Coagulation abnormalities as predictors of renal dysfunction in heart failure with reduced ejection fraction

Zaburzenia krzepnięcia jako czynnik prognostyczny niewydolności nerek u pacjentów z niewydolnością serca z obniżoną frakcją wyrzutową

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Słowa kluczowe: zaburzenia krzepnięcia, niewydolność serca, niewydolność nerek.

Abstract

Introduction: Heart failure (HF) is a prothrombotic state that is also associated with the progression of renal dysfunction. However, it is unknown whether coagulation abnormalities are associated with progressive cardiorenal syndrome.
Aim of the research: To evaluate activators and inhibitors of coagulation and fibrinolysis and their relationship with renal failure in HF patients.
Material and methods: Coagulation biomarkers such as thrombin-antithrombin III, human tissue-type plasminogen activator, human plasminogen activator inhibitor, von Willebrand factor (vWF), soluble thrombomodulin (sTM), human prothrombin fragments (F1+F2), and protein C were evaluated in 36 consecutive HF patients without anticoagulation and in 19 controls matched in age and gender.
Results: HF patients, compared to controls, had lower levels of C protein ($p = 0.04$) and F1 + F2 ($p < 0.001$) but higher levels of vWF ($p < 0.001$) and borderline sTM ($p = 0.07$). Similarly, haemoglobin ($p < 0.001$) and glomerular filtration rate (GFR) ($p = 0.004$) were lower in HF, while INR ($p < 0.001$), NT-proBNP ($p < 0.001$), and asymmetric dimethylarginine (ADMA) ($p < 0.001$) were higher. Most of the echocardiographic parameters differed between the 2 groups. From coagulation biomarkers, sTM ($r = –0.66$; $p < 0.001$) and vWF ($r = –0.41$; $p = 0.002$) were associated with eGFR. Most of the echocardiographic and laboratory parameters were also related to eGFR. After classifying all variables into 5 categories; laboratory tests, echocardiographic parameters, vascular reactivity, haemodynamics, and coagulation parameters, multivariable linear regression showed that coagulation parameters were the most strongly associated with eGFR ($r^2 = 0.48$, $p < 0.001$).
Conclusions: In the study population, coagulation disorders were most strongly associated with impaired renal function, independently of other parameters.

Streszczenie

Wprowadzenie: Niewydolność serca (HF) jest stanem zwiększonej gotowości zakrzepowej, z często współwystępującą dysfunkcją nerek. Jednak dotąd nie wykazano związku zaburzeń w obrębie biomarkerów zakrzepowych z postępującym zespołem sercowo-nerkowym.
Cel pracy: Ocena związku biomarkerów zakrzepowych z upośledzeniem funkcji nerek u chorych z niewydolnością serca.
Materiał i metody: Biomarkery zakrzepowe, takie jak kompleksy trombina-antytrombina III, tkankowy aktywator plazminogenu, czynnik von Willenbranda (vWF), rozpuszczalna trombomodulina (sTM), fragmenty protrombiny (F1 + F2) oraz białko C, zostały ocenione u 36 chorych z niewydolnością serca nieleczonych przeciwzakrzepowo oraz u 19 zdrowych ochotników w grupie kontrolnej, dobranej pod względem wieku i płci.
Wyniki: Pacjenci z niewydolnością serca w porównaniu z grupą kontrolną mieli niższą aktywność białka C ($p = 0,04$), ale wyższe stężenia vWF ($p < 0,001$) i graniczną istotność dla sTM ($p = 0,07$). Hemoglobina ($p < 0,001$) oraz przesączanie kłębuszkowe (eGFR) ($p = 0,004$) były niższe w grupie z HF, podczas gdy INR ($p < 0,001$), NT-proBNP ($p < 0.001$) i asymetryczna

dimetyloarginina (ADMA) ($p < 0,001$) były wyższe. Większość parametrów echokardiograficznych różniła się pomiędzy grupami. Spośród biomarkerów zakrzepowych, sTM ($r = –0,66$; $p < 0,001$) i vWF ($r = –0,41$; $p = 0,002$) były związane z eGFR. Większość parametrów echokardiograficznych i parametrów laboratoryjnych także miała związek z eGFR. Po podzieleniu wszystkich zmiennych w 5 kategorii: badania laboratoryjne, parametry echokardiograficzne, parametry reaktywności naczyniowej, parametry hemodynamiczne i biomarkery zakrzepowe, regresja liniowa wielu zmiennych wykazała, że to biomarkery zakrzepowe były najbardziej związane z eGFR ($r^2 = 0,48$, $p < 0,001$).
Wnioski: W badanej populacji zaburzenia w obrębie biomarkerów zakrzepowych były najmocniej związane z upośledzoną funkcją nerek, niezależnie od pozostałych badanych parametrów.

