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ORIGINAL ARTICLE

Sex-related differences in plasma amino acids of patients with ST-elevation myocardial infarction and glycine as risk marker of acute heart failure with preserved ejection fraction

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Abstract

Nowadays, the problem of preventing acute heart failure (AHF) in patients with ST-elevation myocardial infarction (STEMI) and preserved left-ventricular ejection fraction (pLVEF) is still not completely resolved, especially in late-presented patients. The purpose of study was: (1) assessment of free plasma amino acid (PAA) alterations in STEMI patients [not receiving reperfusion therapy (RT)], depending on sex and LVEF; (2) analysis of development of late/persistent AHF more than 48 h after admission (pAHF) in STEMI patients with pLVEF depending on PAA levels. This prospective cohort study included 92 STEMI patients (33 women and 59 men), not receiving RT. The free PAA were investigated by ion-exchange liquid-column chromatography. The women had significantly higher PAA levels than men in general cohort and cohort with pLVEF ($n=69$). There were associations between female sex and pAHF in general cohort (OR 3.7, $p=0.004$) and cohort with pLVEF (OR 11.4, $p=0.0001$) by logistic regression. The association between pAHF and glycine level [OR 2.5, $p<0.0001$; AUC 0.84, $p<0.0001$; 86.7% sensitivity and 77.8% specificity for > 2.6 mg/dL] was revealed in cohort with pLVEF (including female and male). Glycine remained a predictor of pAHF with pLVEF by multivariable logistic regression adjusting for comorbidities, demographic and clinical variables. Higher rate of pAHF in female than in male STEMI patients with pLVEF is associated with higher plasma glycine in women. The glycine level may be genetically determinated by female sex. The plasma glycine > 2.6 mg/dL is a predictor of pAHF in STEMI with pLVEF (including female and male).

Keywords STEMI · Heart failure · Sex differences · Amino acids · Glycine

Introduction

The one of the risk factors of acute heart failure (AHF) in patients with ST-elevation myocardial infarction (STEMI) is female sex (Shah et al. 2012; Vicent et al. 2017). According to ACTION registry, 48% of STEMI patients with AHF have preserved left-ventricular ejection fraction (pLVEF) (Shah et al. 2012). Heart failure (HF) with pLVEF is observed almost twice as often in female patients and associated with increased vascular and myocardial stiffness in women compared to the men of the same age (Lam et al. 2011; Scantlebury and Borlaug 2011; Garg et al. 2017). Indeed, the microvascular disorders associated with diastolic dysfunction play an important role in the short-term and long-term prognoses of STEMI with pLVEF in patients receiving reperfusion therapy (RT) as well as not receiving RT (Reinstadler et al. 2020). Nowadays, the reperfusion therapy is a cornerstone in the treatment of STEMI. According to the recent studies, the percentage of STEMI patients

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not receiving RT has been decreased to 14% following the establishment of STEMI management network in developed European countries and USA (Dasari et al. 2016), but the situation could be exacerbated by the COVID-19 pandemic (Azul Freitas et al. 2021). However, 15 years ago in cohort of STEMI patients of OASIS-6 randomized study (2006) also, there were 17% patients presenting within 24 h after symptom onset and not receiving RT (Yusuf et al. 2006). Therefore, the percentage of STEMI patients not receiving RT remains unchanged (approximately 15% in Western Europe) for the last 15 years (Dharma 2020). Nowadays, in Southern Europe, approximately 20% of STEMI patients do not receive RT and up to 50% those STEMI patients are present in low-income and middle-income countries (Rosselló et al. 2017). These STEMI patients are characterized by the highest rates of complications and mortality.

However, regardless of treatment strategy for STEMI, the pathogenesis of AHF in patients with pLVEF is characterized by similar mechanisms of development. Maladaptive molecular processes can be an important cause of complications of STEMI; thus, amino acid metabolomic approach is important for improving short-term and long-term prognoses. The myocardial and vascular stiffness are accompanied by coronary microvessel inflammation, nitric oxide bioavailability disorders, mast cell infiltration of myocardium with development of myocardial fibrosis and associated with hyperhomocysteinemia (Vizzardi et al. 2009; Okuyan et al. 2010; Paulus and Tschöpe 2013). In recent studies, high plasma level of branched-chain amino acids has been associated with hospital mortality and increased risk of AHF after PCI in patients with STEMI (Du et al. 2018). In other study, the lowest and highest plasma levels of betaine (trimethyl derivative of glycine) were associated with increased risk of complications in patients with acute coronary syndrome. The association between higher plasma level of betaine and AHF development has been revealed (Garcia et al. 2019).

That is why important to elucidate, whether the amino acids can be indicators of the key causes of metabolic impairments and whether PAA can be causal biomarkers for the prediction of disease/complication; or PAA alterations are secondary and result from disease and hemodynamic disorders (Vizzardi et al. 2009; Xie et al. 2013). Moreover, some amino acids strongly associated with the genetic variants can provide useful tools for understanding causal directions of correlated phenotypes (Mittelstrass et al. 2011; Xie et al. 2013).

In clinical conditions, the development of cardiovascular complications is reliably associated with an increase in plasma homocysteine level, which can be higher in women than in men (Page et al. 2010; Zhong et al. 2017). The role of homocysteinemia in pathogenesis of AHF is controversial. In some studies, higher plasma level of homocysteine was associated with increased risk of complications regardless of LVEF value (Washio et al. 2011), while in others, the plasma level of homocysteine was not an independent predictor in patients with pLVEF (Agoston-Coldea et al. 2011).

The purpose of our study was: (1) assessment of free PAA alterations in STEMI patients (not receiving RT), depending on sex and LVEF value; (2) analysis of development of late/persistent AHF more than 48 h after admission (pAHF) in STEMI patients with pLVEF depending on PAA levels.

Methods

Participants

This prospective single-center cohort study included 92 patients with STEMI presenting within 24 h after symptom onset. The median age of patients was 57.6 (Interquartile Range (IQR) 9.0). There were 33 women and 59 men in the general STEMI cohort. The detailed characteristics of study cohort are presented in Table 1.

There was a control group ($n = 17$) with no difference by sex and age variables in comparison with the STEMI cohort (Table 1).

