Procoagulant State in Heart Failure With Preserved Left Ventricular Ejection Fraction

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Summary

The impact of heart failure with preserved left ventricular ejection fraction (LVEF) on activated hemostasis is still unclear. We sought to compare the activation of hemostasis in patients with heart failure with preserved LVEF, with impaired LVEF, and in healthy controls. Biomarkers of coagulation and fibrinolysis (D-dimer, tPA and PAI-1) were determined in outpatients with chronic stable (NYHA I-III), optimally managed heart failure with preserved LVEF (n = 46) and with impaired LVEF (n = 52), and in healthy age- and gender-matched controls (n = 14). In comparison to healthy controls, patients with heart failure and preserved LVEF had increased median D-dimer levels (606 [330-1222] μg/L versus 174 [86-249] μg/L; $P < 0.001$), and median PAI-1 (20 [15.3-33.1] μg versus 6.2[3.4-8.9] μg/L; $P < 0.001$) and tPA antigen concentrations (9.6 [8.1-13.3] versus 3.6 [2.2-5.0] μg/L; $P < 0.001$). However, unlike tPA and PAI antigens, D-dimer levels in preserved LVEF did not reach values as high as in impaired LVEF (917 [454-1185] μg/L; P = 0.013). Moreover, in patients with impaired LVEF, but not in those with preserved LVEF, age and NT-proBNP emerged as independent predictors of log-transformed D-dimer levels. Heart failure with preserved LVEF is associated with a procoagulant state as determined by increased levels of D-dimer, tPA and PAI-1 antigens. D-dimer levels are significantly higher in patients with impaired LVEF, while tPA and PAI-1 levels are increased regardless of LVEF. (Int Heart J 2009; 50: 591-600)

Key words: Heart failure, Diastolic, Blood coagulation, Biological markers, Fibrin fragment D-dimer, Tissue plasminogen activator, Plasminogen activator inhibitor

HEART failure is associated with an increased risk of thromboembolic events.[1-4] Observational studies and post-hoc analysis of randomized trials have documented an increased rate of stroke and peripheral embolic events in patients with heart failure and/or impaired systolic function.[5,6] Blood stasis in enlarged cardiac chambers, vascular (endothelial) abnormalities and deranged blood

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coagulation properties – a modified Wirchow triad – have been proposed as predisposing mechanisms to a procoagulant state in heart failure with impaired systolic function.

Whereas the presence of a procoagulant state in heart failure with impaired systolic function has been clearly established,[7,8] the impact of heart failure with preserved left ventricular ejection fraction (LVEF) on activated hemostasis is unknown. Despite the fact that more than one half of patients with heart failure are believed to have preserved systolic function,[9] reports on activated hemostasis in this large subset of patients with heart failure are scarce. A study in patients with ischemic heart disease found no association between plasma levels of fibrinogen, D-dimer and von Willebrand factor, and diastolic dysfunction as determined by transmitral flow Doppler indices.[10] A recent study confirmed the lack of association between these haemostatic parameters and Doppler indices of transmitral flow, although it did demonstrate a close association between von Willebrand factor, P-selectin and fibrinogen, and diastolic dysfunction as determined by tissue Doppler indices.[11] However, both studies included patients with coronary artery disease regardless of the presence of heart failure.

In the present study, we sought to measure markers of coagulation and fibrinolysis in patients with heart failure and preserved LVEF and compare them with patients with heart failure and impaired left ventricular systolic function, and healthy controls.

Methods

Participants: Participants were recruited from the University Clinical Center, Heart Failure Outpatient Clinic in Ljubljana (Slovenia) and were compared with age- and gender-matched healthy controls. The diagnosis of heart failure (based on signs and symptoms of heart failure or on history of hospitalization because of heart failure within 12 months prior to inclusion) was confirmed by two independent cardiologists. Patients were prospectively divided into two groups: A) patients with impaired left ventricular ejection fraction (≤ 50% as measured by the Simpson biplane method) and B) patients with preserved left ventricular ejection fraction (LVEF > 50%) and either i) an E/Em ratio > 15 or alternatively ii) an E/Em ratio between 8 and 15 plus one of the following: a) elevated NT-proBNP levels or b) increased left ventricular mass or left atrial volume index, c) indices of diastolic dysfunction as determined by transmitral or pulmonary vein flow Doppler indices (E/A ratio, dt, IRT, S/D).[12] Patients were in NYHA functional class I-III, optimally managed according to current guidelines and stable for at least 3 months prior to inclusion.