Introduction

Heart failure (HF) is a chronic progressive disease that has many adverse consequences and systemic complications. Among many coexisting conditions, renal dysfunction is one of the most commonly reported [1–3]. There is extensive crosstalk between the kidney and heart about salt and water content on the one hand, and blood flow and generated pressure on the other. However, the interaction is disrupted in the course of HF and is known as a cardio-renal syndrome. Cardio-renal syndrome can only partially be explained by haemodynamic factors [4]. Therefore, the pathophysiology of renal dysfunction in HF is complex, including many biochemical, structural, thrombotic, and endocrinological abnormalities that affect this condition [5]. It must also be realized that both HF and renal failure (RF) are characterized by a hypercoagulability state [6–11], which is one of the 3 basic elements of the Virchow triad, including endothelial dysfunction and blood stasis, with inflammation recently added. Endothelial dysfunction also plays an independently important role in increasing the risk of thrombotic complications [12].

Many studies have been conducted to assess the potential beneficial effect of anticoagulation in HF. However, in large randomized studies (WARCEF, WATCH, HELAS, COMMANDER-HF), no beneficial effect on survival was demonstrated [13]. On the other hand, small studies revealed the beneficial effect of anticoagulation in selected subjects with an improved coagulation profile, increased response to diuretics, and improvement in contractility [11, 14].

Aim of the research

Therefore, the objective of this study was to analyse activators and inhibitors of coagulation and fibrinolysis and their association with RF in patients with HF, independently of other parameters.

Material and methods

Study population

This is a cross-sectional study that incorporates subsequently electively admitted patients with HF (NYHA class II–IV) with ejection fraction (EF) < 40% and sinus rhythm, hospitalized in the Department of Heart Failure of the National Institute of Cardiology in Warsaw. These patients were referred as potential candidates for heart transplantation. The key exclusion criteria were neoplasm, anticoagulation therapy within 3 months before the study, dementia, atrial fibrillation, and RF caused by primary kidney disease or diabetic nephropathy. The study comprised 36 patients and 19 age- and gender-matched volunteers without HF (control group). All clinical information on the health status and existing comorbidities of the patients was obtained from medical documentation. All patients and controls signed informed consent forms, and the study protocol was approved by the local Ethics Board.

Echocardiographic examinations were performed and analysed by one physician. Endothelial function and arterial compliance by pulse waveform analysis were assessed in all subjects. In summary, endothelial function was evaluated using a standard ultrasound procedure that evaluated flow-mediated dilation (FMD) of the brachial artery after 5 min of blood flow occlusion (cuff placed just above the wrist). Pulse waveform analysis was performed using an applanation tonometer (HDI/PulseWaveTM CR-2000). Pressure waveforms were recorded from the right radial artery with simultaneous measurement of arterial pressure from the opposite limb. The arterial reactivity of the small and large arteries was automatically calculated, corresponding to endothelial function and arterial compliance, respectively. The cardiac output was also calculated during the same study. All subjects underwent a standard laboratory evaluation during the first 2 days after admission. The estimated glomerular filtration rate was calculated according to the MDRD formula.

Coagulation biomarkers

The biomarkers selected for the analysis were subjectively chosen based on a review of the literature that indicated a potential association with worsening renal function [15–18].

Blood samples for the thrombotic factor assay were taken on the same day as those for other laboratory tests. Platelet-poor plasma collected from EDTA was used for all assays. Blood samples were centrifuged immediately after collection and were then aliquoted and kept frozen at –70°C until analysis. All assay analyses were performed according to the manufacturers' instructions. The ADMA concentration was determined by the ADMA Express ELISA Kit (Immundiag-

nostik AG, Bensheim, Germany). The concentration of human prothrombin fragment 1 + 2 (F1 + F2) was measured by enzyme-linked immunoassay (ELISA) (Shanghai Sunred Biological Technology Co. Ltd., China). The TAT complex measurements were made using an enzyme-linked immunoassay (IMUBIND, American Diagnostica, Inc., Greenwich, CT). The vWF ELISA (IMUBIND, American Diagnostica, Inc., Greenwich, CT) was used for the measurement of the antigen (vWF). For PAI-1 measurements, we used the IMUBIND Plasma PAI-1 ELISA. sTM was measured using an enzyme-linked immunoassay (Diaclone sCD141 ELISA Kit, France). The concentration of tissue plasminogen activator (tPA) was determined by enzyme-linked immunoassay (AssayMax™ Human tPA ELISA Kit, AssayPro, United States). Other tests were carried out at the institute's central laboratory.

