Clin. Cardiol. 24, 724–729 (2001)

Effects of Acute Exercise on Hemorheological, Endothelial, and Platelet Markers in Patients with Chronic Heart Failure in Sinus Rhythm

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Summary

Background: Chronic heart failure (CHF) is associated with an increased risk of thrombosis and thromboembolic events, including stroke and venous thromboembolism, which may be related to a prothrombotic or hypercoagulable state. Acute vigorous exercise has been associated with activation of hemostasis, and this risk may well be particularly increased in patients with CHF.

Hypothesis: The study was undertaken to determine whether acute exercise would adversely affect abnormalities of hemorheological (fibrinogen, plasma viscosity, hematocrit), endothelial (von Willebrand factor), and platelet markers (soluble P selectin) in patients with CHF.

Methods: We studied 22 ambulant outpatients (17 men; mean age 65 ± 9 years) with stable CHF (New York Heart Association class II–III and a left ventricular ejection fraction of ≤40%) who were exercised to exhaustion on a treadmill. Results were compared with 20 hospital controls (patients with vascular disease, but free of CHF) and 20 healthy controls.

Results: Baseline von Willebrand factor ($p = 0.01$) and soluble P-selectin ($p = 0.006$) levels were significantly elevated in patients with CHF when compared with controls. In the patients with CHF who were exercised, plasma viscosity, fibrinogen, and hematocrit levels increased significantly, both immediately post exercise and at 20 min into the recovery period (repeated measures analysis of variance, all $p < 0.05$). There was a positive correlation between exercise workload and the maximal changes in plasma viscosity in the patients with CHF (Spearman $r = 0.5$, $p = 0.02$). Plasma viscosity levels increased with exercise in the hospital control group, although no other exercise-induced changes were noted in this group.

Conclusion: The present study indicates that the hemorheological indices, fibrinogen, and hematocrit specifically increase during acute exercise in patients with CHF. Although moderate exercise should be encouraged in patients with CHF, vigorous exercise should probably be avoided in view of its potential prothrombotic effects in this high-risk group of patients.

Key words: congestive heart failure, fibrinogen, plasma viscosity, exercise

Introduction

Chronic heart failure (CHF) is associated with an increased risk of thrombosis and thromboembolic events, including stroke and venous thromboembolism,[1,2] which contribute to the high morbidity and mortality rates in these patients. For example, it has been estimated that up to 15% of all hospital inpatient bed-days with heart failure are stroke related, and that over 20% of admissions with heart failure are related to episodes of myocardial ischemia or infarction.[3]

The pathophysiology of thromboembolism in CHF is complex and multifactorial, although heart failure is known to be associated with a hypercoagulable or prothrombotic state, even in the presence of sinus rhythm.[4–8] Indeed, abnormalities in hemorheological function (e.g., plasma viscosity) have been demonstrated in CHF, along with elevated markers of fibrin turnover (fibrinogen, thrombin-antithrombin 3 complex, fibrin D-dimer), endothelial function (von Willebrand factor), and platelet activity (beta-thromboglobulin, soluble P-selectin).[4–8] These abnormalities of blood constituents, when combined with abnormalities of systolic function in patients with left

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Received: September 29, 2000
Accepted with revision: January 22, 2001

ventricular impairment, seem likely to contribute to the development of intracardiac thrombus and predispose to in situ thrombosis and vascular occlusion.[9] Of importance is the fact that there is long-established association between elevated levels of certain hemostatic factors (such as fibrinogen and von Willebrand factor) and the risk of future cardiovascular events, including unstable angina, myocardial infarction, and sudden cardiac death.[10, 11]

Epidemiologic studies have reported that exercise or regular leisure activities are associated with lower plasma viscosity and fibrinogen levels,[12, 13] while the effects of acute and long-term exercise on hemostatic markers has been studied in healthy subjects and in various cardiovascular disease states.[14] For example, in healthy subjects, acute vigorous exercise is associated with activation of platelets and blood coagulation, with some associated increase in the risk of sudden death.[14] Nevertheless, exercise in healthy individuals, with normal baseline hemostasis and an intact endothelium with normal antithrombotic properties, is probably not associated with an increased risk of thrombosis.[14] However, this risk may well be significantly increased in patients with abnormal baseline hemostasis and endothelial abnormalities, such as those with CHF. Indeed, regular exercise is now routinely advocated in CHF,[15, 16] although there is limited information on the effects of acute exercise on these hemostatic markers in stable patients with CHF.

