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Von Willebrand factor (vWF) in patients with heart failure with preserved ejection fraction (HFpEF)

A retrospective observational study

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is associated with endothelial damage and inflammation. In addition, von Willebrand factor (vWF) has been discovered as a biomarker of endothelial dysfunction. Therefore, the study aims to investigate the association between vWF level and HFpEF. Moreover, we analyzed a potential correlation between vWF and inflammatory factors, such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin (IL)-6.

We recruited altogether 272 hospitalized patients from The Fifth Affiliated Hospital of Xinjiang Medical University, 88 of whom were HFpEF patients, 88 were non-heart failure patients, and 96 were healthy controls from the medical examination center of the hospital. Enzyme-linked immunosorbent assay and double antibody sandwich immunochromatography were used for testing vWF, tissue plasminogen activator, galectin-3, nitric oxide, TNF-α, IL-6, and CRP.

The HFpEF group's levels of vWF, IL-6, TNF-α, CRP, tissue plasminogen activator, galectin-3, and nitric oxide were statistically higher than those of non-heart failure and healthy control ones (F = 403.563, 21.825, 20.678, 39.609, 35.411, 86.407, 74.605; all P = .000). the highest level of vWF was observed in class IV (New York Heart Association) of HFpEF patients and the significant difference is <.05 (P < .001). An increasing level of vWF were shown in groups (CRP: CRP >3 mg/L group and CRP ≤3 mg/L group; IL-6: IL-6 <7.0 pg/mL group and IL-6 ≥7.0 pg/mL group; TNF-α: TNF-α <5.5 pg/mL group and TNF-α ≥5.5 pg/mL group) with higher level of IL-6, TNF-α, CRP. A multiple regression analysis regarding the relationship of vWF and inflammation markers was performed among the HFpEF patients. Further, statistical significance of the analysis remained after adjusting variables such as body mass index, low-density lipoprotein cholesterol, total cholesterol, coronary artery disease, and type 2 diabetes mellitus (β = 0.406, t = 4.579, P < .001; β = 0.323, t = 3.218, P < .001; β = 0.581, t = 6.922, P < .001).

Our study shows that elevated vWF levels are associated with HFpEF, and it may serve as a potential biomarker for HFpEF severity. We also found that increased vWF levels are positively correlated to IL-6, TNF-α, and CRP, which may provide a clue for further researching the pathogenesis of HFpEF.

Abbreviations: BMI = body mass index, BNP = B-type natriuretic peptides, CAD = coronary artery disease, CRP = C-reactive protein, DHF = diastolic heart failure, DM = diabetes mellitus, EH = essential hypertension, Gal-3 = galectin-3, HDL-C = high-density lipoprotein cholesterol, HF = heart failure, HFpEF = heart failure preserved ejection fraction, IL-6 = interleukin-6, LDL-C = low-density lipoprotein cholesterol, LV = left ventricular, MMP = matrix metalloproteinases, NHF = non-heart failure, NO = nitric oxide, TC = total cholesterol, TG = triglyceride, TPA = tissue plasminogen activator, TNF-α = tumor necrosis factor-alpha, vWF = von Willebrand factor.

Keywords: endothelial dysfunction, HFpEF, inflammation, plasmabiomarkers, vWF

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome characterized by typical symptoms and signs of heart failure (HF), diastolic HF, and HF with normal ejection fraction. HFpEF has become one of the most common type of HF with high morbidity, mortality, and rehospitalization rates.[1,2]

HFpEF is regarded as an inflammatory disease, and many risk factors of HFpEF such as aging, obesity, coronary artery disease (CAD), type 2 diabetes mellitus (DM2), and renal insufficiency cause systemic proinflammatory state.[3–7] This proinflammatory state leads to left ventricular (LV) fibrosis, diastolic dysfunction, and HFpEF.[8]

Recent studies indicate that plasma biomarkers play a vital role in the development of HFpEF. Therefore, plasma

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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What was done?

- Heart failure preserved ejection fraction (HFpEF) is regarded as an inflammatory disease, and plasma biomarkers play a vital role in the development of HFpEF. Von Willebrand factor (vWF) is a biomarker of endothelial damage and dysfunction and aggravates inflammatory state and metabolic disorders.
- Our previous study showed that higher level of interleukin-6, tumor necrosis factor-alpha, and C-reactive protein, as well as matrix metalloproteinase-2, matrix metalloproteinase-9, and galectin-3 were associated with the severity of HFpEF, and these biomarkers might be helpful for early diagnosis of HFpEF patients.