Statistical analysis

The characteristics of the population were summarized as means (SD) or medians (25^{th}, 75^{th} percentiles) for continuous variables and as percentages for categorical data. Differences between normally distributed data were tested using the Student's *t*-test, while abnormally distributed data were tested using the Wilcoxon rank sum test. Categorical variables are compared using the χ^2 test of independence or Fisher exact test. Correlations were evaluated using Pearson or Spearman correlation tests. In the case of correlation and regressions, the calculation of estimated glomerular filtration rate (eGFR) levels was performed after a natural logarithmic transformation to correct for the skewed distribution. Similarly, the approach was implemented whenever applicable. In further analysis, due to the large number of variables and the limited number of subjects, we analysed the variables in 5 separate categories (laboratory tests, echocardiographic parameters, vascular reactivity, haemodynamic parameters, and coagulation parameters) to examine the strength of the association with renal function. For each of these categories, using the canonical correlation method, we defined the score (index) that had the highest canonical correlation with the logarithmic eGFR. Then, to test the independence of the effects of each category on kidney function, we used multivariate linear and logistic regression using indices and clinical variables created by a stepwise approach. All hypotheses were 2-tailed with a type I error of 0.05 (multivariable regression: 0.15; exception for age and gender in linear regression). All statistical analyses were performed with SAS statistical software, Version 9.4 (SAS Institute, Cary, NC, USA).

Results

There were 36 subjects with HF and 19 subjects in the control group (Table 1). The 2 groups did not differ with respect to demographic variables such as age and gender distribution, but males were more prevalent. Blood pressure was higher in the control group, but heart rate was the similar. In the HF group, non-ischaemic aetiology was the dominant cause of HF, and half of the patients had advanced HF (NYHA classes III and IV). Among HF patients, 20 subjects had an implantable cardioverter-defibrillator (ICD), 8 patients had ICD-CRT (cardiac resynchronization therapy), 3 patients were referred for ICD or ICD-CRT, and in 2 cases the decision was postponed for further evaluation. The remaining 3 subjects did not have an ICD.

Among previously identified comorbidities, hyperlipidaemia (52.8%), coronary artery disease (44.4%), hyperuricaemia (30.6%), renal dysfunction (30.6%), diabetes mellitus (25%), and hypertension (13.9%) were the most common in patients with HF. The control group did not report any important comorbidities. The HF group, in most cases, received optimal pharmacotherapy with β-blockers 94.4% (n = 34), angiotensin convertase enzyme inhibitor (ACEI) 89% (n = 32), aldosterone antagonists 91.7% (n = 33), and statins 69.4% (n = 25); 89% (n = 32%) were on loop diuretics. As shown in Table 1, of the laboratory tests selected, blood count tests, erythrocyte count, haemoglobin level, and haematocrit were lower in the HF group. However, RDW-CV and RDW-SD were significantly higher in HF. Likewise, creatinine, INR, and NT-proBNP were higher in HF, but eGFR was lower.

In echocardiography (Table 2), the HF group presented larger sizes of both ventricles and all haemodynamic variables were significantly altered, compared to controls. As presented in Table 2, the vascular reactivity tests did not show uniform results. The concentration of ADMA, a biomarker of endothelial dysfunction, was lower in controls. On FMD, both groups had similar endothelial-dependent vascular reactivity. However, based on pulse wave analysis, endothelial-dependent vascular reactivity was slightly higher in controls while the elasticity of the large arteries was lower.

