomised to comprehensive hospital-based (n=40) or home-based (n=41) cardiac rehabilitation. Plasma levels of vWf, D-dimer, fibrinogen, soluble P-selectin and plasma viscosity, as well as FMD and 24-h ABP, were measured at baseline and after 3 months of cardiac rehabilitation.

Results: In patients who completed cardiac rehabilitation, levels of vWf, fibrinogen and D-dimer were significantly lower and FMD improved (all $p \leq 0.001$), whereas levels were unchanged in controls. Significant reductions were also observed in 24-h mean systolic blood pressure, diastolic blood pressure and mean aortic pressure after completion of cardiac rehabilitation (all $p < 0.05$). No significant differences were observed between the hospital-based and home-based cardiac rehabilitation programmes on these indices.

Conclusions: Cardiac rehabilitation improves haemostasis, endothelial function and ABP in patients with coronary heart disease, with no significant differences between home-based and hospital-based cardiac rehabilitation programmes. These effects may contribute to the beneficial effects of cardiac rehabilitation programmes on CV outcomes.

Cardiac rehabilitation, with either exercise alone or exercise as part of a comprehensive rehabilitation programme, in patients after myocardial infarction and after revascularisation considerably reduces all-cause or total cardiac mortality by at least 26–31%.¹ In addition to the reduction of cardiovascular morbidity and mortality, cardiac rehabilitation also considerably improves functional capacity and quality of life, as well as lipid profile and blood pressure.² However, less-explored beneficial effects of cardiac rehabilitation may be mediated via effects on haemostatic, endothelial and platelet factors.

Indeed, raised levels of plasma viscosity, fibrinogen, fibrin D-dimer (indices of thrombogenesis) and von Willebrand factor (vWf, an index of endothelial damage or dysfunction) are known independent predictors of cardiovascular outcome in patients with coronary heart disease (CHD).^{3–10} Increased platelet reactivity has also been closely associated with adverse cardiovascular events and can be assessed by levels of soluble P-selectin in the plasma.^{11–13} Notably, lifestyle modifications through a comprehensive cardiac rehabilitation programme incorporating a stepwise increment of physical training/exercise, patient education/advice, dietary modifications and psychosocial stress management could have a marked effect on patients' prothrombotic profile and hence, would beneficially influence overall cardiovascular

risk.¹⁴ The mechanisms by which exercise rehabilitation programmes provide benefit also include an increase in fibrinolytic capacity and lower plasma fibrinogen levels.^{15–16}

In addition, studies in the coronary^{17–18} and forearm circulation^{19–20} have shown that endothelial dysfunction is an independent predictor of future cardiovascular events in patients with CHD. Rehabilitative exercise training improves coronary, as well as peripheral and arterial endothelium function in patients with CHD.^{21–25} Thus, correction of endothelial dysfunction may be a valuable therapeutic aim in patients with CHD undergoing cardiac rehabilitation.²⁶

Most cardiac rehabilitation programmes in the UK are hospital-based combined programmes, which include exercise, psychological and educational interventions.^{27–29} Randomised controlled trials comparing home-based cardiac rehabilitation programmes to supervised centre-based cardiac rehabilitation programmes have reported similar improvements in exercise capacity, systolic blood pressure or serum cholesterol at follow-up between the home-based

Abbreviations: BRUM, Birmingham Rehabilitation Uptake Maximisation; CABG, coronary artery bypass grafting; CHD, coronary heart disease; FMD, flow-mediated dilatation; HDL-C, high-density lipoprotein-cholesterol; NMD, nitroglycerin-mediated dilatation; sP-sel, soluble P-selectin; vWf, von Willebrand factor

and centre-based groups.^{30–33} However, no previous study has reported on the overall effects of a comprehensive cardiac rehabilitation programme on haemostatic, endothelial and platelet factors; most have mainly focused on the effects of acute or regular physical activities on fibrinolytic responses, in patients after myocardial infarction or after coronary artery bypass grafting (CABG).¹⁴

The Birmingham Rehabilitation Uptake Maximisation (BRUM) Study is a prospective randomised controlled trial of home-based compared with hospital-based cardiac rehabilitation in a hospital serving a multiethnic inner city population in the UK.³⁴ We used this project to test the hypothesis that a hospital-based cardiac rehabilitation programme and a home-based programme would be comparable in reducing plasma indices of haemostasis, endothelial and platelet function, as well as endothelial function (using flow-mediated dilatation, FMD) and the 24-h ambulatory blood pressure profile.