The control group consisted of healthy age-matched volunteers without de-

monstrable structural heart abnormalities on echocardiographic examination and without signs or symptoms of heart failure. We excluded patients with recent (< 3 months) myocardial infarction, stroke or thromboembolism, patients with significant liver (enzymes > 3-times the upper reference limit) or renal dysfunction (creatinine level > 250 μg/L), and patients with chronic autoimmune or inflammatory diseases and malignancies. Anticoagulation therapy was an exclusion criterion. At inclusion, patients underwent a thorough clinical examination and echocardiographic assessment, and blood samples were collected.

Informed consent was obtained from all patients for participation in the study according to a protocol approved by the National Committee for Medical Ethics and Biomedical Investigation.

Biochemical analysis: All patients had venous blood samples (EDTA) taken after 30 minutes of rest in the supine position from the cubital vein. Samples were centrifuged at 3000 rpm for 10 minutes at 0°C and separated immediately afterwards. D-dimer levels were measured by quantitative sandwich enzyme immunoassay (Asserachrom® D-dimer, Diagnostica Stago). Intra- and interassay coefficient variations were 6.4 and 14.4%, respectively. Tissue plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1) antigen concentrations were measured by quantitative sandwich enzyme immunoassay (Imulyse®, Biopool). Intra- and interassay coefficient variations were 7.0 and 17.7% for tPA, and 5.2 and 8.5% for PAI1.

Statistical methods: Sample size calculation suggested that at least 34 patients had to be included in each of the heart failure groups (impaired versus preserved LVEF) in order to detect a difference of at least half a SD in a continuous variable with a type II error of 0.05 and a type I error of 0.20.

Baseline characteristics were summarized by mean (standard deviation) for normally and by median (interquartile range) for nonnormally distributed continuous variables, and by frequency (percentage) for categorical variables. Differences were tested by *t*-test and one-way ANOVA, or the Mann-Whitney U test and Kruskal-Wallis test, with Bonferroni's post-hoc analysis, as appropriate. Correlations were performed by Spearman's rank correlation method. Multiple regression analysis was performed to determine independent predictors for log-transformed D-dimer concentration using significant univariate predictors (age, gender, presence of coronary artery disease, systolic blood pressure and log-transformed NT-proBNP concentration) as covariates.

All statistical calculations were performed on a microcomputer using a commercially available statistical package (SPSS 13.0 for Windows). A 2-tailed *P* value of less than 0.05 was considered statistically significant.

Table I. Baseline Comparison of Patients With Impaired and Preserved Left Ventricular Ejection Fraction (LVEF), and Healthy Age-Matched Controls

	Preserved LVEF	Impaired LVEF	Controls	*P*
Number of patients	46	52	16	
Age (years)	72 ± 8	70 ± 12	72 ± 14	0.624
Gender (male; *n*, %)	15 (32.6)	37 (71.2)	7 (50.0)	0.013
HF duration (months)	20 ± 13	25 ± 11	/	0.536
Etiology (*n*, %)				
Ischemic	12 (26.1)	28 (53.8)	/	< 0.001
Hypertensive	31 (67.4)	9 (17.3)	/	
Dilatational	0 (0)	11 (21.2)	/	
Other	4 (8.7)	4 (7.7)	/	
Diabetes (*n*, %)	8 (17.4)	19 (36.5)	/	0.144
Arterial hypertension (*n*, %)	38 (82.6)	34 (65.4)	/	0.189
Dyslipidemia (*n*, %)	19 (41.3)	25 (48.1)	/	0.475
NYHA class (*n*, %)				
I	4 (8.7)	1 (1.9)	/	0.414
II	23 (50)	34 (65.4)	/	
III	19 (41.3)	17 (32.7)	/	
Systolic BP (mmHg)	145 ± 17	123 ± 19	127 ± 28	< 0.001
Diastolic BP (mmHg)	80 ± 10	74 ± 10	77 ± 16	0.049
HR (min-1)	65 ± 22	70 ± 20	65 ± 27	0.479
6-minute walk test (m)	210 (150-380)	285 (175-385)	430 (310-615)	0.133
MLHFQ	43 (35-59)	36 (17-51)	/	0.369
Therapy (*n*, %)				
Beta blocker	31 (67.4)	43 (82.7)	/	0.179
Spironolactone	23 (50)	26 (50)	/	0.596
Loop diuretic	27 (58.7)	32 (61.5)	/	0.528
Aspirin	15 (32.6)	20 (38.5)	/	0.765
Digoxin	8 (17.4)	12 (23.1)	/	0.491
Statin	15 (32.6)	20 (38.5)	/	0.496
ACE inhibitor	31 (67.4)	43 (82.7)	/	0.179
ARB	15 (32.6)	10 (19.2)	/	0.201
NT-proBNP (pg/mL)	867	4284	66	< 0.001