What was found?

- Our study shows that elevated vWF levels are associated with HFpEF, and it may serve as a potential biomarker for HFpEF severity. We also found that increased vWF levels are positively correlated to interleukin-6, tumor necrosis factor-alpha, and C-reactive protein, which may provide a clue for further researching the pathogenesis of HFpEF.

biomarkers were used as tools for diagnosing and predicting diseases.[9,10] These plasma biomarkers are as follow: the B-type natriuretic peptides (BNP), soluble suppression of tumorigenicity 2, galectin-3 (Gal-3), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), propeptide of type I/II procollagen, procollagen I intact N-terminal, terminal telopeptide of collagen type I, matrix metalloproteinases (MMP-1, -2, -8, -9), and tissue inhibitor of MMP-1 and MMP-2.[10,11] Our previous study showed that higher levels of IL-6, TNF-α, and CRP, as well as MMP-2, MMP-9, and Gal-3 were associated with the severity of HFpEF, and these biomarkers might be helpful for early diagnosis of HFpEF patients.[12,13]

Von Willebrand factor (vWF) is a biomarker of endothelial damage and dysfunction[14–16] and aggravates inflammatory state and metabolic disorders.[17] The Framingham Offspring Study proved that vWF is a risk factor for patients with cardiovascular disease and DM2.[18] According to the possible mechanism and previous researches,[10,19,20] we hypothesize that there might be an association between vWF and inflammatory factors, which leads to proinflammatory state during the development of HFpEF. If there truly exists such a relationship between vWF level and HFpEF, then we might be able to make an early predictions regarding HFpEF subjects.

2. Methods

2.1. Ethics statement

The written informed consent was obtained from all participants. This study was approved by the Ethics Committee of The Fifth Affiliated Hospital of Xinjiang Medical University (Urumqi, China) and conducted by strictly following the requirements of the Declaration of Helsinki.

2.2. Sample size

α = 0.05 (2 sided), power: 1 − β = 0.90, 1:1 for non-HF (NHF) and HFpEF group.

$$n = \left(\frac{Z_{1-\alpha/2} \times \sqrt{p \times (1-p)}}{\delta} \right)^2$$

We used the sensitivity and specificity for the disease according to the previous research[12] (Pse = 0.8, Psp = 0.9). We calculated the sample size (n = 90) for each group.

2.3. Participants

All the procedures were completed by professional doctors and nurses from the Department of Cardiology in the Fifth Affiliated Hospital of Xinjiang Medical University.

The hospitalized and HFpEF and NHF patients were recruited from the Fifth Affiliated Hospital of Xinjiang Medical University among from July 2016 to June 2017. They were all hospitalized and stable HF patients. Meanwhile, the healthy control subjects were recruited from the medical examination center of the above hospital. HFpEF group included 39 male and 49 female participants, and the NHF group included 41 male and 47 female participants and the healthy control group included 48 male and 48 female participants.

The definition and classification of HFpEF patients, as well as the functional severity of HF (the New York Heart Association [NYHA] classification), were strictly followed by the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF.[21] The meeting criteria were based on the clinical history, including clinical symptoms and signs (significant exertional dyspnea or fatigue, paroxysmal nocturnal dyspnea, pulmonary congestion on X-ray), LV ejection fraction ≥50%, high level of natriuretic peptide (N-terminal proB-type natriuretic peptide ≥125 pg/mL, proB-type natriuretic peptide ≥35 pg/mL), changes in the structure of the heart (LV hypertrophy or left atrial enlargement), or diastolic dysfunction. Those who do not show the above signs and symptoms with a normal range of natriuretic peptide and no structural changes in the heart or diastolic dysfunction were categorized for the NHF groups. HFpEF and NHF subjects were free from acute or chronic inflammatory disease, autoimmune system diseases, tumor, renal and liver dysfunction, acute coronary syndrome, cardiac valvular and pericardial disease, and hypertrophic and restrictive cardiomyopathy. Healthy control subjects were free of hypertension, CAD, metabolic syndrome, hyperlipidemia, infectious disease, immune disease, and tumor. CAD was defined as the presence of at least 1 significant coronary artery stenosis with >50% luminal diameter on coronary angiography. Hypertension was established if patients were on antihypertensive medication or if the mean of the 3 measurements of systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg. DM was diagnosed according to the criteria of the American Diabetes Association.[22]

2.4. Anthropometric and biochemical variables measurement

Height and body weight were measured as described previously[23] and body mass index (BMI) was calculated by dividing the weight in kilogram to the square of height in meter. Venous blood samples were obtained from all the subjects who had fasted >8 hours and collected into the anticoagulant ethylenediaminetetraacetic acid tube. Then the samples were centrifuged at 3000*g* for 15 minutes and separated into plasma or serum, and stored at –80°C for further analysis.