METHODS

Study population

All patients included in the present substudy ($n = 81$) were recruited from within the Birmingham Rehabilitation Uptake Maximisation (BRUM) Study³⁴—this was a prospective

randomised controlled trial of home-based versus hospital-based cardiac rehabilitation in patients after myocardial infarction, percutaneous coronary intervention or CABG. The home-based programme is nurse facilitated (with home visits and telephone contact), using the Heart Manual (West Lothian Health Care Trust, Edinburgh, Scotland). A total of 525 patients were recruited into the BRUM Study.³⁴ All patients are seen before discharge from hospital and provided with information on their condition and counselling about risk factor modification. Both rehabilitation programmes offered individualised exercise programmes, relaxation, education and lifestyle and risk factor counselling, with referral for psychological treatments as indicated. The hospital arm includes supervised exercise sessions twice weekly for 12 weeks. Patients in the “home arm” followed the Heart Manual that covered the first 6 weeks after the event, facilitated by cardiac rehabilitation specialist nurses. We extended contact with patients in the home programme until 3–4 months to coincide with the end of the hospital programme. Regular telephone contacts and home visits were made by the specialist nurse to ensure that patients in the home programme group adhered to their rehabilitation activities.³⁴

Table 1 Clinical and demographic characteristics of patients and controls

	All patients with CHD ($n = 101$)	Controls ($n = 40$)	p Value
Age (years)	60 (11)	59 (8)	0.74
Men (%)	82 (81)	32 (80)	0.87
Ethnic			
Caucasians	62 (61)	25 (63)	0.90
Indo-Asians	39 (39)	15 (37)	
BMI (kg/m^2)	27 (4)	28 (5)	0.39
Smoker (%)	30 (30)	4 (10)	0.014
Clinical SBP (mmHg)	139 (18)	136 (16)	0.26
Clinical DBP (mmHg)	78 (10)	81 (10)	0.23
Cholesterol (mmol/l)	4.0 (0.8)	5.3 (1.0)	<0.001
HDL-C (mmol/l)	1.15 (0.4)	1.6 (0.5)	<0.001
TC:HDL ratio	3.7 (1.1)	3.6 (1.1)	0.54
Glucose (mmol/l)	6.3 (2.3)	5.0 (0.7)	0.001
Creatinine ($\mu\text{mol}/\text{l}$)	92 (17)	79 (17)	<0.001
Known risk factors (%)			
Prior MI	70 (69)	—	—
Prior PCI	42 (42)	—	—
Prior CABG	9 (9)	—	—
Hypertension	36 (36)	—	—
Diabetes mellitus	22 (22)	—	—
Drugs (%)			
Aspirin	99 (98)	—	—
β blocker	78 (77)	—	—
ACE inhibitor	56 (55)	—	—
Statin	95 (94)	—	—
ARB	11 (11)	—	—
CCBs	16 (16)	—	—
Nitrate	22 (22)	—	—
Clopidogrel	13 (13)	—	—
Nicorandil	13 (13)	—	—
Insulin	8 (8)	—	—
vWf (IU/dl)	193 (56)	120 (16)	<0.001
D-dimer (mg/l)	0.25 (0.22–0.38)	0.18 (0.13–0.30)	<0.001
Fibrinogen (g/l)	3.18 (0.8)	2.58 (0.60)	<0.001
sP-sel (ng/ml)	80 (72–92)	66 (59–80)	0.002
PV (mPas)	1.7 (0.14)	1.63 (0.08)	0.001
Baseline BA diameter (mm)	4.18 (0.84)	3.93 (0.78)	0.11
FMD (%)	4.42 (1.73–7.30)	9.83 (6.3–11.8)	<0.001
NMD (%)	13.7 (9.52–17.6)	12.0 (8.77–18.4)	0.253

ARB, angiotensin receptor blocker; BA, brachial artery; BMI, body mass index; CABG, coronary bypass grafting; CCB, calcium channel blocker; CHD, coronary heart disease; DBP, diastolic blood pressure; FMD, flow-mediated dilatation; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; NMD, nitroglycerine-mediated dilatation; PCI, percutaneous coronary intervention; PV, plasma viscosity; SBP, systolic blood pressure; sP-sel, soluble P-selectin; TC, total cholesterol; vWf, von Willebrand factor.