HF indicates heart failure; BP, blood pressure; HR, heart rate; MLHFQ, Minnesota living with heart failure questionnaire score; and ARB, angiotensin receptor blocker.

Results

A total of 112 subjects were included: 46 patients with heart failure and preserved LVEF, 52 patients with heart failure and impaired LVEF, and 14 healthy controls. Participants were on average (SD) 72 (12) years old, and 32% were female. There were no significant differences in demographic characteristics between the 3 groups (Table I).

Patients with heart failure and preserved LVEF had higher median D-dimer levels than healthy controls ($P < 0.001$), but still lower than patients with heart failure and impaired LVEF ($P = 0.013$) (Figure). In fact, across all 3 groups, D-dimer levels paralleled NT-proBNP levels with a statistically significant univariate correlation ($r = 0.366$; $P < 0.001$).

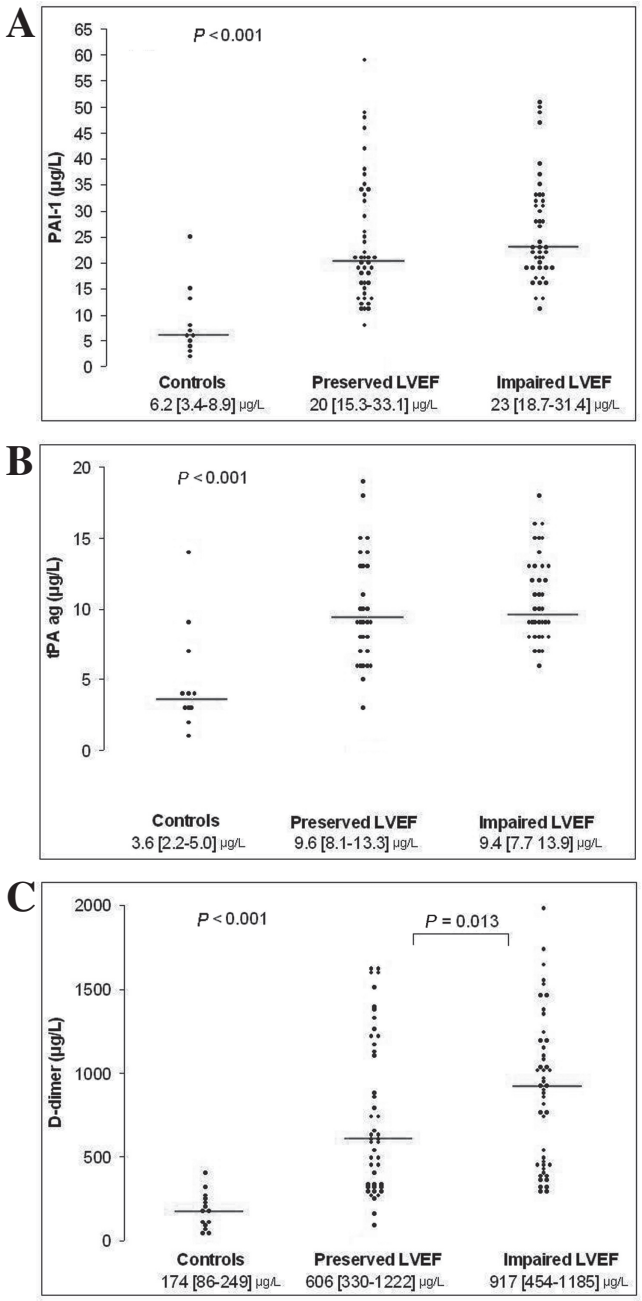

Figure. Concentrations of plasminogen activator inhibitor 1 (PAI-1) antigen (**A**), tissue plasminogen activator (tPA) antigen (**B**) and D-dimer (**C**) in patients with heart failure and preserved left ventricular ejection fraction (LVEF), in patients with heart failure and impaired LVEF, and in healthy controls. Values represent median concentration (interquartile range).