We hypothesized that acute exercise would adversely affect abnormalities of hemorheological (fibrinogen, plasma viscosity, hematocrit), endothelial (von Willebrand factor), and platelet markers (soluble P selectin[17]) in patients with CHF. Together, increases in these indices would shift the overall hemostatic balance toward a more prothrombotic or hypercoagulable state in CHF.[9] To investigate this further, we studied ambulant patients with stable CHF who were in sinus rhythm, who were exercised to exhaustion using an exercise treadmill test.

Patients and Methods

Stable ambulant patients with CHF (New York Heart Association [NYHA] class II–III) and left ventricular ejection fraction of ≤ 40%, as assessed by two-dimensional (2-D) echocardiography, were studied with exercise testing. All patients were in sinus rhythm and all had a history of ischemic heart disease (defined as documented previous myocardial infarction, previous coronary revascularization, and/or positive coronary angiography) and stable CHF (stable NYHA class, without hospital admission for deteriorating CHF within 3 months). All subjects with CHF were receiving stable cardiovascular therapy with low-dose aspirin and angiotensin-converting enzyme (ACE) inhibitors. Exclusion criteria were regular angina (> 2 episodes/week), a history of atrial or ventricular arrhythmias, uncontrolled hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 95 mmHg), or a recent (≤ 3 months) history of myocardial infarction, unstable angina, or stroke. Systolic and diastolic blood pressures were recorded in all subjects following a minimum of 10 min rest, and the subject's smoking status was verbally defined.

Baseline (pre-exercise) samples in patients with CHF were compared with two groups of age- and gender-matched controls in sinus rhythm: (1) healthy controls, and (2) hospital controls (patients with vascular disease, i.e., hypertension, cerebrovascular, coronary artery or peripheral artery disease, but without CHF). Age- and gender-matched healthy control subjects were recruited from those attending the hospital for nonacute minor surgical conditions, such as cataract surgery, varicose veins, and hernia surgery, and from members of the hospital staff. None of the patients or healthy controls had a history of renal or liver disease, ongoing infection, maligancy, connective tissue disease, deep vein thrombosis, infections, inflammatory disorders, pulmonary embolism, and none were taking warfarin or regular nonsteroidal anti-inflammatory drugs or were treated with lipid-lowering or hormone replacement therapy. As a second control group of patients in sinus rhythm, we studied patients with vascular disease (hospital controls) to ascertain whether the hemostatic abnormalities in CHF (and their changes with exercise) were simply due to vascular disease; these patients were also subjected to treadmill exercise.

The project had the approval of the research Ethics Committee of the West Birmingham Health Authority, although the exercise component was only allowed for the patients with CHF and the hospital controls, and not the healthy controls. Informed consent was obtained.

Exercise Testing

All patients with CHF and the hospital controls underwent an exercise treadmill test (modified Bruce protocol), with constant electrocardiographic (ECG) monitoring during exercise, and blood pressure levels were recorded pre exercise and subsequently every 3 min until the end of the recovery period. Maximal exercise was continued until patient exhaustion, or for one of the predefined safety criteria (ECG evidence of significant ischemia, complex ventricular ectopy, sustained atrial and/or ventricular arrhythmias, decrease in blood pressure ≥ 10% of the previously recorded level).

Blood Samples and Assays

All blood samples (each 15 ml) were obtained from the antecubital fossa with a clean venepuncture. Each subject was seated for 15 min before the first sample was obtained, and further blood samples were taken immediately post exercise and 20 min into the recovery period. Whole blood was aliquoted into tubes containing 3.8% trisodium citrate dihydrate or dipotassium ethylenediamine tetra-acetic acid (EDTA).

Citrated plasma was obtained from venous blood by centrifugation at 2,500 rpm for 15 min at 4°C. Aliquots were stored at −70°C to allow batch analysis. Soluble P-selectin and von Willebrand factor were measured by ELISA using commercial reagents (R&D Systems, Abingdon; and Dako-

Patts, Ely, U.K., respectively). The unit for von Willebrand factor is IU/dl and was standardized by reference von Willebrand factor from the National Institute for Biological Standards and Controls, Blanche Lane, South Mimms, Potters Bar, Hertfordshire, UK. Other indices (units: ng/ml) were standardized by recombinant product supplied by the manufacturer. Intra-assay coefficients of variation for all ELISA assays were < 5%, interassay variances were < 10%. Plasma fibrinogen (g/l) was measured by a modified Clauss technique on a Pacific Hemostasis (Huntersville, N.C., USA) coagulometer and reagents from Alpha Laboratories (Eastleigh, Hants, U.K.). The EDTA samples were used for serial assays of the hematocrit (Hawksley, Sussex, England) and plasma viscosity (Coulter Viscometer, Luton, Beds, U.K.).