In addition to the BRUM Study exclusion criteria,³⁴ patients with atrial fibrillation, intermittent claudication, significant heart valvular disease, congestive heart failure or left ventricular dysfunction with ejection fraction <50% were also excluded from this study. Furthermore, patients with cancer, infectious or inflammatory diseases, renal or hepatic failure, connective tissue diseases, history of deep vein thrombosis or pulmonary embolism, and those prescribed steroids and other immunosuppressants, cytotoxic drugs, hormone replacement therapy and warfarin were also excluded. Only patients who fulfilled these criteria were randomly recruited into this substudy in equal proportions, according to their BRUM Study arm (hospital-based, $n = 40$; home-based, $n = 41$).

A subgroup of patients who were randomised to the hospital arm in the main BRUM Study but did not participate in the programme owing to non-medical reasons were identified and invited to return for blood sampling 12 weeks from the baseline. These patients served as “non-rehabilitation controls” (ie, “non-participants”; $n = 20$). To also provide an additional perspective, baseline values were compared with 40 age-matched and sex-matched “healthy controls”, who were recruited from healthy hospital staff, or spouses or relatives of patients. All were “healthy” by virtue of detailed clinical history and examination, and basic blood tests. The study was approved by the local ethics committee and all patients and controls gave written informed consent.

Hospital-based exercise programme protocol

Patients participated in an outpatient phase III and IV cardiac rehabilitation exercise training programme. The phase III programme is 24 sessions long and meets twice a week. Initially, the patients undergo a simple, closely supervised 15-min normal and 5-min fast walking with the pace being dictated by the patient. Initially for the first session the patient exercises on a stationary bike while they are symptom free and up to no more than 80% of the maximum heart rate. The training sessions consist of 10 min walk/cycle warm-up, 30–40 min aerobic exercise, resistance, strength and mobility training. The intensity of the aerobic exercise is prescribed individually on the basis of the patient’s rate of perceived exertion (measured on a 10-point scale) in consultation with the exercise physiologist. Cycling, rowing, walking and stepping are used for the aerobic exercise. In addition to the supervised exercise sessions, each patient is encouraged to exercise up to three times a week outside the formal programme.

Home rehabilitation programme: the Heart Manual

The Heart Manual is a comprehensive home-based programme that includes an exercise regimen, relaxation and stress management techniques, specific self-help treatments for psychological problems commonly experienced by patients with myocardial infarction and advice on coronary risk-related behaviours. The Heart Manual comprises a book and two audio tapes. The book is in two parts. Part 1 is in six weekly sections and provides a phased programme of health education, stress management and a daily incremental “fitness plan”. Part 2 contains answers to questions that are commonly asked by patients with myocardial infarction, including information on medicines, anxiety and stress, and chest pain. One of the audio tapes contains a series of relaxation exercises and information that is of particular relevance to the patient’s partner or family. The Heart Manual was originally designed specifically for patients after myocardial infarction and has been expanded and specifically tailored for patients after percutaneous coronary intervention as well as patients after CABG.