The serum concentration of total cholesterol (TC), triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and fasting glucose were measured by using the autobiochemical analyzer (BECKMAN AU5800 LX-20, USA) in Clinical Laboratory Department of the Fifth Affiliated Hospital of Xinjiang Medical University.

Finally, the level of vWF, tissue plasminogen activator (tPA), Gal-3, NO, and TNF-α were tested by using enzyme-linked

immunosorbent assay. Double antibody sandwich immunochromatography was provided to detect the plasma level of IL-6, and CRP. The kits were purchased from Beijing Rejing Biotechnology Co., Ltd. and Shanghai Lianshi Biotechnology Development Co., Ltd. All the procedures thoroughly followed the instructions.

2.5. Statistical methods

All continuous variables were expressed via mean ± standard deviation and compared using the analysis of variance. Differences in categorical variables were analyzed using the chi-square test or Fisher exact test. Multiple regression analysis was performed after adjusting variables such as BMI, LDL-C, TC, CAD, and DM2 among HFpEF patients. A P value <.05 was considered to be statistically significant. All statistical calculations were performed using SPSS 23.0 (SPSS Inc., Chicago, IL) computer software.

3. Results

1. Characteristics of included subjects and the levels of vWF and other plasma biomarkers among HFpEF, NHF patients, and healthy controls are shown in Table 1.
2. The levels of vWF, IL-6, TNF-α, CRP, tPA, Gal-3, and NO were statistically higher than the HFpEF group when compared to the NHF and healthy control ones in Table 2 (F = 403.563, 21.825, 20.678, 39.609, 35.411, 86.407, 74.605, all P < .001).
3. Figure 1 showed the distribution of vWF levels in NYHA functional class II to IV HFpEF patients. The highest level of vWF was observed in grade IV (NYHA) and the significant difference was <.05 (P < .001).
4. The levels of TNF-α, IL-6, and CRP were categorized according to the previous study and reference range[12] (CRP: CRP >3 mg/L group and CRP ≤3 mg/L group; IL-6: IL-6 <7.0 pg/mL group, and IL-6 ≥7.0 pg/mL group; TNF-α: TNF-α <5.5 pg/mL group, and TNF-α ≥5.5 pg/mL group). Increasing levels of vWF were shown in groups with higher TNF-α, IL-6, and CRP (Fig. 2).
5. In Table 3, a multiple regression analysis was performed in HFpEF groups: vWF was positively correlated with IL-6, TNF-α, and CRP and the statistical significance remained after adjusting variables such as BMI, LDL-C, TC, CAD, and DM2 (β =0.406, t = 4.579, P < .001; β = .323, t = 3.218, P < .001; β = 0.581, t = 6.922, P < .001).

4. Discussion

4.1. Findings and possible mechanisms

Recently, >50% of all HF patients are classified as HFpEF, thereby rapidly increasing health burden worldwide.[24] The pathogenesis of HFpEF remains unclear; however, studies have indicated that HFpEF is associated with endothelial damage and inflammation.[25] Therefore, it is crucial to find a new approach to prevent and delay the prognosis of HFpEF.

Table 1

Characteristics of subjects.

	NHF (n = 88)	HFpEF (n = 88)	Healthy Controls (n = 96)	X^2/t	*P* value
Age (yr)	60.9 ± 11.8	60.7 ± 11.4	60.5 ± 11.3	0.114	.909
Male (%)	41 (46.59)	39 (44.32)	48 (50)	0.092	.880
BMI (kg/m^2)	26.26 ± 3.13	26.23 ± 3.51	25.22 ± 3.33	0.057	.955
SBP (mm Hg)	146.0 ± 19.7	142.1 ± 23.4	140.0 ± 16.7	1.192	.235
DBP (mm Hg)	84.8 ± 13.1	81.7 ± 14.7	80.2 ± 13.0	1.412	.160
EH (%)	39 (36.8)	37 (34.9)	30 (28.3)	3.814	.149
DM (%)	27 (30.68)	35 (39.77)	25 (26.04)	1.594	.269
CAD (%)	64 (72.73)	72 (81.82)	60 (62.60)	2.071	.150
Smoking (%)	26 (29.55)	24 (27.27)	28 (29.17)	0.112	.867
TC (g/L)	4.34 ± 0.87	3.85 ± 1.12	3.78 ± 0.65	3.133	.002*
TG (mmol/L)	1.87 ± 0.68	1.55 ± 0.79	1.76 ± 0.70	2.792	.006*
HDL-C (g/L)	1.25 ± 0.29	1.23 ± 0.34	1.23 ± 0.26	0.489	.626
LDL-C (mmol/L)	2.84 ± 0.76	2.43 ± 0.79	2.34 ± 0.72	3.402	.001*