Analysis of Data and Statistics

Baseline data between patients with CHF and healthy controls were analyzed by *t* testing or the Mann-Whitney U test for data distributed normally or non-normally (respectively) as defined by the Shapiro-Wilks test. Sequential data in the patients with CHF and hospital controls pre- and postexercise testing were analyzed by Friedman's repeated measures analysis of variance (RMANOVA) which compared variables at baseline, immediately post exercise, and 20 min into the recovery period. Correlations were performed using Spearman rank correlation. Data were entered onto a computerized database (Microsoft Excel, Windows 98) and analyzed using computer-based statistical software (Minitab-12, Windows 98). Statistical significance was accepted at an alpha level of $p < 0.05$.

Results

We studied 22 ambulant patients with stable CHF (NYHA class II–III) and left ventricular ejection fraction of ≤ 40%, as assessed by 2-D echocardiography (mean ejection fraction 31%, range 18–40). They were compared with two groups of patients in sinus rhythm: 20 hospital controls (patients with vascular disease) and 20 healthy controls in sinus rhythm (Table I). As expected in patients with coronary artery disease, baseline von Willebrand factor ($p = 0.01$) and soluble P-selectin ($p = 0.006$) levels were elevated in those with CHF compared with the matched healthy controls. However, there were no statistically significant differences in mean baseline plasma viscosity, hematocrit, and fibrinogen levels between the patients with CHF and the healthy controls ($p = 0.1$) (Table II).

TABLE I Demographic data for patients with chronic heart failure and controls in sinus rhythm

	Healthy controls	Hospital controls	Chronic heart failure
No. of patients	20	20	22
Age (mean ± SD)	63 ± 9	63 ± 11	64 ± 10
Males:females (M/F)	15 M:5 F	13 M:7 F	17 M:5 F
Systolic BP mmHg	123 ± 22	171 ± 13	147 ± 24
Diastolic BP mmHg	80 ± 12	95 ± 8	75 ± 22
Smokers (n)	3	5	2
Concomitant disease			
Hypertension	0	20	8
PVD	0	2	0
IHD	0	4	20
CVA	0	0	1
Drugs			
Aspirin	0	7	22
ACE inhibitor	0	3	22
Beta blocker	0	3	13
Nitrates	0	3	9
Diuretic	0	0	13

Age and blood pressures are expressed as mean ± standard deviation (SD).

Abbreviations: IHD = ischemic heart disease, BP = blood pressure, CVA = cerebrovascular disease, PVD = peripheral vascular disease, ACE = angiotensin-converting enzyme.

Hemodynamic exercise characteristics in heart failure and hospital control patients are summarized in Tables III and IV. The mean exercise duration in patients with CHF (7.1 min ± standard deviation [SD] 1.1) and hospital controls (7.1 min ± SD 3.8) was not significantly different. The mean exercise workload (Metabolic Equivalents) was lower in patients with CHF than in hospital controls (6.0 ± 2.2 vs. 8.1 ± 3.2 metabolic equivalents, $p < 0.05$).

In the patients with CHF there was an increase in plasma viscosity, fibrinogen, and hematocrit during exercise, which was significant for both the immediate postexercise samples

TABLE II Baseline indices of thrombogenesis in patients with chronic heart failure and controls in sinus rhythm

	Healthy controls	Hospital controls	Chronic heart failure	p Value (one-way ANOVA)
Soluble P-selectin (ng/ml)	35 ± 8	33 ± 22	46 ± 15[a]	0.006
von Willebrand factor (IU/dl)	101 ± 14	103 ± 20	121 ± 28[a]	0.01
Fibrinogen (g/l)	2.80 ± 0.9	2.41 ± 0.40	2.85 ± 0.89	0.1
Plasma viscosity (mPa)	1.70 ± 0.08	1.79 ± 0.17	1.71 ± 0.07	0.1
Hematocrit (%)	40.2 ± 3.2	40.4 ± 3.6	41.7 ± 4.7	0.1

Data expressed as mean ± standard deviation.