Table II. Multivariate Analysis of Univariate Predictors of Log-Transformed D-Dimer Values (Heart Failure Impaired versus Preserved Left Ventricular Ejection Fraction/LVEF)

	Impaired LVEF*			Preserved LVEF**		
	B	SE	*P*	B	SE	*P*
Age	0.0086	0.0026	0.002	0.0073	0.0056	0.206
Gender (male)	0.0315	0.0796	0.692	0.0708	0.1137	0.540
Coronary artery disease	0.0665	0.0675	0.327	-0.2029	0.1271	0.125
Systolic blood pressure	0.0004	0.0014	0.803	-0.0020	0.0029	0.505
Log NT-proBNP	0.1657	0.0587	0.006	-0.1030	0.1204	0.402

* LVEF ≤ 0.50 and ** > 0.50, respectively.

Patients with preserved LVEF had also higher median concentrations of PAI-1 and tPA antigens than healthy controls ($P < 0.001$ and $P < 0.001$, respectively), however, there were no significant differences in median PAI-1 and tPA antigen concentrations between patients with preserved and patients with impaired LVEF (Bonferroni $P = 0.586$ and $P = 0.727$, respectively) (Figure 1). We confirmed a statistically significant correlation between the E to Em ratio and D-dimer levels ($r = 0.178$; $P = 0.039$) and tPA ($r = 0.186$; $P = 0.031$). The correlation between E to Em ratio and PAI-1 levels, though expressing a similar trend, failed to reach statistical significance ($r = 0.160$; $P = 0.064$). We found no statistically significant correlation between PAI-1 antigen and NT-proBNP concentrations ($r = 0.011$; $P = 0.952$) or between tPA antigen and NT-proBNP concentrations ($r = 0.077$; $P = 0.288$)

On multivariate analysis exploring the impact of significant univariate predictors of D-dimer levels (age, gender, presence of coronary artery disease, systolic blood pressure, and NT-proBNP levels, E to Em ratio), only age and NT-proBNP emerged as independent predictors of D-dimer levels in patients with heart failure and impaired LVEF. Neither age nor NT-proBNP retained their predictive value when stratified for heart failure with preserved LVEF (Table II).

Discussion

In the present study, we have shown that heart failure with preserved LVEF is associated with a procoagulant state. Markers of disrupted fibrin turnover (D-dimer) and impaired fibrinolysis (tPA and PAI-1) were significantly elevated in patients with heart failure; however, while D-dimer levels were significantly higher in patients with heart failure and impaired LVEF (and in this respect paralleled NT-proBNP levels), there were no statistically significant differences in tPA and PAI-1 antigen concentrations between heart failure patients with preserved LVEF as opposed to those with impaired LVEF.

Previous studies have shown that heart failure with systolic dysfunction is

associated with a procoagulant state. Increased activity of beta-thromboglobulin, fibrinopeptide A, endothelial procoagulant, von Willebrand factor, fibrinolytic products, D-dimer, tPA, and thrombin have all been reported in patients with heart failure and impaired left ventricular systolic function.[7,8,13-15] In patients with left ventricular diastolic dysfunction the evidence is less convincing. Transmitral flow patterns suggestive of diastolic dysfunction do not predict derangements of hemostasis;[10] on the other hand, tissue Doppler derived indices suggestive of diastolic dysfunction are closely associated with markers of activated hemostasis in patients with coronary artery disease.[11] However, neither study addressed haemostatic derangements in a population with documented heart failure (where derangements of hemostasis are expectedly more pronounced and thus more detectable). Our findings suggest that heart failure with preserved LVEF (as defined primarily by tissue Doppler derived indices) is indeed associated with a procoagulant state.