According to the criteria of American Heart Association (2013) and European Society of Cardiology (2018), a diagnosis of STEMI was defined as symptoms characteristic of cardiac ischemia with persistent ST segment elevation or a new left bundle branch block (LBBB) on electrocardiography (ECG) (O'Gara et al. 2013; Ibanez et al. 2018). The ECG criteria of STEMI included ST segment elevation of 2 mm in men and 1.5 mm in women for leads V_2 and V_3; 1 mm for leads V_1, $V_{4–6}$, I, II, III, aVL, and aVF; and 0.5 mm for leads V_3R and V_4R (right-sided leads) and $V_{7–9}$ (posterior leads) (Thygesen et al. 2012). Troponin *T* test was used in patients with LBBB without information about the time of LBBB onset.

The patients with pLVEF ($n = 69$) have been extracted from the general STEMI cohort of study. There were 26 women and 43 men in STEMI cohort with pLVEF (Table 1).

The cohort with pLVEF (including female and male STEMI patients) has been divided into two groups: the group of patients with pAHF ($n = 15$) and the group of patients without pAHF ($n = 54$) (Table 1).

The design of study is presented in Fig. 1.

The diagnosis of AHF was defined using the classification by Killip-Kimball (Ponikowski et al. 2016). The pAHF was defined as a persistence or onset symptoms of AHF Killip II–III more that 48 h after admission.

All the patients were recruited from the Cardiology Department of Kyiv City Clinical Hospital No. 3 (Kyiv, Ukraine) during 3 years. The study was approved by the local ethics committees and conducted in accordance

Table 1 Demographic and clinical characteristics of the study cohort

Variables[a]	Control group ($n=17$)	All STEMI patients ($n=92$)				STEMI with pLVEF ($n=69$)				STEMI with pLVEF ($n=69$)		
		Total[b] $n=92$	Women $n=33$	Men $n=59$	p[c]	Total[d] $n=69$	Women $n=26$	Men $n=43$	p[e]	With pAHF $n=15$	Without pAHF $n=54$	p[f]
Age, years	57.6 (9.0)	59.0 (10.0)	62.0 (11.0)	58.0 (10.0)	0.093	58.0 (13.0)	60.5 (13.0)	53.9 (16.0)	0.031	62.0 (11.0)	57.0 (14.0)	0.352
Female	8 (47.1)	33 (35.9)	–	–	–	26 (37.7)	–	–	–	12 (80.0)	14 (25.9)	< 0.001
BMI, kg/m^2	27.7 (5.4)	27.8 (3.7)	28.7 (3.3)	26.8 (2.4)	< 0.001	27.5 (3.5)	28.5 (3.5)	26.9 (2.5)	0.003	28.3 (4.0)	26.9 (3.1)	0.065
Obesity (BMI > 30 kg/m^2), n (%)	5 (33.3)	19 (20.6)	13 (39.4)	6 (10.2)	0.001	13 (18.8)	9 (34.6)	4 (9.3)	0.009	5 (33.3)	8 (14.8)	0.212
Time from symptoms onset to hospitalization, hours	–	12.0 (19.0)	12.0 (20.0)	12.0 (18.0)	0.955	12.0 (18.0)	15.5 (20.0)	12.0 (16.0)	0.708	10.0 (20.0)	12.0 (17.0)	0.449
AH, n (%)	–	77 (83.7)	30 (90.9)	47 (79.7)	0.161	57 (82.6)	24 (92.3)	33 (76.7)	0.098	13 (86.7)	44 (81.5)	0.639
Stable angina, n (%)	–	50 (54.4)	22 (66.7)	28 (47.5)	0.076	33 (47.8)	18 (69.2)	15 (34.9)	0.006	11 (73.3)	22 (40.7)	0.025
Previous MI, n (%)	–	11 (11.9)	5 (15.1)	6 (10.2)	0.710	5 (7.25)	4 (15.4)	1 (2.33)	0.122	3 (20.0)	2 (3.7)	0.112
CHF, n (%)	–	50 (54.4)	25 (75.8)	25 (42.4)	0.002	29 (42.0)	19 (73.1)	10 (23.3)	< 0.001	10 (66.7)	19 (35.2)	0.029
T2DM, n (%)	–	8 (8.7)	5 (15.1)	3 (5.1)	0.208	6 (8.7)	5 (19.2)	1 (2.3)	0.048	4 (26.7)	2 (3.7)	0.023
Smoking, n (%)	6 (35.3)	46 (50.0)	7 (21.2)	39 (66.1)	< 0.001	36 (52.2)	6 (23.1)	30 (69.8)	< 0.001	8 (53.3)	28 (51.9)	0.919
Clinical variables on admission												
Anterior MI, n (%)	–	40 (43.5)	17 (51.5)	35 (59.3)	0.468	33 (47.8)	14 (42.4)	19 (44.2)	0.436	6 (40.0)	27 (50.0)	0.493
AHF Killip II–III, n (%)	–	32 (34.8)	19 (57.6)	23 (38.9)	0.086	15 (21.7)	12 (46.2)	7 (16.3)	0.007	9 (60.0)	10 (18.5)	0.001
AF, n (%)	–	6 (6.5)	4 (12.1)	2 (3.4)	0.235	3 (4.4)	3 (11.5)	0	0.095	3 (20.0)	0	0.008
VT/VF, n (%)	–	10 (10.9)	3 (9.1)	7 (11.9)	0.682	2 (2.9)	0	2 (4.7)	0.707	0	2 (3.7)	0.910
Heart rate, per min	75.0 (18.0)	74.7 (16.5)	76.0 (19.0)	71.0 (16.0)	0.506	70.0 (15.0)	74.0 (14.0)	69.0 (15.0)	0.109	80.0 (13.0)	69.5 (18.0)	0.005
Sinus tachycardia > 80/min, n (%)	4 (23.5)	29 (31.5)	14 (42.4)	15 (25.4)	0.092	19 (27.5)	12 (46.2)	7 (16.3)	0.007	8 (53.3)	11 (20.4)	0.011
SBP, mm Hg	130 (10.0)	135.0 (40.0)	130.0 (40.0)	140.0 (40.0)	0.351	140.0 (40.0)	130.0 (50.0)	160.0 (30.0)	0.020	120.0 (50.0)	150.0 (30.0)	0.043
DBP, mm Hg	80.0 (5.0)	80.0 (20.0)	80.0 (0)	90.0 (20.0)	0.058	90.0 (20.0)	80.0 (10.0)	90.0 (20.0)	< 0.001	80.0 (15.0)	90.0 (20.0)	0.011
MAP, mm Hg	96.7 (8.3)	100.0 (23.3)	96.7 (13.3)	103.3 (26.7)	0.124	103.3 (23.3)	96.7 (16.7)	113.3 (23.3)	0.003	93.3 (26.7)	113.3 (23.3)	0.016
Sum of elevation ST in 12-ECG leads (mm)	–	5.0 (11.0)	6.0 (10.0)	5.0 (12.0)	0.560	5.0 (11.0)	7.0 (10.0)	5.0 (10.0)	0.955	5.0 (13.0)	5.0 (9.0)	0.930
Number of leads with elevation ST > = 1 mm	–	3.0 (3.0)	3.0 (3.0)	3.0 (2.0)	0.703	4.0 (3.0)	4.0 (3.0)	3.5 (3.0)	0.836	3.0 (4.0)	4.0 (2.0)	0.714