Among the markers of increased procoagulant activity (Table 3), vWF levels was increased in the HF group, while sTM showed borderline significance and F1 + F2 was lower. Furthermore, decreased levels of anticoagulation factors in HF were reported only with respect to protein C. The correlations among the parameters analysed with eGFR are presented in Table 4. Age had a negative correlation with eGFR. In laboratory tests, erythrocytes, haemoglobin, platelets, and alanine transaminase (ALT) were positively correlated with eGFR, while red blood cell distribution width (RDW-CV), red blood cell distribution width standard deviation (RDW-SD), international normalized ratio (INR), and NT-proBNP showed a negative association. As shown in the table, all echocardiography parameters associated with remodeling or func-

Table 1. Clinical characteristics of the study population

Parameter	Study group *N* = 36	Control group *N* = 19	*P*-value
Age [years]	51.1 (12.9)	52.1 (8.6)	0.91
Duration of HF [years]	5.5 [1.0–10.0]	–	–
Non-ischaemic aetiology of HF, *n* (%)	21 (58.3)	–	–
Male, gender, *n* (%)	30 (83.3)	15 (78.9)	0.72
NYHA class, *n* (%):			
I	–	–	–
II	17 (47.2)	–	–
III	17 (47.2)	–	–
IV	2 (5.6)	–	–
BMI [kg/m^2]	27.1 (4.2)	26.0 (3.0)	0.35
SBP [mm Hg]	110.2 (12.8)	123.1 (9.9)	< 0.001
DBP [mm Hg]	64.3 (7.1)	73.6 (6.6)	< 0.001
HR [*n*/min]	63.4 (11.3)	66.1 (6.1)	0.28
eGFR [ml/min/1.73 m^2]	67.9 (18.8)	80.2 (11.1)	0.004
Creatinine [mg/dl]	1.10 [1.0–1.4]	1.00 [0.9–1.0]	0.005
Erythrocytes [10^6/µl]	4.66 (0.41)	5.11 (0.32)	< 0.001
Haemoglobin [g/dl]	14.10 (1.40)	15.61 (0.80)	< 0.001
Haematocrit (%)	42.2 (3.98)	45.9 (2.41)	< 0.001
INR	1.08 (0.10)	0.99 (0.04)	< 0.001
Leukocytes [K/µl]	7.28 (1.96)	6.51 (1.51)	0.15
Platelets [K/µl]	197.5 (48.5)	215.3 (44.5)	0.2
RDW-SD [fl]	48.1 (6.8)	43.4 (2.3)	< 0.001
RDW-CV (%)	15.0 (2.5)	13.4 (0.42)	< 0.001
NT-proBNP [pg/ml]	1533.5 [607.8–2978]	42.9 [19.0–68.0]	< 0.001
ALT [IU/l]	25 [18–43]	25 [21–34]	0.81
Total bilirubin [mg/dl]	0.73 [0.53; 0.98]	0.65 [0.47; 0.79]	0.18

Data are presented as a median with [range]; mean (SD) or a number of observations (percentage) as appropriate. Categorical variables are compared using a Fisher test. Other data were tested using a T-student test, except for those without a normal distribution (Wilcoxon test). BMI – body mass index, DBP – diastolic blood pressure, eGFR – estimated glomerular filtration rate, HF – heart failure, HR – heart rate, INT – international normalized ratio, RDW – red cell distribution width, NT-proBNP – N-terminal prohormone of brain natriuretic peptide, SBP – systolic blood pressure.

tional impairment of myocardial function were negatively correlated with eGFR. Vascular reactivity tests revealed that a positive correlation with eGFR was limited only to a small artery reactivity index. Furthermore, blood pressure parameters were also positively correlated with eGFR. A negative correlation with renal function was observed for some of the biochemical markers of coagulation activity and endothelial dysfunction, such as sTM, vWF, and ADMA.

To estimate the potential association with eGFR, 5 categories of variables were created (for both combined groups). The correlation between each parameter and the eGFR was analysed to identify the variables most significantly associated with renal function. We documented that the models for each of the 5 research areas (indexes) were highly associated with renal function (Table 5). The most predictive model included coagulation biomarkers. sTM, vWF, and activated protein C were the most significant parameters in this model.