Blood samples and laboratory analyses

All fasting blood samples were always taken by direct venepuncture into vacuum tubes with no venostasis and before blood pressure measurement. Blood samples were taken at two time points: 6 weeks after the event (before starting the hospital cardiac rehabilitation programme, ie, the “baseline” sample) and after completion of the programme (ie, at 18 weeks after the event). Firstly, a sample for plasma viscosity 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/1000 g for 15 min at 4°C. Plasma was separated and stored in multiple aliquots at -70°C until analysis. vWf and soluble P-selectin (an index of platelet activation) levels were measured by ELISA using commercial reagents (Dako-Patts, Ely, UK, and R&D Systems, Abingdon, UK, respectively). Fibrin D-dimer levels were determined with an ELISA from Agen (Huntingdon, UK). Plasma fibrinogen (g/l) and plasma viscosity, were measured by the Routine Hospital Haematology Laboratory, City Hospital, Birmingham, on an MDA coagulation analyser and a Coulter viscometer respectively. A serum sample was analysed routinely in the hospital biochemistry laboratory for total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels. All laboratory work was carried out in blinded fashion with respect to the identity of the samples. Intra-assay and interassay coefficients of variation for all assays were <5% and <10%, respectively.

Clinical blood pressure and 24 hour ambulatory blood pressure measurements

Clinical blood pressure and 24-h ambulatory blood pressure (ABP) were performed at the same time points as blood sampling. The clinical (or office) blood pressure was measured in the sitting position in accordance with the recommendations of the British Hypertension Society, using the Omron HEM-705CP blood pressure monitors (OMRON Healthcare Europe, Hoofddorp, The Netherlands), as previously described in detail.³⁵

Assessment of FMD and nitroglycerin-mediated dilation by reactive hyperaemia

Standard assessment of FMD (endothelium dependent) and nitroglycerine-induced (NMD, endothelium independent) vasodilatation of the brachial artery using high-resolution vascular ultrasound (GE Vingmed System V; Slough, Berkshire, UK) were carried out as previously described.³⁵ Vasodilation (FMD% and NMD%) was calculated as percentage change in diameter compared with baseline. Interobserver and intraobserver variation was <10%.³⁵

Power calculation

We hypothesised that a hospital-based cardiac rehabilitation programme and a home-based programme would be equally effective in reducing clinical and plasma indices of haemostasis, thrombosis and vascular biology. In effect, this reduces to an unpaired t test or Mann–Whitney U test of the differences in the research indices between the two groups. We defined an effective response to the intervention to be a change in at least 0.5 of a standard deviation in a normally distributed index such as fibrinogen or vWf (molecules known to be increased in cardiovascular disease, to be predictive of poor prognosis and lowered by exercise programmes^{4–6,16}). For this to be significant at one-sided $p < 0.05$ and $1 - \beta = 0.85$, a minimum of 30 data points are demanded. However, as we set out to examine several indices (some of which may be dependent), for additional confidence we recruited in excess of this figure (ie, to $n = 40$ per group),

Table 2 Between-group comparisons (participants v non-participants in a cardiac rehabilitation programme) on baseline haemostatic indices and endothelial function, and within-group comparisons between baseline and after 3 months of a cardiac rehabilitation programme

	CR (n = 81)	No CR (n = 20)	Intergroup (baseline)* p Value	Baseline v after CR† p Value	
				CR	No CR
vWf _{baseline} (IU/dl)	191 (59)	198 (46)	0.64		
vWf _{after}	170 (52)	195 (32)		<0.001	0.69
Fibrinogen _{baseline} (g/l)	3.25 (0.8)	2.90 (0.8)	0.12		
Fibrinogen _{after}	2.87 (0.7)	2.90 (0.8)		<0.001	0.57
D-dimer _{baseline} (mg/l)	0.26 (0.22–0.45)	0.23 (0.21–0.26)	0.16		
D-dimer _{after}	0.20 (0.12–0.30)	0.23 (0.2–0.29)		<0.001	0.51
sP-sel _{baseline} (ng/ml)	80 (72–93)	77 (66–87)	0.17		
sP-sel _{after}	80 (68–93)	79 (68–89)		0.17	0.22
PV _{baseline} (mPa s)	1.71 (0.15)	1.69 (0.10)	0.57		
PV _{after}	1.62 (0.13)	1.64 (0.08)		<0.001	0.015
FMD _{baseline} (%)	4.16 (1.46–7.42)	5.07 (3.79–6.09)	0.27		
FMD _{after}	6.90 (2.34–11.5)	5.45 (4.13–7.25)		0.001	0.17
NMD _{baseline} (%)	13.6 (9.5–16.9)	15.4 (9.0–20.3)	0.54		
NMD _{after}	13.8 (10.0–17.5)	16.7 (9.95–20.0)		0.72	0.19

CR, cardiac rehabilitation; FMD, flow-mediated dilatation; NMD, nitroglycerine-mediated dilatation; PV, plasma viscosity; sP-sel, soluble P-selectin; vWf, von Willebrand factor.