Table 1 (continued)

Variables[a]	Control group ($n=17$)	All STEMI patients ($n=92$)				STEMI with pLVEF ($n=69$)				STEMI with pLVEF ($n=69$)		
		Total[b] $n=92$	Women $n=33$	Men $n=59$	p[c]	Total[d] $n=69$	Women $n=26$	Men $n=43$	p[e]	With pAHF $n=15$	Without pAHF $n=54$	p[f]
Sum of elevation and depression ST in 12-ECG leads (mm)	–	11.5 (15.0)	14.5 (12.5)	9.5 (19.0)	0.288	8.5 (10.5)	11.0 (10.0)	6.5 (10.0)	0.235	14.0 (10.0)	7.0 (11.0)	0.157
Number of leads with elevation and depression ST > = 1 mm	–	6.0 (5.0)	8.0 (4.0)	6.0 (4.0)	0.017	6.0 (4.0)	7.0 (3.0)	5.0 (3.0)	0.043	8.0 (4.0)	5.0 (3.0)	0.026
Echocardiography variables on the admission												
LVEDI, ml/m^2	63.4 (16.5)	68.6 (19.7)[b]*	67.6 (19.8)	71.6 (20.3)	0.616	67.1 (15.3)	66.2 (14.0)	67.6 (16.8)	0.708	65.2 (19.2)	67.6 (11.9)	0.548
CI, L/min × m^2	2.9 (1.0)	2.3 (1.1)[b]*	2.5 (1.2)	2.2 (1.0)	0.360	2.4 (1.1)[d]*	2.7 (1.1)	2.2 (1.0)	0.118	2.8 (1.5)	2.3 (1.0)	0.323
LVEF, %	60.0 (11.2)	47.0 (12.8)[b#]	47.1 (9.9)	46.9 (15.5)	0.506	48.3 (8.4)[d#]	48.0 (10.6)	49.0 (7.9)	0.744	48.6 (8.8)	48.1 (9.2)	0.724
rLVEF (n, %)	–	23 (25.0)	7 (21.2)	16 (69.6)	0.530	–	–	–	–	–	–	–
Akinetic segments, score	–	4.0 (6.0)	4.0 (4.0)	3.0 (6.0)	0.890	2.0 (4.0)	2.0 (5.0)	2.0 (4.0)	0.745	2.0 (5.0)	2.0 (4.0)	0.619
Hypokinetic segments, score	–	4.0 (3.0)	3.0 (2.0)	5.0 (3.0)	0.063	4.0 (3.0)	3.0 (2.0)	4.0 (3.0)	0.378	4.0 (3.0)	4.0 (3.0)	0.503
Normokinetic segments, score	–	9.0 (6.5)	8.0 (6.0)	9.0 (7.0)	0.821	9.0 (3.0)	9.0 (3.0)	10.0 (4.0)	0.495	9.0 (4.0)	10.0 (3.0)	0.440
WMSI, score	–	1.7 (0.69)	1.8 (0.5)	1.6 (0.8)	0.808	1.6 (0.4)	1.7 (0.38)	1.5 (0.38)	0.286	1.7 (0.5)	1.6 (0.4)	0.703
V_E/V_A	1.2 (0.4)	0.85 (0.19)[b#]	0.82 (0.12)	0.89 (0.21)	0.013	0.85 (0.20)[d#]	0.78 (0.14)	0.89 (0.21)	0.025	0.76 (0.11)	0.87 (0.21)	0.073
$AccRate_E$, m/sec^2	7.2 (2.2)	6.0 (1.93)[b]*	6.4 (4.8)	6.0 (1.9)	0.730	5.7 (1.5)[d]**	6.4 (1.6)	5.7 (1.2)	0.392	8.6 (9.0)	5.7 (1.6)	0.957
$DecRate_E$, m/sec^2	3.8 (2.0)	3.3 (1.8)	3.0 (1.4)	3.3 (1.7)	0.188	3.2 (1.4)	2.9 (1.4)	3.2 (1.6)	0.954	2.9 (1.6)	3.2 (1.4)	0.682
$DecT_E$, msec	169.0 (87.0)	171.0 (38.0)	181.0 (53.0)	169.0 (35.0)	0.062	180.0 (45.0)	182.0 (58.0)	177.5 (36.0)	0.420	183.0 (23.0)	175.0 (44.5)	0.571
Blood test on the admission												
Hemoglobin, g/L	137.0 (16.0)	134.0 (18.0)	128.0 (22.0)	138.0 (20.0)	0.001	135.0 (18.0)	131.0 (22.0)	138.0 (20.0)	0.001	129.1 (15.5)	137.6 (16.4)	0.078
WBC, 10^9/L	6.1 (1.3)	9.4 (3.4)[b#]	9.4 (2.6)	9.2 (4.0)	0.808	9.2 (3.6)[d#]	9.4 (3.8)	9.1 (3.5)	0.811	9.8 (5.6)	9.2 (3.3)	0.521
ESR, mm/h	6.0 (4.0)	10.0 (8.0)[b#]	13.0 (7.0)	10.0 (6.0)	0.004	10.0 (7.0)[d]**	13.5 (7.0)	8.0 (5.0)	<0.001	14.0 (16.0)	9.0 (6.0)	0.005
FPG, mmol/L	4.4 (0.8)	5.7 (2.3)[b&]	6.2 (4.4)	5.2 (2.0)	0.084	6.0 (2.1)[d#]	6.5 (4.0)	5.5 (1.7)	0.013	6.5 (5.7)	5.7 (1.6)	0.029
Total protein, g/L	72.0 (9.0)	73.0 (11.0)	72.0 (9.0)	73.0 (12.0)	0.503	74.5 (11.0)	77.0 (11.0)	73.0 (12.0)	0.551	71.0 (12.0)	76.0 (9.0)	0.538
Albumin, g/L	32.0 (5.0)	34.5 (6.0)	32.0 (5.0)	36.0 (6.0)	0.281	32.0 (7.0)	32.0 (6.0)	36.0 (8.0)	0.148	32.0 (18.0)	34.0 (6.0)	0.473
Urea, mmol/L	5.6 (1.9)	6.9 (2.7)[b#]	6.7 (2.8)	6.9 (2.3)	0.961	6.7 (2.0)[d&]	6.7 (3.1)	6.8 (2.0)	0.859	6,8 (5.4)	6.7 (1.7)	0.137
Creatinine, mcmol/L	70.0 (35.0)	88.0 (21.0)[b&]	96.0 (22.0)	88.0 (20.0)	0.064	88.0 (16.0)[d]**	88.0 (30.0)	80.0 (10.0)	0.027	88.0 (32.0)	84.0 (10.0)	0.107