[a] Raised relative to controls ($p < 0.05$, Tukey's posthoc analysis).

TABLE III Effect of exercise on indices of thrombogenesis in patients with chronic heart failure

	Pre exercise	Immediately after exercise	20 min post exercise	p Value
Heart rate (beats/min)	88 ± 12	128 ± 26	77 ± 14	—
Systolic blood pressure (mmHg)	146 ± 24	174 ± 22	140 ± 20	—
Diastolic blood pressure (mmHg)	75 ± 11	88 ± 17	81 ± 13	—
Plasma viscosity (mPa)	1.71 ± 0.07	1.76 ± 0.08 [a]	1.74 ± 0.07 [a]	<0.0001
Fibrinogen (g/l)	2.85 ± 0.89	3.00 ± 0.92 [a]	2.98 ± 0.92 [a]	0.004
Soluble P selectin (ng/ml)	46 ± 16	46 ± 16	55 ± 32	0.15
Hematocrit (%)	41.7 ± 4.7	43.1 ± 4.3 [a]	42.0 ± 4.1 [a]	0.02
von Willebrand factor (IU/dl)	121 ± 28	124 ± 27	123 ± 31	0.4

[a] Raised relative to pre-exercise level ($p < 0.05$).
Data are expressed as mean ± standard deviation.
Testing for pre exercise, immediately post, and 20 min post exercise was done using Friedman's repeated measures analysis of variance.

and the samples taken 20 min into the recovery period (Table III). Plasma viscosity increased in the hospital control group, although no other exercise-induced changes were noted in this group (Table IV). In particular, plasma von Willebrand factor and soluble P-selectin levels were not significantly altered by acute exercise in either group (Tables III and IV).

There was a positive correlation between exercise workload and the maximal changes in plasma viscosity (Spearman $r = 0.5$, $p = 0.02$), but not with changes in either hematocrit ($r = -0.02$, $p = 0.9$), or fibrinogen ($r = 0.24$, $p = 0.3$).

Discussion

The cross-sectional comparison suggests that patients with CHF demonstrate abnormal soluble P-selectin and von Willebrand factor at baseline, with a trend toward higher fibrinogen levels, compared with matched hospital controls with associated vascular disease and healthy controls.

Fibrinogen is a major determinant of fibrin formation which contributes to blood flow abnormalities and the prothrombotic state in a variety of cardiovascular disorders.[18] Although the relationship between plasma fibrinogen and acute exercise has been extensively studied, the available evidence is conflicting.[19] Indeed, a number of studies have shown that exercise has no significant effect on plasma fibrinogen,[19–25] while others have indicated either an increase[26] or a decrease[27–29] following exercise. It is important to realize that alterations in plasma fibrinogen may occur as a result of transient fluid shifts into the intravascular space, resulting in hemodilution, or out of the intravascular space leading to hemoconcentration. In some studies, postexercise fibrinogen levels have been corrected for these changes,[22–26, 30–32] while others have not accounted for exercise-induced changes in plasma volume.[21, 22, 29, 33–36] Indeed, these methodological inconsistencies may well account for the conflicting results in previously published studies. Other studies have reported that the increase in plasma fibrinogen during exercise does indeed occur as a result of hemoconcentration,[24, 31] with comparable responses in healthy individuals[23] and in patients with cardiovascular[37] and pulmonary disease.[38] Hemoconcentration also occurs in response to intense exercise, with a reported linear relationship between alterations in plasma volume and exercise intensity.[39]

TABLE IV Effect of exercise on indices of thrombogenesis in patients with vascular disease (hospital controls)

	Pre exercise	Immediately after exercise	20 min post exercise	p Value
Heart rate (beats/min)	81 ± 14	143 ± 28	87 ± 18	—
Systolic blood pressure (mmHg)	160 ± 25	180 ± 28	145 ± 19	—
Diastolic blood pressure (mmHg)	96 ± 11	100 ± 15	87 ± 18	—
Plasma viscosity (mPa)	1.79 ± 0.17	1.87 ± 0.18 [a]	1.81 ± 0.17	0.001
Fibrinogen (g/l)	2.41 ± 0.4	2.48 ± 0.7	2.48 ± 0.7	0.40
Soluble P selectin (ng/ml)	33 ± 22	34 ± 26	35 ± 28	0.38
Hematocrit (%)	40.4 ± 3.6	41.1 ± 2.7	40.4 ± 2.8	0.78
von Willebrand factor (IU/dl)	103 ± 20	104 ± 22	106 ± 33	0.91

[a] Raised relative to pre-exercise level ($p < 0.05$).
Data are expressed as mean ± standard deviation.
Testing for pre exercise, immediately post, and 20 min post exercise was done using Friedman's repeated measures analysis of variance.