After testing for the multivariable predictive model, the model presented for eGFR included co-

Table 2. Echocardiography examination and parameters of vascular reactivity

Parameter	Study group (1)	Control group (2)	Study vs. control group *P*-value
LVEDD [mm]	70.1 (6.8)	45.2 (4.9)	< 0.001
EF biplane (%)	22.4 (6.1)	65.7 (4.9)	< 0.001
LV S' [cm/s]	4.41 (1.37)	8.95(1.84)	< 0.001
RVIT [mm]	39.9 (8.8)	32.5 (3.75)	< 0.001
FAC (%)	31.0 (11.8)	44.3 (10.7)	< 0.001
TV S' [cm/s]	9.0 (2.76)	12.5 (2.11)	< 0.001
TAPSE [mm]	16.9 (3.8)	22.3 (3.04)	< 0.001
ADMA [µmol/l]	1.13 (0.32)	0.63 (0.18)	< 0.001
VTI LVOT [cm]	11.1 (2.5)	18.9 (2.69)	< 0.001
FMD (%)	4.61 (5.60)	4.23 (2.60)	0.75
HR [n/min]	63.4 (11.3)	66.1 (6.1)	0.28
CO [l/min]	5.13 (0.71)	5.38 (0.47)	0.18
CET [ms]	296.3 (30.7)	313.6 (21.1)	0.03
LAEI [ml/mm Hg × 10]	19.2 (4.8)	15.2 (3.95)	0.003
SAEI [ml/mm Hg × 100]	5.72 (2.60)	7.18 (3.48)	0.09

Data are presented as mean and (SD). Data are compared using Student's t-test. Abbreviations (in addition to the previous table): CET – estimated cardiac ejection time, CO – estimated cardiac output, EF – ejection fraction (Simpson method), FAC – change in fractional area change of the right ventricle, FMD – flow-mediated dilatation, LAEI – large artery elasticity index, LVEDD – diastolic diameter of the left ventricle, LV S' – mean of lateral and septal mitral annular systolic velocity, TV S' – tricuspid lateral annular systolic velocity, RVIT – right ventricle inflow tract, SAEI – small artery elasticity index, TAPSE – tricuspid annular plane systolic excursion, VTI LVOT – integral velocity time in left ventricle outflow tract.

Table 3. Coagulation parameters

Parameter	Study group	Control group	*P*-value
sTM [ng/ml]	13.2 (5.8)	11.07 (2.71)	0.07
TAT[a] [ng/l]	0.73 [0.20–3.68]	0.74 [0.34–3.64]	0.94
F1 + F2 [nmol/l]	6.16 (3.37)	9.65 (3.25)	< 0.001
PAI [ng/ml]	39.8 (13)	44.4 (8.8)	0.2
vWF [mU/ml]	1034.0 (299.0)	544.3 (246.3)	< 0.001
C protein [% of normal activity]	103.9 (22.3)	116.9 (20.4)	0.04
tPA[a] [U/l]	23.8 [15.7–32.0]	20.2 [14.2–22.1]	0.19

Data are presented as median with [range] or mean (SD). Data were tested using Student's t-test, except those without normal distribution a (Wilcoxon test). ADMA - asymmetric dimethylarginine, F1 + F2 – human prothrombin fragments, PAI – plasminogen activator inhibitor, sTM – soluble thrombomodulin, TAT – thrombin-antithrombin complex, tPA – tissue plasminogen activator, vWF – von Willebrand factor.

agulation, haemodynamic, and echocardiography indexes (Table 6). The coagulation index was most strongly associated with eGFR. It was responsible for 48% of the variation in eGFR, while the remaining parameters played a minor role. When the population was stratified by stage of renal dysfunction (eGFR < 60 ml/min/1.73 m^2) (Table 7), male sex and coagulation index were independently associated with decreased renal function (model AUC = 0.925; $p < 0.001$).

Discussion

Numerous studies have evaluated coagulation abnormalities in heart failure patients [11, 19, 20]. However, to our knowledge, this is the first to look at the broader aspects of abnormalities in coagulation factors, also taking into account other parameters. We have documented that coagulation abnormalities in HF patients are more strongly associated with eGFR