Table 1 (continued)

Variables[a]	Control group ($n=17$)	All STEMI patients ($n=92$)				STEMI with pLVEF ($n=69$)				STEMI with pLVEF ($n=69$)		
		Total[b] $n=92$	Women $n=33$	Men $n=59$	p[c]	Total[d] $n=69$	Women $n=26$	Men $n=43$	p[e]	With pAHF $n=15$	Without pAHF $n=54$	p[f]
eGFR, mL/min	109.8 (19.5)	79.4 (51.9)[b]**	52.8 (22.8)	90.9 (47.6)	< 0.001	83.3 (59.1)	52.8 (23.9)	98.4 (41.2)	< 0.001	61.2 (24.2)	92.1 (54.8)	< 0.001
TC, mmol/L	5.1 (1.6)	4.9 (2.4)	5.5 (3.3)	4.9 (1.8)	0.087	5.0 (2.3)	6.3 (3.3)	4.8 (1.8)	0.087	3.4 (1.7)	5.2 (2.5)	0.201
LDLC, mmol/L	3.1 (1.2)	3.0 (1.8)	3.5 (2.6)	3.0 (1.6)	0.147	3.1 (1.6)	4.2 (2.6)	2.9 (1.5)	0.147	2.1 (1.6)	3.2 (2.0)	0.145
HDLC, mmol/L	1.1 (0.3)	1.1 (0.16)	1.1 (0.7)	1.1 (0.04)	0.234	1.1(0.2)	1.2 (0.7)	1.1 (0.04)	0.234	0.7 (0.6)	1.1 (0.16)	0.271
TG, mmol/L	1.3 (0.6)	1.5 (0.5)	1.9 (1.1)	1.5 (0.53)	0.576	1.5 (0.6)	1.5 (1.1)	1.4 (0.5)	0.576	1.5 (0.9)	1.4 (0.6)	0.310
Medications												
ACE inhibitors, *n* (%)	–	49 (53.3)	19 (57.6)	30 (50.9)	0.535	35 (50.7)	13 (50.0)	22 (51.2)	0.925	8 (53.3)	27 (50.0)	0.819
Beta-blockers, *n* (%)	–	81 (88.0)	30 (90.9)	51 (86.4)	0.526	59 (85.5)	24 (92.3)	35 (81.4)	0.212	14 (93.3)	45 (83.3)	0.330
Loop diuretic, *n* (%)	–	40 (43.5)	18 (54.6)	22 (37.3)	0.109	26 (37.7)	15 (57.7)	11 (25.9)	0.008	11 (73.3)	15 (27.8)	0.001
Statins, *n* (%)	–	83 (90.2)	29 (87.9)	54 (91.5)	0.531	60 (87.0)	21 (80.8)	39 (90.7)	0.230	12 (80.0)	49 (90.7)	0.472
MCRA, *n* (%)	–	28 (30.4)	16 (48.5)	12 (20.3)	0.005	15 (21.7)	10 (38.5)	5 (11.6)	0.020	7 (46.7)	8 (14.8)	0.008
Antidiabetic, *n* (%)	–	8 (8.7)	5 (15.1)	3 (5.1)	0.208	6 (8.7)	5 (19.2)	1 (2.3)	0.048	4 (26.7)	2 (3.7)	0.023

AH arterial hypertension, *AF* atrial fibrillation (paroxysmal), *AHF* acute heart failure, $AccRate_E$ acceleration rate of early mitral diastolic inflow velocity, *BMI* body mass index, *CHF* chronic heart failure, *CI* cardiac index, *DBP* diastolic blood pressure, $DecRate_E$ deceleration rate of early mitral diastolic inflow velocity, $DecT_E$ deceleration time of early mitral diastolic inflow velocity, *ESR* erythrocyte sedimentation rate, *eGFR* estimated glomerular filtration rate, *FPG* fasting plasma glucose, *HDLC* high-density lipoprotein cholesterol, *LDLC* low-density lipoprotein cholesterol, *LVEDI* left-ventricular end-diastolic index, *LVEF* left-ventricular ejection fraction, *MAP* mean arterial pressure, *MCRA* mineralocorticoid receptor antagonists, *MI* myocardial infarction, *rLVEF* reduced left-ventricular ejection fraction, *SBP* systolic blood pressure, *STEMI* ST-elevation myocardial infarction, *TC* total cholesterol, *T2DM* type 2 diabetes mellitus, *TG* triglycerides, *pAHF* persistent/late AHF after 48 h of admission, V_E/V_A ratio of the peak early (V_E) to peak late atrial (V_A) of mitral diastolic inflow velocity, *WBC* white blood cells of complete blood count test, *WMSI* wall motion score index