Continuous variables are expressed as mean ± standard deviation (SD). A P value of continuous variables was calculated by the independent t test. The P value of the categorical variable was calculated by the Fisher exact test.

BMI = body mass index, CAD = coronary artery disease, DBP = diastolic blood pressure, DM = diabetes mellitus, EH = essential hypertension, HDL-C = high density lipoprotein cholesterol, HFpEF = heart failure preserved ejection fraction, LDL-C = low-density lipoprotein cholesterol, NHF = non-heart failure, SBP = systolic blood pressure, SD = standard deviation, TC = total cholesterol, TG = triglyceride.

*P < .05.

Table 2

Levels of plasma biomarkers of subjects between 3 groups ($\bar{x} \pm s$).

	NHF group (n = 88)	HFpEF group (n = 88)	Healthy Control (n = 96)	*F*	*P* value
Plasma biomarkers					
vWF (ng/mL)	13.24 ± 1.85	15.43 ± 3.45	10.28 ± 2.06	95.612	.000
IL-6 (pg/mL)	3.80 ± 0.42	7.27 ± 1.32	3.60 ± 0.32	21.825	.000
TNF-α (pg/mL)	2.52 ± 0.55	5.86 ± 1.08	2.92 ± 0.35	20.678	.000
CRP (mg/L)	0.39 ± 0.12	3.30 ± 0.61	0.30 ± 0.02	39.609	.000
tPA (ng/mL)	5.54 ± 2.10	3.95 ± 2.34	6.67 ± 2.88	35.411	.000
Gal-3 (ng/mL)	20.51 ± 4.27	33.65 ± 10.30	22.66 ± 3.22	86.407	.000
NO (pg/mL)	2.90 ± 1.04	1.80 ± 0.91	2.88 ± 0.94	74.605	.000

Results are expressed as mean ± SD.

CRP = C-reactive protein, Gal-3 = galectin-3, HFpEF = heart failure preserved ejection fraction, IL-6 = Interleukin-6, NHF = non-heart failure, NO = nitric oxide, SD = standard deviation, TNF-α = tumor necrosis factor-alpha, tPA = tissue plasminogen activator, vWF = von Willebrand factor.

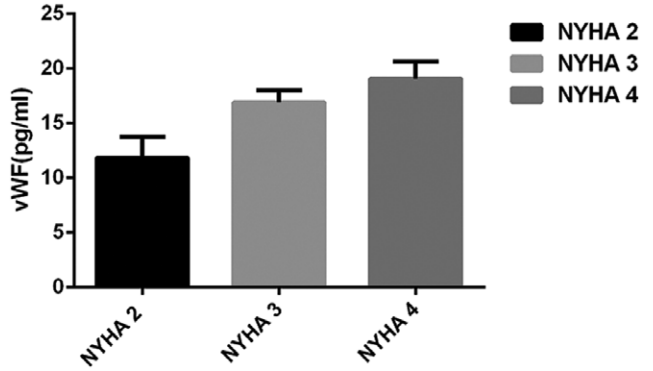

Figure 1. The distribution of vWF levels in NYHA functional class II to IV HFpEF patients. HFpEF = heart failure preserved ejection fraction, NYHA = New York Heart Association, vWF = von Willebrand factor.