*Unpaired Student's t or Mann–Whitney U tests; †paired Student's t or Wilcoxon signed rank tests.

therefore recruiting 81 patients to the rehabilitation programme. To ensure that we did not recruit a biased subgroup of all patients after acute myocardial infarction, we compared these 81 patients with a group of 20 similar patients who did take part in the programme. These numbers provide the power at $1p < 0.05$ and $1-\beta = 0.8$ to detect a difference of 0.56 of a standard deviation (based on $n = 20$ v $n = 20$). Therefore, our actual comparison of $n = 81$ versus $n = 20$ is considerably more powerful. To confirm the presence of deleterious changes in our research indices in the entire patient group, we recruited 40 controls, providing the $1p < 0.05$ and $1-\beta = 0.8$ power to detect a difference of at least 0.4 of a standard deviation (based on $n = 40$ v $n = 40$); once again, our actual recruitment number ($n = 121$ v $n = 40$) provides an excess of power and confidence.

Statistical analysis

Data were expressed as mean (SD) or as medians with interquartile ranges dependent on distribution. Categorical variables were compared by using the χ^2 test. For continuous variables, data were compared within groups using paired Student's t or Wilcoxon signed rank tests and between groups using unpaired Student's t or Mann–Whitney U tests, as appropriate. A two-way (group $\times$ time (before and after cardiac rehabilitation)) analysis of variance with repeated measures was used to evaluate whether the mean responses of rehabilitation differed between hospital and home on research indices before and after rehabilitation. Non-parametric data were logarithmically transformed before analysis of variance analyses. The significance level was set at $p < 0.05$. All statistical analyses were carried out using SPSS V.11.

RESULTS

Table 1 shows the clinical and demographic characteristics of all patients with CHD (including non-rehabilitation controls) and controls. The groups also did not differ in the use of established secondary preventive treatment. All patients were in sinus rhythm and had preserved left ventricular systolic function (ie, left ventricular ejection fraction $> 50\%$). As expected, all haemostatic indices and FMD were significantly abnormal compared with controls. We found no significant differences in the clinical and demographic characteristics between patients with CHD who participated and those who

did not participate in a cardiac rehabilitation programme, and between patients randomised to hospital-based and home-based cardiac rehabilitation programmes, indicating that we have not selected any unrepresentative samples (data not shown).

Haemostatic indices

Baseline indices were not significantly different between patients with CHD who participated in the cardiac rehabilitation programme, and non-participants (table 2). After 3 months, patients who participated in cardiac rehabilitation had significantly lower plasma vWf, fibrinogen, D-dimer and plasma viscosity; only plasma viscosity was significantly lower in those who did not participate in cardiac rehabilitation when compared with baseline. Levels of soluble P-selectin (sP-sel) did not change from baseline in both groups after 3 months.

Baseline indices were not significantly different between patients with CHD of hospital-based and home-based cardiac rehabilitation programmes (table 3). After 3 months, patients of both groups had significantly lower vWf, fibrinogen, D-dimer and plasma viscosity—but not sP-sel—when compared with baseline, with no significant difference between the two programmes.

Vasomotor function

Mean baseline diameter of the brachial artery did not differ between patients with CHD who participated and non-participants (4.18 (0.81) and 4.17 (0.95) mm, respectively). Baseline FDM and NMD levels were not significantly different between the two groups (table 2). The diameter of the brachial artery at rest did not change significantly between study entry and the 3-month evaluation in either group (4.17 (0.74) and 4.17 (0.93) mm, respectively). After 3 months, patients who participated in cardiac rehabilitation had significantly higher FMD than non-participants, when compared with baseline. NMD did not change from baseline in both groups after 3 months (table 2).