[a]Continuous variables are presented as median and interquartile range (IQR). Categorical variables are presented as frequency and percentage [*n* (%)]

[b]Statistically significant differences between control group and general STEMI cohort (all patients) are presented as $*p<0.05$, $**p<0.01$, $^{\&}p<0.001$, $^{\#}p<0.0001$

[c]Statistically significant differences between female and male groups of general STEMI cohort

[d]Statistically significant differences between control group and STEMI cohort with pLVEF (all patients) are presented as $*p<0.05$, $**p<0.01$, $^{\&}p<0.001$, $^{\#}p<0.0001$

[e]Statistically significant differences between female and male groups of STEMI cohort with pLVEF

[f]Statistically significant differences between groups with pAHF and without pAHF of STEMI cohort with pLVEF (including female and male patients)

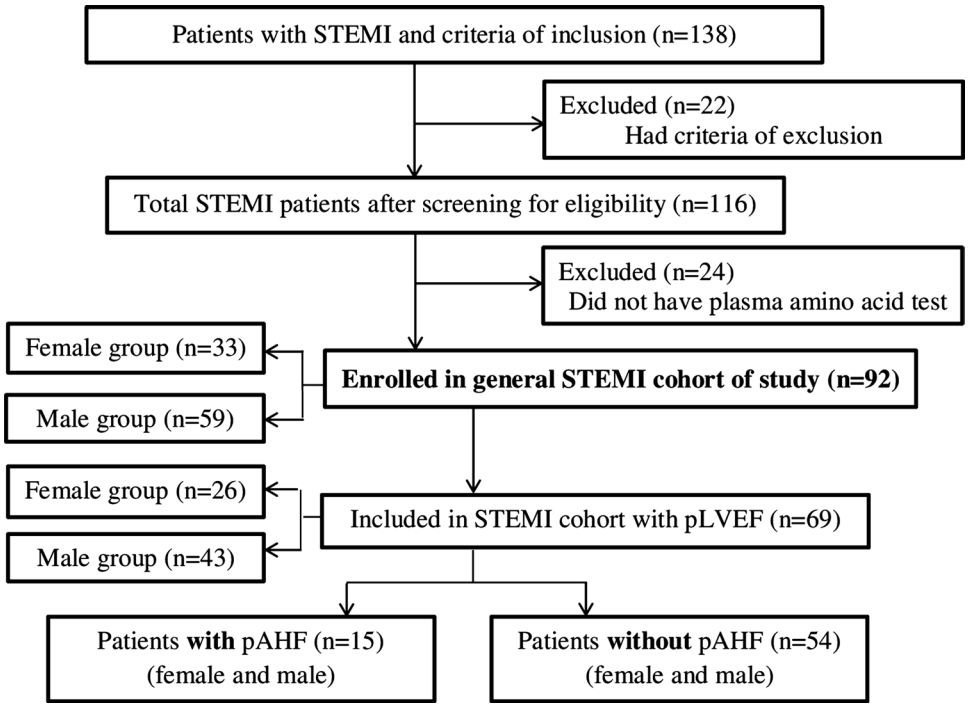

Fig. 1 The design of study. *pAHF* persistent/late AHF more than 48 h after admission, *pLVEF* preserved left-ventricular ejection fraction, *STEMI* ST-elevation myocardial infarction

with the Helsinki Declaration of 1971, as revised in 1982. Informed consent was obtained from all participants.

In general STEMI cohort, the median time from symptom onset to admission was 12.0 (IQR 19.0) hours [50 (54.3%) patients presented more than 12 h after symptom onset]. There were no significant differences by this variable between the groups of study (Table 1).

The inclusion criteria were diagnosis of STEMI, admission within 24 h after symptom onset, not receiving RT, age up to 74. The reasons for not receiving RT were late presentation of STEMI (more than 12 h after symptom onset), inability to transfer the patients to PCI center within 12 h after symptom onset with contraindications to thrombolysis (current oral anticoagulants [6 patients (6.5%)], internal bleeding within last month [6 patients (6.5%)], stroke or transient ischemic attack within last 6 months [5 patients (5.4%)], surgery within last 3 weeks [7 patients (7,6%)], retinal hemorrhage [2 patients (2.2%)], head/facial trauma within last 3 month [4 patients (4.3%)], arterial blood pressure systolic > 180 mm Hg or diastolic > 110 mm Hg [9 patients (9.8%)], known cerebral vascular lesion [2 patients (2.2%)] and non-compressible vascular puncture [1 patients (1.1%)].

The exclusion criteria were cardiogenic shock on admission, complete atrioventricular block; permanent, long-standing persistent, persistent (sustained beyond 7 days) or paroxysmal (with more than 24-h episode of arrhythmia) variants of atrial fibrillation, that making impossible the evaluation of diastolic function of left ventricle by echocardiography (EchoCG); severe valvular heart diseases, previous chronic HF (CHF) NYHA III-IV, type 1 diabetes mellitus and type 2 diabetes mellitus complicated by hyperglycaemic hyperosmolar state, diabetic ketoacidosis or severe hypoglycaemia (according to the ISPAD guidelines) (Wolfsdorf et al. 2018), renal failure (estimated glomerular filtration rate (eGFR) < 30 mL/min), diagnosis of chronic liver disease, chronic obstructive pulmonary disease and/or bronchial asthma, anemia (hemoglobin level < 100 g/L).

The patients received basic treatment including angiotensin-converting enzyme (ACE) inhibitors, β-blockers and statins without significantly differences between groups (Table 1). All patients received anticoagulation and dual antiplatelet therapy. The opiates, diuretics, nitroglycerin infusion, dobutamine, antiarrhythmic drugs were used according to medical indications.