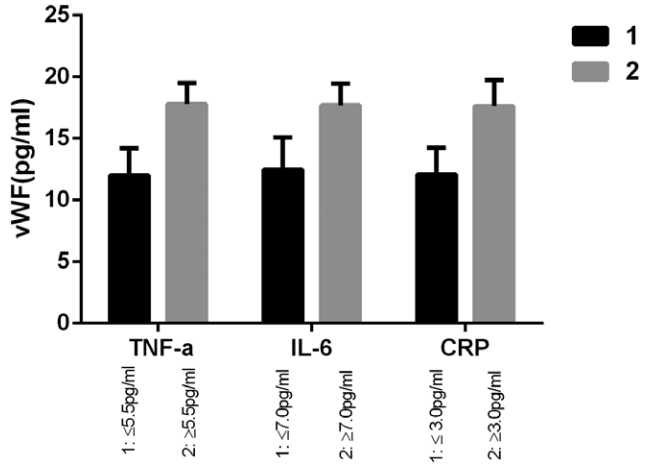

Figure 2. The distribution of vWF among 2 levels of TNF-α, IL-6, and CRP. CRP = C-reactive protein, IL-6 = interleukin-6, TNF-α = tumor necrosis factor-alpha, vWF = von Willebrand factor.

Table 3

Multiple regression analysis between vWF and variables.

Variables	β	SE	t	*P* value
BMI	0.939	0.033	0.414	.680
LDL-C	0.634	0.012	2.566	.000*
TC	0.179	0.889	–2.939	.000*
CAD	0.331	0.015	2.871	.006*
DM	0.137	0.019	1.382	.171
IL-6	0.406	0.013	4.579	.000*
TNF-α	0.323	0.014	3.218	.002*
CRP	0.581	0.012	6.922	.000*

BMI = body mass index, CAD = coronary artery disease, CRP = C-reactive protein, DM = diabetes mellitus, IL-6 = Interleukin-6; LDL-C = low-density lipoprotein cholesterol, SE = standard error, TC = total cholesterol, TNF-α = tumor necrosis factor-alpha, vWF = von Willebrand factor.

Plasma biomarkers are becoming a potential target to predict the development of HFpEF nowadays.[26]

vWF is known as glycoprotein, which appears and completes synthesis in endothelial cells and is stored in Weibel-Palade bodies.[27,28] vWF injured vascular endothelium through adhesion and recruitment of platelet and leukocytes and has become a reliable biomarker of endothelial dysfunction due to its role in inflammation and thrombosis.[29–32] In the Framingham Offspring Study, elevated vWF levels were associated with the risk of CVD in people with DM2 or insulin resistance.[33]

Moreover, vWF levels are associated with CAD, according to the ECAT study and increased incidence of myocardial infarction.[34–36] In a pilot, case–control study, patients with chronic cerebrovascular disease had higher vWF levels.[37] Evidence also suggests patients with HF disease tend to have higher level of vWF.[38–42] Nevertheless, the role of vWF in HF is still needed to be further studied, especially in HFpEF patients.

Many research works have shown that inflammation mediators such as CRP, IL-6, IL-8, and TNF-α were associated with increased vWF levels.[43] Martínez-Sales et al[44] reported that elevated levels of CEC is positively correlated to vWF, which may accelerate the development of the HF.[44]

Continuously, our previous data showed that serum concentrations of IL-6, TNF-α, and CRP were associated with severe HF.[45] So we think there may exit a strong interaction between those markers and vWF, and they together induce a proinflammatory state. Eventually, vWF serves as a potential biomarker for HFpEF severity.

In this study, first of all, we have found that HFpEF subjects have higher levels of vWF, IL-6, TNF-α, CRP, tPA, Gal-3, and NO. Then, we investigated the distribution of those plasma biomarkers among different grades of HFpEF patients, the results showed that highest levels vWF, IL-6, TNF-α, and CRP were observed in the most severe degree of HFpEF patients. We have further analyzed the level of vWF and those inflammatory factors and found that there was a positive association between graded IL-6, TNF-α, CRP, and high vWF levels. Finally, we conducted the multiple regression analysis and aforementioned association remained after adjustment for several variables.

4.2. Study limitation

We calculated the cutoff value for vWF as 16.02 ng/mL among HFpEF patients. We also analyzed the difference of all variables between low/medium/high vWF in HFpEF patients, and there was no significant difference between low/medium/high vWF but systolic blood pressure and high-density lipoprotein cholesterol. However, the results may be biased because of the sample size. Therefore, a larger number of patients are required to support the results of this study, and further background investigation might be needed to confirm the role of vWF in HFpEF.

5. Conclusion

Our study suggests that elevated vWF levels are associated with HFpEF and may serve as a potential biomarker for HFpEF severity. We also have found that increased vWF levels are positively correlated to IL-6, TNF-α, and CRP, which may provide a clue for further researching the pathogenesis of HFpEF.

Author contributions

MA wrote and reviewed the paper. YKG analyzed curated the data and responsible for the software and methodology. BB curated the data and references. JX supervised and validated the paper. All authors read and approved the final manuscript.

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