Table 4. Correlation coefficients with the eGFR logarithm

Variable	Correlation coefficients	*P*-value
Age [years]	–0.44	< 0.001
BMI [kg/m^2]	0.07	0.62
Laboratory tests:		
Creatinine* [mg/dl]	0.82	< 0.001
Erythrocytes [10^6/ml]	0.38	0.01
Haemoglobin [g/dl]	0.46	< 0.001
Haematocrit (%)	0.36	0.01
INR	–0.37	0.01
Leukocytes [thousand/µl]	–0.08	0.59
Platelets [thousand/µl]	0.38	0.004
RDW-SD [fl]	–0.40	0.003
RDW-CV (%)	–0.39	0.004
NT-proBNP** [pg/ml]	–0.53	< 0.001
ALT** [IU/l]	0.30	0.03
Total bilirubin** [mg/dl]	–0.21	0.15
Echocardiography:		
LVEDD [mm]	–0.20	0.15
EF biplane (%)	0.30	0.03
LV S [cm/s]	0.41	0.002
RVIT [mm]	–0.40	0.003
FAC (%)	0.27	0.05
TV S' [cm/s]	0.09	0.53
TAPSE [mm]	0.06	0.68
VTI LVOT [cm]	0.24	0.08
Vascular reactivity parameters:		
ADMA [µmol/l]	–0.40	0.002
Maximum post ischemic vessel diameter [mm]	–0.22	0.11
FMD (%)	0.07	0.59
LAEI [ml/mm Hg × 10]	–0.23	0.1
SAEI [ml/mm Hg × 100]	0.28	0.046
Hemodynamic parameters:		
SBP [mm Hg]	0.30	0.03
DBP [mm Hg]	0.34	0.01
CO [l/min]	0.24	0.08
CET [ms]	–0.23	0.1
SV [ml]	0.13	0.37
HR [n/min]	0.10	0.499
Coagulation parameters:		
Thrombomodulin [ng/ml]	–0.66	< 0.001
TAT** [g/l]	0.07	0.63
F1 and F2 [fl]	0.06	0.64
PAI [ng/ml]	0.15	0.27
vWF [mU/ml]	–0.41	0.002
C protein [% of normal activity]	0.23	0.1
S protein [% of normal activity]	0.03	0.86
tPA** [U/l]	–0.19	0.17

Spearman correlation, otherwise Pearson correlation; **logarithmic transformation. Abbreviations as previously stated.*

Table 5. Canonical correlation of selected categories with a glomerular filtration rate

Parameter	Standardized canonical coefficients with SCORE	Correlation coefficient *R*	Wilks' Lambda *P*-value
Laboratory tests:			
Haemoglobin [g/dl]	0.39	0.64	< 0.001
Platelets [K/µl]	0.38		
NT proBNP (log) [pg/ml]	–0.37		
ALT (log) [U/l]	0.16		
INR	–0.06		
RDW-SD [fl]	–0.05		
Echocardiography parameters:			
LVEDD [mm]	1.03	0.63	0.003
EF biplane (%)	0.57		
LV S'	1.09		
RVIT [mm]	–0.71		
FAC (%)	–0.20		
TV S' [cm/s]	–0.22		
TAPSE [mm]	–0.34		
Vascular reactivity:			
ADMA [µmol/l]	–0.60	0.5	0.007
SAEI [ml/mm Hg × 100]	0.58		
LAEI [ml/mm Hg × 10]	–0.41		
FMD (%)	–0.07		
Hemodynamic parameters:			
CET [ms]	–0.72	0.52	0.004
DBP [mm Hg]	0.63		
SV [ml]	0.58		
CO [l/min]	0.27		
Coagulation parameters:			
sTM [ng/ml]	–0.81	0.70	< 0.0001
vWF [mU/ml]	–0.26		
C protein [% of normal activity]	0.19		
tPA (log) [U/l]	–0.09		

Abbreviations as previously stated.

compared to other parameters studied, which has not been reported before.

Renal and liver dysfunction are the most prominent organ complications of HF. Renal dysfunction, regarded as the most important comorbidity that significantly modifies the prognosis [1, 3], is reported in 23–65% of the population with HF population [2]. The underlying pathophysiology of organ failure is complex, and a better understanding of the causes of reduced eGFR in patients with HF is necessary to find new strategies to improve the prognosis.

Our study population represents a specific group with advanced HF. We showed a significantly decreased kidney function and a mildly decreased liver function, reflected in slightly prolonged INR. A significant change in blood count parameters, such as RDW, is consistent with our previous report [21]. Some authors postulate that activation of proinflammatory cytokines in HF is responsible for inhibition of erythropoietin and red cell maturation leading to increased variability, constituting a marker of increased inflammatory response in HF [21, 22]. The pa-

Table 6. Multivariable prediction of the logarithm of eGFR by linear regression model