The information about medications of chronically treatment of patients before the onset of STEMI symptoms has been analyzed. In general STEMI cohort, 50 (54.3%) patients took ACE inhibitors, 35 (38.1%)—calcium channel blockers, 44 (47.8)—β-blockers, 42 (45.6%)—statins, 6 (6.5)—antidiabetic drugs. There were no statistically significant differences by these variables between the clinical groups of the study.

The comorbidities, demographic, clinical, laboratory, and instrumental data were collected on admission. Obesity was defined as the body mass index (BMI) > 30 kg/m^2; eGFR was calculated using Cockroft–Gault formula. In all cases, the daily standard 12-lead electrocardiogram (ECG) was registered and complete standard transthoracic echocardiography (EchoCG) using the ultrasound system

Aloka SSD 1700 (Japan) was performed on the admission day. The pLVEF was defined as value of LVEF > 40%.

Sample collection and amino acid analysis

Free PAA were investigated by ion-exchange liquid-column chromatography according to the classical method of Stein and Moore (using the automatic amino acid analyzer Mikrotechna AAA-339, Czech Republic). Venous blood samples for the PAA measurement were obtained as early as possible after admission with the condition of 12-h fasting period before the collection of blood sample. Blood samples were drawn into evacuated glass tubes as quickly as possible. Plasma samples were obtained by centrifugation of the blood samples (15 min, 3000 g). The proteins of 1 mL plasma samples were precipitated by the addition 1 mL of 3% (vol/vol) sulfosalicylic acid/water and centrifugation (30 min, 4500 g) for separation of the supernatant. Amino acids were separated on a 295 × 3.7 mm column with sulfopolystyrene cation (Ostion LG ANB). The elution was performed at different temperatures conditions 38ºC and 58.5ºC with eluent flow rate 12 mL/h. As the eluents were used five buffer solutions (pH 2.75, 2.95, 3.2, 3.8, and 5.0) of 0.25 mol/L citrate lithium. After postcolumn reaction with ninhydrin reagent, amino acids were detected spectrophotometrically.

Statistical analysis

All statistical tests were performed with software package StatSoft, Inc. (2004) STATISTICA 7.0 and MedCalc Statistical Software version 12.7.8 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

The distributions of continuous variables were analyzed by Shapiro–Wilk's *W* normality test.

The continuous variable, possibly normally distributed, is presented as mean and standard deviations (SD). Statistical analysis was performed using ANOVA followed by Tukey's post hoc test which was applied if a significant difference among means of variable between groups was detected.

Not-normally distributed continuous variable is presented as median and interquartile range (IQR). The Mann–Whitney *U* criterion was used to analyze the differences in not-normal distributed variables between independent groups.

Categorical variable is presented as frequency and percentage (*n*, %). Pearson Chi-square (χ^2) criterion (adjusted Yeats, if the frequency of one of the parameters was less than five) was used to analyze the differences in categorical variables between independent groups.

Results were considered statistically significant at $p < 0.05$.

Logistic regression models

The associations between comorbidities, demographic, clinical, PAA predictors and pAHF were analyzed in general STEMI cohort and STEMI cohort with pLVEF (including female and male patients) using univariable logistic regression. The results are presented as odds ratio (OR) and 95% confidence interval (95% CI). Multivariable logistic regression analysis (by forward stepwise variable selection with "*P*- to-enter" set at 0.05, and the "*P*-to-remove" at 0.10) was applied to examine the independent association between every PAA variable (significant by the result of univariable logistic regression analysis) and pAHF in general STEMI cohort and STEMI cohort with pLVEF (including female and male patients). All comorbidities, demographic, and clinical variables (significant by the results of univariable logistic regression analysis) were included in the five multivariable logistic regression models: model 1 including PAA variable, AHF on admission, number of ECG leads with elevation and depression more than 1 mm, EchoCG ratio of the early peak to late atrial peak of mitral diastolic inflow velocity (V_E/V_A); model 2—PAA variable, age, sex, stable angina, CHF, smoking; model 3—PAA variable, sex, CHF, type 2 diabetes mellitus, obesity; model 4—PAA variable, sinus tachycardia > 80/min, paroxysmal atrial fibrillation, erythrocyte sedimentation rate (ESR) value, eGFR value, plasma level of urea on admission; model 5—PAA variable, AHF on admission, type 2 diabetes mellitus, eGFR value.

The quality of regression models, their sensitivity and specificity were examined using receiver-operator characteristic (ROC) analysis. The results of ROC analysis are presented as area under curve (AUC) with standard error (SE) and 95% CI.

The differences were considered statistically significant at $p < 0.05$.

Results

Descriptives of general STEMI cohort

The significant differences in EchoCG variables [higher value of left-ventricular end-diastolic index (LVEDI), lower values of LVEF, cardiac index, EchCG ratio V_E/V_A and acceleration rate of early mitral diastolic inflow velocity ($AccRate_E$)] were revealed in general STEMI cohort compared to the control group (Table 1). The patients with STEMI had significantly higher levels of white blood cells (WBC), ESR, fasting plasma glucose, urea, creatinine and lower eGFR compared to the control group. There was no significant difference in lipidogram between general STEMI cohort and control group (Table 1).

Descriptives of female and male groups in general STEMI cohort

There was no significant difference in the age between women and men in general STEMI cohort (Table 1). The female group had significantly higher BMI, higher prevalences of obesity and CHF, much fewer smokers than male group. There was no significant difference in prevalences of anterior localization of STEMI and AHF Killip II–III on admission between female and male groups. The higher number of ECG leads with elevation and depression more than 1 mm and lower EchoCG ratio V_E/V_A of diastolic function of left ventricle were revealed in female group than in male. There were no differences in other EchoCG variables between female and male groups. Women had significantly lower levels of hemoglobin and eGFR, and higher ESR compared to the men. There was no significant difference in lipidogram between female and male groups (Table 1).

In female group of general STEMI cohort, there was significantly higher prevalence of pAHF compared to the male group (17 (51.5%) vs 15 (25.4%), $p = 0.012$, respectively).

Descriptives of STEMI cohort with pLVEF (including female and male)

There were no significant differences in the age and sex characteristics between STEMI cohort with pLVEF and control group (Table 1). The significantly lower values of LVEF, cardiac index, EchoCG ratio V_E/V_A and $AccRate_E$ were revealed in STEMI cohort with pLVEF compared to control group. The patients of STEMI cohort with pLVEF had significantly higher levels of WBC, ESR, fasting plasma glucose, urea and creatinine compared to the control group. There were no significant differences in eGFR and lipidogram between STEMI cohort with pLVEF and control group (Table 1).