Recent evidence suggests that haemostatic derangements in heart failure result from a cross-talk between the coagulation and fibrinolytic systems, neuroendocrine hyperactivation, and inflammatory processes.[15-22] Activation of the sympathetic and renin-angiotensin-aldosterone systems provokes a simultaneous increase in molecules of both the coagulation and fibrinolysis pathways within minutes, resulting in net hypercoagulability.[23-25] Since neurohormonal, inflammatory, and endothelial changes are disrupted in heart failure regardless of the type of ventricular impairment (systolic or diastolic), an increase in haemostatic markers is expected in heart failure regardless of whether the underlying left ventricular failure is systolic or isolated diastolic in origin.

D-dimer levels were more increased in patients with impaired LVEF than in those with preserved LVEF, while tPA and PAI-1 antigens were similarly increased in both groups regardless of whether heart failure was systolic or isolated diastolic in origin. We hypothesize that the coagulation system in heart failure is activated primarily by endothelial dysfunction (both tPA and PAI-1 antigens as opposed to tPA and PAI-1 activity reflect the extent of vascular injury); however, systolic dysfunction probably confers an additional haemostatic derangement favored by central hemodynamic changes (suggested by an increased NT-proBNP and its association with D-dimer levels in our study). Our study was not designed to address a possible mechanistic explanation of such changes; central hemodynamic derangements in patients with heart failure represent a complex interplay of several factors, such as impaired ventricular pump function, atrial contractility and the functional integrity of the mitral apparatus, among others.[26-28] Moreover, patients at high risk of thrombus formation because of cardiac hemodynamic derangements (ie, patients with severely impaired LVEF or atrial fibrillation) have to be anticoagulated[29-32] and were thus excluded from

our study (anticoagulation therapy was an exclusion criterion in order to avoid obvious confounding interactions between anticoagulation therapy and hemostatic derangements). In our study, transthoracic echocardiographic imaging did not detect a thrombus in any of the included patients. This approach minimized the possibility of including patients with left ventricular or atrial thrombi which might in turn be reflected by elevated levels of hemostatic parameters. However, it is still plausible to assume that the risk of (undetectable) thrombus formation is continuous across different extents of central hemostatic derangements in heart failure (ie, it is not restricted to patients with a current indication for anticoagulation); therefore, further research is needed to explore possible (especially central hemodynamic) mechanisms of coagulation activation in patients with heart failure.

Haemostatic derangements in heart failure with preserved LVEF could also be attributed to comorbidities and concomitant cardioprotective treatment. For instance, arterial hypertension and left ventricular hypertrophy are associated with activated hemostasis;[33-36] a higher prevalence of arterial hypertension and hypertensive etiology of heart failure in the preserved LVEF group could therefore partially explain haemostatic activity in heart failure with preserved LVEF; however, arterial hypertension did not emerge as an independent predictor of D-dimer levels. Moreover, several cardioprotective drugs influence hemostasis; ACE inhibitors and spironolactone have been shown to decrease haemostatic activity.[37] However, as there was no significant difference in therapy between patients with impaired and preserved LVEF, it is unlikely that cardioprotective therapy would affect our results.

Our study has demonstrated that hemostasis is disrupted in patients with heart failure, regardless of whether LVEF is impaired or preserved. However, we identified several limitations. Firstly, echocardiographic assessment was carried out as part of a routine cardiological examination; a comprehensive echocardiographic assessment would provide more specific data about the extent of association between markers of hemostasis and indices of left ventricular function. Secondly, measurement of PAI-1 and tPA antigen levels, rather than PAI-1 and tPA activity, provides information on release of haemostatic proteins into the bloodstream; this may reflect the extent of vascular injury rather than an actual procoagulant state in heart failure. Thirdly, the relatively small number of included participants limits a more widespread applicability of our results. A larger number would provide us a better understanding of the underlying mechanisms of haemostatic derangement in heart failure (eg, differences between left ventricular dysfunction of different etiology), however, this issue is beyond the aim of our study – ie, to determine the extent of haemostatic derangements in patients with heart failure and preserved LVEF as compared to those with im-

paired LVEF and healthy controls.

In conclusion, our study demonstrated that heart failure is associated with deranged hemostasis regardless of whether LVEF is impaired or preserved. Our findings suggest that heart failure with preserved LVEF is associated with an unfavorable thromboembolic profile and that further research is needed to specifically address this issue and possibly contribute to a better antithrombotic management strategy for this population of heart failure patients.

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