Parameter	Univariate		Multivariate		
	Regression coefficient	*P*-value	Regression coefficient	Partial r^2	*P*-value
Age [years]	–0.011 (0.003)	< 0.001	–0.005 (0.003)	0.03	0.08
Males	0.103 (0.104)	0.32	–	–	
BMI [kg/m^2]	0.006 (0.011)	0.62	–	–	
DM	–0.406 (0.093)	< 0.001	–	–	
HT	0.123 (0.093*)	0.194	–	–	
Laboratory test index	0.196 (0.034)	< 0.001	–	–	
Vascular reactivity index	0.126 (0.038)	0.002	–	–	
Coagulation parameter index	–0.207 (0.029)	< 0.001	–0.122 (0.037)	0.48	0.002
Haemodynamic parameter index	0.155 (0.036)	< 0.001	0.079 (0.033)	0.05	0.021
Echocardiography parameter index	0.192 (0.033)	< 0.001	0.106 (0.037)	0.1	0.007

*Selection: stepwise: $r^2 = 0.64$, $p < 0.001$. *(SE of the regression coefficient). DM – diabetes mellitus, HT – hypertension.*

Table 7. Multivariate prediction of decreased renal function (eGFR < 60 ml/min)

Variable	Univariate		Multivariate	
	Odds ratio [95% CI]	*P*-value	Odds ratio [95% CI]	*P*-value
Age [years]	1.065 [1.001–1.138]	0.046	–	
Male	0.250 [0.059–1.054]	0.06	0.079 [0.01–0.615]	0.015
BMI [kg/m^2]	0.965 [9.813–1.146]	0.69	–	
DM	9.498 [1.953–46.191]	0.005	–	
HT	0.455 [0.009–2.364]	0.35	–	
Laboratory tests index	0.149 [0.046–0.480]	0.001	–	
Vascular reactivity index	0.192 [0.065–0.567]	0.003	–	
Coagulation parameter index	6.878 [2.152–21.979]	0.001	8.111 [2.326–28.292]	0.001
Haemodynamic parameter index	0.387 [0.183–0.821]	0.01	–	
Echocardiography parameter index	0.147 [0.044–0.490]	0.002	–	

AUC = 0.925, P < 0.001. DM – diabetes mellitus, HT – hypertension.

tients in the study group had significantly lower haemoglobin concentrations compared with the control group, which can lead to haemodynamic compensatory mechanisms, especially a reduction in peripheral vascular resistance and increased heart rate [23].

HF patients, compared to healthy controls, have vascular remodeling, increased arterial stiffness, and endothelial dysfunction [24]. However, there are also contrary data, especially in non-ischaemic patients, that are consistent with our findings [12, 25]. This may be due to the beneficial effect of optimized HF pharmacotherapy [26], but it can also be caused by the aetiology, age, physical activity, measurement conditions, and some specific genetic and epigenetic characteristics [25, 27]. HF patients showed much higher levels of ADMA and vWF, consistent with the first stage of endothelial dysfunction, endothelial activation [6, 12, 19, 20, 28, 29]. In HF, endothelial dysfunction occurs in multiple vascular beds, also affecting the regulation of the renal vascular bed [26, 28]. Due to endothelium damage and blood stasis, prothrombotic capacity increases [12, 14, 30]. Endothelial-damaging agents lead to cleavage of the TM molecule, so that it loses its anticoagulant properties. The soluble TM is a cleaved molecule, and its higher concentration becomes a marker of endothelial damage [6].

The pathogenesis of RF in the HF population is highly complex, including haemodynamic disorders, neurohormonal adaptations, reduced perfusion, endothelial dysfunction, atherosclerosis, and oxidative in-

jury [5, 31]. Both cardiac output and increased venous pressure, causing renal hyperaemia, appear to have a significant effect on renal function [31]. Our data support this concept, as both left and right ventricular parameters were shown to be significantly associated with renal function. Furthermore, in laboratory tests, NT- has been reported as a negative predictor of eGFR and an increased risk of mortality [32, 33].

There are many reports that evaluate the role of the blood coagulation system in patients with RF [8–10, 34], some of them underlining the importance of endothelial dysfunction [10, 35]. In RF, there is also excessive cytokine activation consistent with an inflammatory state, which unfavourably modifies renal function, parallel to that observed in HF [31, 36]. It is indirectly confirmed by the association between RDW and deterioration of renal function [9].