Descriptives of female and male groups of STEMI cohort with pLVEF

The female group with pLVEF was significantly older [60.5 (IQR 13.0)] than male (53.9 (IQR 16.0), $p = 0.031$). There were significantly higher BMI, higher prevalence of obesity, stable angina, CHF, type 2 diabetes mellitus and lower prevalence of smoking in female group than in male with pLVEF (Table 1). Higher prevalence of AHF Killip II–III on admission was revealed in women compared to the men of STEMI cohort with pLVEF (46.2% vs 16.3%, $p = 0.007$, respectively). On admission the values of arterial blood pressure [systolic (SBP), diastolic (DBP), mean arterial pressure (MAP)] were lower and the prevalence of cases with heart rate > 80/min was higher in the female group with pLVEF than in male (Table 1).

The higher number of ECG leads with elevation and depression more than 1 mm was revealed in ECG of women compared to men with STEMI and pLVEF (Table 1).

There were no differences in EchoCG variables between female and male groups with pLVEF, except significantly lower ratio V_E/V_A in women compared to the men. There was no difference in LVEF values on admission between female and male group with pLVEF. Women with pLVEF had significantly lower hemoglobin and eGFR, higher ESR and creatinine compared to the men. There was no significant difference in lipidogram between female and male groups (Table 1).

Women with STEMI and pLVEF had significantly higher prevalence of pAHF compared to the men [12 (46.2%) vs 3 (7.0%), $p = 0.0004$, respectively]. There was significant difference in the prevalence of diuretic therapy between these groups: higher in female than in male (Table 1).

Descriptives of groups with pAHF and without pAHF in STEMI cohort with pLVEF (including female and male)

There was no significant difference by age between groups with pAHF and without pAHF (Table 1). These was a significant difference in sex variable between these groups [12 women (80.0%) in group with pAHF vs 14 (25.9%) in group without pAHF, $p < 0.001$]. There were higher prevalences of stable angina, CHF and type 2 diabetes mellitus in group with pAHF than in group without pAHF (Table 1). The patients with pAHF had higher rate of AHF on admission than patients without pAHF (60.0% vs 18.5%, $p = 0.001$, respectively). The higher prevalences of sinus tachycardia > 80/min and paroxysmal atrial fibrillation, lower values of SBP, DBP, MAP and higher number of ECG leads with elevation and depression more than 1 mm were revealed in patients with pAHF compared to the patients without pAHF. There was no significant difference in EchoCG variables between groups with pAHF and without pAHF. The group with pAHF had higher ESR, higher fasting plasma glucose and lower eGFR compared to the group without pAHF. There was no significant difference in lipidogram between the groups with pAHF and without pAHF (Table 1).

PAA characteristics

General STEMI cohort (including female and male)

As shown in Table 2, the patients with STEMI had significantly higher plasma levels of ornithine (by 2.2 times), glutamic acid (by 2.2 times), alanine (by 1.7 times), glutamine (by 1.6 times), leucine (by 1.6 times), serine (by 1.5 times) and lower level of arginine (by 1.6 times) compared to the