The baseline diameters of the brachial artery were also comparable in patients with CHD in the hospital-based and home-based cardiac rehabilitation programmes (4.18 (0.82) and 4.19 (0.81) mm, respectively). Baseline FDM and NMD were also not significantly different between these two

Table 3 Between-group and within-group comparisons between patients with coronary heart disease of hospital-based and home-based cardiac rehabilitation with regard to haemostatic indices and endothelial function at baseline and after completion of a cardiac rehabilitation programme

	Hospital (n = 40)	Home (n = 41)	Intergroup p Value	Hospital _{Baseline-After} [†] p Value	Home _{Baseline-After} [†] p Value	Group × Rehab effects [‡]	
						F _{1,79}	p Value
vWf _{baseline} (IU/dl)	201 (61)	182 (56)	0.15				
vWf _{after}	173 (52)	168 (51)		<0.001	0.001	1.77	0.19
Fibrinogen _{baseline} (g/l)	3.28 (0.7)	3.21 (0.9)	0.74				
Fibrinogen _{after}	2.94 (0.8)	2.80 (0.6)		<0.001	0.003	0.42	0.52
D-dimer _{baseline} (mg/l)	0.28 (0.22–0.45)	0.26 (0.21–0.43)	0.48				
D-dimer _{after}	0.20 (0.12–0.28)	0.20 (0.10–0.30)		<0.001	<0.001	0.05	0.83
sP-sel _{baseline} (ng/ml)	82 (72–92)	80 (75–95)	0.87				
sP-sel _{after}	79 (68–94)	81 (71–89)		0.21	0.27	0.002	0.96
PV _{baseline} (mPas)	1.71 (0.14)	1.71 (0.15)	0.86				
PV _{after}	1.59 (0.13)	1.65 (0.13)		<0.001	0.018	1.1	0.29
FMD _{baseline} (%)	4.45 (1.70–6.69)	4.14 (1.22–6.17)	0.49				
FMD _{after}	7.50 (4.86–11.7)	6.80 (1.75–11.3)		0.021	0.006	0.59	0.44
NMD _{baseline} (%)	14.1 (11.3–18.1)	13.2 (9.41–16.4)	0.27				
NMD _{after}	14.3 (11.2–20.0)	13.2 (8.83–16.5)		0.23	0.52	2.12	0.15

FMD, flow-mediated dilatation; NMD, nitroglycerine-mediated dilatation; PV, plasma viscosity; sP-sel, soluble P-selectin; vWf, von Willebrand factor.

*Unpaired Student's *t* or Mann–Whitney *U* tests; †paired Student's *t* or Wilcoxon signed ranks tests; ‡two-way analysis of variance with repeated measures of the rehabilitation effect. Group × rehabilitation indicates group-by-rehabilitation interactions.

groups (table 3). The diameter of the brachial artery at rest did not change significantly between study entry and the 3-month evaluation in either group (4.17 (0.76) and 4.18 (0.72) mm, respectively). After 3 months, patients of both groups had significantly improved FMD compared with baseline, with no difference between the two programmes (table 3). NMD did not change from baseline in both groups after 3 months.

ABP and lipid profile

Baseline 24-h ABP and lipid profile were not significantly different between patients with CHD of hospital-based and home-based cardiac rehabilitation programmes (table 4). After 3 months, patients of both groups had significantly lower systolic ABP. Levels of serum total cholesterol and HDL-C were significantly improved in hospital-based patients, whereas these were unchanged in home-based patients after 3 months when compared with baseline (table 5).

DISCUSSION

This study shows that a comprehensive cardiac rehabilitation programme incorporating a “package” of regular exercise training, psychological and educational interventions is associated with lower levels of vWf, fibrinogen and fibrin D-dimer, as well as improvements in endothelium-dependent vasomotor function in patients after myocardial infarction or revascularisation; specifically, we found no significant differences between home-based and hospital-based rehabilitation programmes. Notably, these levels were unchanged in the non-participants in rehabilitation. Levels of sP-sel and endothelium-independent vasomotor function were also not

altered by participating in cardiac rehabilitation, whereas plasma viscosity was significantly improved both in patients who participated in cardiac rehabilitation programme and non-participants.