In many publications, endothelial dysfunction and prothrombotic state are identified as the main factors modifying renal function [9, 10, 35]. It is already known that ADMA, in addition to being a marker of endothelial dysfunction, can be used to assess cardiovascular risk, while natriuretic peptides represent a negative predictor of eGFR and an independent predictor of adverse clinical outcomes [33, 37, 38]. ADMA levels also increase in RF, contributing to endothelial dysfunction, oxidative stress, and progression of renal damage [9, 28]. Likewise, the increased level of vWF reported in previous publications [11, 14, 20, 28, 29] is a risk factor for cardiovascular death, indicating endothelial damage, and perhaps a contributing factor for thrombosis in arterial disease [39].

The transmembrane portion of TM is not only a marker of endothelial dysfunction [20], but it also plays a major role in the regulation of intravascular coagulation [40]. Consistent with our findings, many reports show increased levels of TM in HF [6, 20]. Lower activity of anticoagulant protein C was also reported in other HF studies [41]. It also reduces damage to the renal microvasculature and restores peritubular capillary blood flow through its additive mechanisms [42]. tPA is one of the key elements that regulate the fibrinolysis process and, as we have shown, it is often elevated in HF patients [6, 43]. It correlates with creatinine concentration [8], and it has been shown to exacerbate inflammation, and it may play an important role in a variety of glomerular diseases, worsening kidney function in reperfusion injury [34].

In our study population, thrombosis markers such as F1 + F2 and TAT were not elevated in the HF group, or they were comparable to the control group, contrary to most other studies [6, 43]. Publication data suggest that other potential factors, such as anaemia or acute events, can modify their concentrations [44]. Furthermore, biomarker concentrations increase rapidly in the period preceding thrombosis or at the time of implantation of the left ventricular assist device (LVAD), and decrease several days after the LVAD procedure [45] or after removal of the thrombus [46]. It is difficult to find an easy explanation for our results, but we cannot exclude that during a stable period, as in our study, thrombin generation may be less pronounced and underestimated, contrary to acute HF [41].

In recent reviews on renal impairment in HF patients, the authors highlighted several pathophysiological abnormalities that contribute to the development and progression of cardio-renal interactions [38]. This publication identified haemodynamic changes (abnormal venous return leading to congestion or low cardiac output), dysregulation of the neurohormonal axis (found in both HF and RF), and other factors such as the activation of inflammation, metabolic changes, and anaemia, as major abnormalities in this process. There is also evidence that endothelial dysfunction and coagulation abnormalities may play an important role in the prognosis of HF patients and the deterioration of renal function [8–10, 20, 28, 36, 47].

We do not question the importance of other mechanisms, but in our opinion the demonstration that 48% of the GFR variability can be explained by coagulation parameters, including those directly related to endothelial dysfunction, deserves attention. For many years, HF has been considered as a prothrombotic state caused by endothelial dysfunction and inflammation [13, 48], being a potential target for therapy. Nevertheless, in all major studies, the potential benefits of anticoagulation treatment have been outweighed by the significant risk of bleeding in patients with sinus rhythm, and there is currently no indication of anticoagulation in HF per se [13]. However, it should be stressed that renal dysfunction in HF is an independent risk factor for thromboembolic events [48]. Given that all data are cross-sectional [6, 9, 10] or retrospective [48], it is difficult to draw unequivocal conclusions about the cause-and-effect relationship between coagulation and RF. On the other hand, it cannot be ruled out that anticoagulation in selected patients may contribute to improving kidney function and improving prognosis in patients with HF. However, this issue needs further investigation to justify the inclusion of additional biomarkers in the broad evaluation of advanced HF patients.

Study limitations: The present study has certain limitations. The main limitation of our study is the small sample size, making it difficult to generalize our results. It should also be stated that we were unable to analyse all haemodynamic parameters and other factors that could influence renal function. Another aspect is the cross-sectional design of our work, which precludes definitive statements. Therefore, the clinical aspects of our findings need to be confirmed in future prospective studies.

Conclusions

Patients with HF are characterized by endothelial activation and higher levels of procoagulant factors that coexist with impaired renal function. Based on our data, we can conclude that abnormalities in coagulation biomarkers in HF patients are one of the most important parameters associated with impaired renal function. From a theoretical point of view, this may provide an attractive basis for identifying coagulation abnormalities as a potential target for therapy in selected patients with HF with progressive renal dysfunction.

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Conflict of interest

The authors declare no conflict of interest.

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