While the clinical relevance of these findings remains to be established, CHF is associated with a hypercoagulable state in association with a reduction in plasma (and whole blood) volumes.[40] It is therefore possible that acute exercise, through its effects on these preexisting abnormalities, may contribute to the exercise intolerance, exertional breathlessness, and chronic fatigue that occur in CHF as a result of a further reduction in cardiac output and a worsening of abnormalities in regional blood flow. Indeed, if these baseline abnormalities are a manifestation of the exercise deconditioning which is observed in some patients with CHF, then chronic exercise training might be expected to improve both the resting abnormalities and the response to exercise in this group of patients. While improvements in plasma viscosity have been observed in healthy subjects,[41,42] small studies have been unable to demonstrate such benefits in patients with CHF.[43,44]

Of importance is the fact that these abnormalities may also contribute to the pathogenesis of acute thrombosis in patients with CHF, particularly as increased fibrin turnover may also enhance platelet aggregation.[45] Our study failed to demonstrate direct platelet activation for the duration of the study, with levels of soluble P-selectin failing to rise significantly during exercise, although there did appear to be a trend toward an increase during the recovery phase. It is therefore possible that, as a result of exercise intolerance in our group of patients, the exercise duration and workload of the exercise performed was insufficient to stimulate direct platelet activation immediately. Indeed, intense exercise in patients with coronary artery disease leads to a several-fold increase in coronary blood flow and an increase in catecholamine concentrations, resulting in increased shear stress and mechanical strain on the coronary arteries. It is therefore conceivable that the increased fibrin turnover observed in our patients, associated with this increased mechanical shear stress that occurs during exercise and preexisting endothelial abnormalities (with abnormal baseline von Willebrand factor levels), may contribute to in situ thrombosis and sudden death in some patients with CHF.[9]

The exact mechanism for the increase observed in plasma fibrinogen has not been established, although it might be linked to an enhanced rate of fibrinogen production resulting from increased mechanical shear stress and stimulation of the intrinsic or extrinsic coagulation pathways. Further studies would be valuable to examine plasma fibrinogen concentration with simultaneous measurements of fibrin/fibrinogen degradation products and/or thrombin activation, in combination with direct measures of platelet activation and aggregability.

Limitations

This study is limited by its small numbers in view of the difficulties of recruiting fit patients with CHF who were capable of treadmill exercise, but is broadly comparable in sample size with previous work of this nature, albeit in a different patient group.[46] Furui *et al.*[46] exercised 20 patients with lone atrial fibrillation, who were younger than the present cohort (mean age 48 years, compared with the mean age of 64 years in the present study), but their exercise was broadly similar (7.65 min, compared with 7.1 min in the present study); they found a significant rise in beta-thromboglobulin (an index of platelet activation) and α_2 plasmin inhibitor levels (an index of impaired fibrinolysis), as well as an impaired anticoagulant response (antithrombin III) after exercise compared with healthy controls.[46] In the present study, our patients with CHF did show significant changes in fibrinogen and hematocrit with acute exercise, which were not seen in the hospital controls. The rise in hematocrit in the patients with CHF following acute exercise raises the possibility that some of the effects may be due to hemoconcentration, but if this were the case, we would have expected to have seen a similar change in the hospital control group.

Conclusion

The present study represents an advance in our understanding of cardiovascular pathophysiology as it indicates that certain hemorheological indices (plasma viscosity, fibrinogen, and hematocrit) show a prompt increase during acute exercise in patients with CHF. Although moderate exercise should be encouraged in such patients, vigorous acute exercise should probably be avoided in view of the potential prothrombotic effects of strenuous exercise in this high-risk group of patients.

Acknowledgments

The authors acknowledge the support of the City Hospital NHS Trust Research and Development Programme for the Haemostasis Thrombosis and Vascular Biology Unit.

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