Previous studies on the effects of regular physical activities in patients with CHD have mainly focused on fibrinolytic responses, in patients after myocardial infarction or after CABG participating in cardiac rehabilitation exercise programmes.¹⁴ Few studies have examined the effects of endurance physical training on plasma haemostatic markers in these patients, particularly by comparison with a control group of patients with myocardial infarction in the same period. Suzuki *et al*¹⁵ found reductions in numerous molecules involved in thrombosis and haemostasis, including fibrinogen and vWf, in a group of 56 patients after myocardial infarction after 1 month of physical training, when compared with 30 controls of patients after myocardial infarction without such training. Wosornu *et al*¹⁶ studied the effects of 6 months aerobic and power exercise training in patients after CABG, finding that both aerobic and power exercise markedly lowered fibrinogen, but not packed cell volume or platelet count, when compared with controls who had no formal exercise training.

Endothelial dysfunction is an independent predictor of future cardiovascular events in patients with CHD.^{17–20} Thus, vascular endothelial function is of prognostic importance and a clinically relevant therapeutic target in vascular disease. Importantly, endothelial dysfunction assessed by FMD of the brachial artery is correlated with the more invasive measures of coronary endothelial dysfunction.^{36–37} Among the non-pharmacological therapeutic options for patients with stable CHD, regular physical exercise/training has been shown to

Table 4 24-h ambulatory blood pressure monitoring and lipid profile between baseline and after completion of cardiac rehabilitation in 81 patients with coronary heart disease

	Baseline	After	p Value
24-h mean SBP (mm Hg) _{baseline}	123 (14)	120 (14)	0.004
24-h mean DBP (mm Hg) _{baseline}	73 (10)	71 (8)	0.032
24-h mean MAP (mm Hg) _{baseline}	90 (10)	88 (9)	0.002
Total cholesterol (mmol/l) _{baseline}	4.0 (0.9)	3.7 (0.7)	0.01
HDL-C (mmol/l) _{baseline}	1.14 (0.4)	1.26 (0.3)	0.009

DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; MAP, mean arterial pressure; SBP, systolic blood pressure.

*Unpaired Student's *t* or Mann–Whitney *U* tests; †paired Student's *t* or Wilcoxon signed rank test.

Table 5 Between-group and within-group comparisons of patients with coronary heart disease of hospital-based and home-based cardiac rehabilitation on 24-h ambulatory blood pressure monitoring and lipid profile at baseline and after completion of a cardiac rehabilitation programme

	Hospital (n = 40)	Home (n = 41)	Intergroup Baseline* p Value	Hospital Baseline - After† p Value	Home Baseline - After† p Value
24-h mean SBP (mm Hg) _{baseline}	122 (14)	125 (14)	0.31		
24-h mean SBP _{after}	118 (13)	122 (14)		0.03	0.013
24-h mean DBP (mm Hg) _{baseline}	72 (9)	74 (10)	0.42		
24-h mean DBP _{after}	70 (7)	72 (9)		0.07	0.16
24-h mean MAP (mm Hg) _{baseline}	88 (10)	92 (11)	0.18		
24-h mean MAP _{after}	86 (8)	89 (10)		0.08	0.01
Total cholesterol (mmol/l) _{baseline}	4.1 (0.8)	3.9 (0.9)	0.35		
Total cholesterol _{after}	3.6 (0.7)	3.8 (0.7)		0.001	0.60
HDL-C (mmol/l) _{baseline}	1.08 (0.3)	1.19 (0.5)	0.23		
HDL-C _{after}	1.28 (0.3)	1.25 (0.3)		<0.001	0.50

DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; MAP, mean arterial pressure; SBP, systolic blood pressure.

*Unpaired Student's *t* or Mann-Whitney U tests; †paired Student's *t* or Wilcoxon signed rank test.

improve endothelial function in the coronary²¹ and peripheral circulation^{22–25} of patients with CHD, and in patients with coronary risk factors.³⁸ The improved coronary endothelial dysfunction after exercise training in patients with CHD has been linked to the improvement in myocardial perfusion without regression of coronary stenosis or recruitment of visible collateral arteries.^{39,40} As far as we are aware, this study is the first prospective randomised study to evaluate the effects of home-based versus hospital-based cardiac rehabilitation programmes on haemostatic and vascular function in patients with documented CHD. In agreement with the previous studies was the finding that FMD after hospital-based exercise training was markedly improved. The assessment of nitroglycerine-induced, endothelium-independent, vasodilatation found no effect on the responsiveness of smooth-muscle cells of the peripheral vasculature to the exogenous application of nitrous oxide.

Many reports are available on the effects of lifestyle changes on coagulation, fibrinolysis and platelet activation. The potential modifications of these thrombogenic variables by simple lifestyle changes or risk factor modifications as a secondary prevention strategy in patients with established CHD has attracted considerable interest. Certainly, there is strong evidence of a close association between the traditional cardiovascular risk factors such as diabetes mellitus, hypertension and dyslipidaemia, with an increased prothrombotic or hypercoagulable state characterised by hypercoagulability, hypofibrinolysis and increase platelet reactivity.⁴¹ Conversely, improvements of these risk factors have been associated with a lower prothrombotic tendency.^{42–45} Despite this, the precise mechanism(s) by which the package of programmed cardiac rehabilitation (with all its individual components) can improve haemostatic profile in patients with CHD are unclear.

We found no changes in platelet reactivity as measured by plasma levels of sP-sel by participating in cardiac rehabilitation. Indeed, the effects of regular exercise training on platelet aggregation and function have not been adequately studied in patients with CHD, and the reported results are conflicting. Church *et al*⁴⁶ found that cardiac rehabilitation and exercise training lowered plasma viscosity in patients with CHD; however, this study was non-randomised with no control group. In this study, we found that plasma viscosity improved whether or not patients participated in a cardiac rehabilitation programme.

Randomised controlled trials comparing home-based cardiac rehabilitation programmes to supervised centre-based cardiac rehabilitation programmes have reported similar improvements in exercise capacity, systolic blood pressure or serum cholesterol at follow-up between the home-based

and centre-based groups.^{30–33} Our data showed an improvement in 24-h mean systolic blood pressure in both hospital-based and home-based patients, whereas total cholesterol and HDL-C levels were improved only in hospital-based patients. These differences may be because patients in the home-based programme began risk factor modification earlier than those in the hospital-based programme. Notably, there were no differences in baseline cholesterol and HDL-C levels, as well as the prescription of statins in both groups. It is also possible that patients in the hospital-based programme received more teaching and greater dietary reinforcement.

Owing to the comprehensive nature of both our hospital-based and home-based rehabilitation programme used in the BRUM Study,³⁴ the observed improvement in FMD and plasma haemostatic indices in both groups of patients cannot be attributed to regular physical/exercise training in itself. It should be emphasised that lifestyle modifications rarely involve a single component, as (for example) an increase in exercise activity may be accompanied by concomitant improvement in diets which may in turn lead to weight loss, better psychological well-being, and vice-versa. In addition, such efforts may also modify other known independent risk factors such as lipids or hypertension that are known to alter haemostatic profiles and vascular function. However, a recent study has shown that exercise-induced improvement in endothelial dysfunction is not solely mediated by changes in cardiovascular risk factors.³⁸ Notably, exercise training has been shown to augment endothelial, nitrous oxide-dependent vasodilatation in both large and small vessels.⁴⁷ However, it remains unknown whether these improvements in endothelial function and haemostatic profile would be maintained in the longer term after completion of the rehabilitation programmes. Indeed, training-induced improvements in peripheral vascular endothelial function may well have disappeared at 1 month after detraining.²² It also remains unknown whether an improvement in endothelial function and haemostatic profile directly translates into improved cardiovascular outcome in patients with CHD engaging regular aerobic exercise in cardiac rehabilitation.

In conclusion, both home-based and hospital-based cardiac rehabilitation programmes improve the haemostatic profile, systemic endothelial function and blood pressure. Larger studies are needed to determine whether these improvements would translate to a beneficial effect on long-term cardiovascular outcomes.

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