Table 2 The free PAA concentrations in STEMI patients

PAA[a], mg/dL	Control group ($n=17$) Median (IQR)[a]	All STEMI patients ($n=92$) Median (IQR)[a]				STEMI and pLVEF ($n=69$) Median (IQR)[a]				STEMI with pLVEF ($n=69$) Median (IQR)[a]		
		Total[b] ($n=92$)	Women ($n=33$)	Men ($n=59$)	p^c	Total[d] ($n=69$)	Women ($n=26$)	Men ($n=43$)	p^e	With pAHF ($n=15$)	Without pAHF ($n=54$)	p^f
Hcy	0.056 (0.048)	0.069 (0.058)	0.075 (0.079)	0.063 (0.044)	0.212	0.069 (0.055)	0.080 (0.057)	0.063 (0.035)	0.020	0.082 (0.035)**	0.064 (0.053)	0.076
Lys	1.870 (1.213)	2.628 (2.015)	3.509 (1.347)	2.147 (1.550)	0.011	2.247 (2.117)	3.468 (2.459)	2.123 (1.538)	0.007	3.628 (1.297)[&]	2.077 (1.893)	0.002
His	1.016 (0.366)	1.300 (0.882)	1.418 (0.809)	1.292 (0.904)	0.146	1.267 (0.882)	1.420 (0.982)	1.182 (0.746)	0.039	1.550 (0.578)**	1.172 (0.739)	0.002
Arg	1.641 (0.609)	1.057 (1.083)*	1.318 (1.177)	0.842 (1.081)	0.031	0.933 (1.147)**	1.192 (1.078)	0.727 (1.215)	0.039	1.318 (1.351)	0.828 (1.173)**	0.037
Orn	0.776 (0.624)	1.710 (1.472)[&]	2.108 (1.796)	1.485 (0.982)	0.063	1.698 (1.476)**	2.081 (1.773)	1.476 (0.919)	0.026	2.480 (1.329)[#]	1.469 (1.172)	0.001
Asp	0.548 (0.455)	0.808 (0.719)	1.061 (0.500)	0.643 (0.565)	0.013	0.705 (0.661)	1.013 (0.914)	0.509 (0.439)	0.009	1.061 (0.357)	0.557 (0.570)	< 0.001
Thr	1.223 (0.565)	1.288 (0.986)	1.431 (0.774)	1.192 (0.988)	0.029	1.192 (0.914)	1.420 (0.928)	0.993 (0.960)	0.023	1.431 (0.404)	0.993 (0.989)	0.013
Ser	1.122 (0.689)	1.738 (1.197)*	2.151 (0.879)	1.554 (0.895)	0.007	1.557 (1.147)	2.193 (1.934)	1.393 (0.648)	0.003	2.237 (0.593)[&]	1.393 (0.903)	< 0.001
Glu	1.704 (0.990)	3.765 (4.746)**	4.032 (4.154)	3.317 (4.091)	0.009	3.317 (1.147)**	3.975 (4.576)	2.833 (3.200)	0.003	5.757 (4.147)**	2.826 (2.916)*	0.009
Pro	0.898 (0.396)	1.159 (1.151)	1.150 (1.332)	1.168 (1.150)	0.593	1.008 (1.247)	1.200 (1.527)	0.808 (1.120)	0.269	1.769 (1.919)*	0.764 (1.289)	0.021
Gly	1.455 (1.319)	2.243 (1.711)	3.248 (1.582)	2.057 (1.262)	0.0007	2.158 (1.810)	3.434 (3.186)	1.826 (0.840)	0.002	3.535 (2.094)**	1.826 (1.386)	< 0.001
Ala	2.355 (2.072)	4.075 (3.071)**	5.330 (3.501)	3.912 (2.559)	0.003	3.912 (2.453)**	5.334 (4.624)	3.145 (1.314)	0.0004	6.737 (3.822)[&]	3.258 (1.566)*	< 0.001
Cys	0.300 (0.199)	0.449 (0.390)	0.422 (0.245)	0.510 (0.584)	0.169	0.423 (0.428)	0.401 (0.280)	0.462 (0.424)	0.052	0.307 (0.184)	0.431 (0.427)	0.493
Val	2.014 (0.935)	2.502 (2.222)	3.238 (1.784)	2.219 (1.651)	0.008	2.338 (1.622)	3.236 (2.446)	1.892 (1.501)	0.005	3.238 (2.335)[&]	1.963 (1.501)	0.001
Met	0.259 (0.158)	0.336 (0.284)	0.420 (0.317)	0.294 (0.207)	0.022	0.294 (0.224)	0.419 (0.317)	0.235 (0.163)	0.004	0.495 (0.136)[&]	0.235 (0.190)	< 0.001
Ile	0.766 (0.470)	0.794 (0.697)	0.854 (0.713)	0.761 (0.444)	0.113	0.764 (0.402)	0.853 (0.668)	0.643 (0.498)	0.058	0.854 (0.489)*	0.646 (0.349)	0.033
Leu	1.241 (1.117)	1.931 (1.630)**	2.751 (1.138)	1.677 (1.248)	0.013	1.684 (1.402)*	2.684 (1.662)	1.520 (0.945)	0.007	2.751 (1.226)[&]	1.521 (0.990)	0.002
Tyr	0.822 (0.249)	0.887 (0.691)	1.283 (0.981)	0.816 (0.598)	0.001	0.881 (0.590)	1.215 (0.638)	0.784 (0.417)	0.001	1.283 (0.343)[#]	0.784 (0.415)	< 0.001
Phe	1.069 (0.320)	1.478 (1.848)	2.503 (1.025)	1.200 (1.409)	0.011	1.200 (1.763)	2.538 (2.793)	0.996 (0.761)	0.005	2.702 (1.655)[&]	0.996 (1.367)	< 0.001
Gln	2.964 (2.623)	4.603 (5.189)**	5.745 (5.551)	4.502 (4.753)	0.105	3.723 (4.206)	4.234 (4.721)	3.703 (3.010)	0.055	5.745 (3.671)**	3.702 (3.015)	0.032
Total PAA	26.505 (5.835)	38.450 (23.512)*	44.548 (18.723)	31.314 (20.853)	0.014	42.671 (19.239)	42.724 (33.276)	27.524 (15.167)	0.012	43.778 (19.317)[&]	27.524 (18.383)	< 0.001

PAA plasma amino acids, *pAHF* persistent/late AHF after 48 h of admission, *pLVEF* preserved left-ventricular ejection fraction, *STEMI* ST-elevation myocardial infarction

[a]IQR, interquartile range; the differences between groups were analyzed using the Mann–Whitney *U* criterion

[b]Statistically significant differences between control group and general STEMI cohort (all patients) are presented as *p < 0.05, **p < 0.01, [&]p < 0.001

[c]Statistically significant differences between female and male groups of general STEMI cohort

[d]Statistically significant differences between control group and STEMI cohort with pLVEF (all patients) are presented as *p < 0.05, **p < 0.01

[e]Statistically significant differences between female and male groups of STEMI cohort with pLVEF

[f]Statistically significant differences between groups with pAHF and without pAHF of STEMI cohort with pLVEF (including female and male patients)

control group. The total aminoacidemia was also higher in general STEMI cohort by 1.5 times in comparison with control group (Table 2).

Female and male groups of general STEMI cohort

The total aminoacidemia was significantly higher (by 1.4 times) in female than in male group. In women with STEMI, there were significantly increased levels of phenylalanine (by 2.1 times), aspartic acid (by 1.7 times), lysine (by 1.6 times), arginine (by 1.6 times), glycine (by 1.6 times), leucine (by 1.6 times), tyrosine (by 1.6 times), glutamine (by 1,6 times), valine (by 1.5 times), serine (by 1.4 times), alanine (by 1.4 times), methionine (by 1.4 times), threonine (by 1.2 times) and glutamic acid (by 1.2 times) in comparison with men (Table 2).

STEMI cohort with pLVEF (including female and male)

The patients of STEMI cohort with pLVEF had significantly higher plasma levels of ornithine (by 2.2 times), glutamic acid (by 1.9 times), alanine (by 1.7 times), leucine (by 1.4 times) and lower level of arginine (by 1.8 times) compared to the control group. There was no difference in the total aminoacidemia between STEMI cohort with pLVEF and control group (Table 2).

Female and male group of STEMI cohort with pLVEF

The total aminoacidemia was significantly higher (by 1.6 times) in female than in male group with pLVEF. In women with STEMI and pLVEF, there were significantly increased levels of phenylalanine (by 2.5 times), aspartic acid (by 2,0 times), glycine (by 1.9 times), methionine (by 1.9 times), leucine (by 1.8 times), alanine (by 1.7 times), valine (by 1.7 times), lysine (by 1.6 times), arginine (by 1.6 times), tyrosine (by 1.5 times), serine (by 1.6 times), ornithine (by 1.4 times), threonine (by 1.4 times), glutamic acid (by 1.4 times), homocysteine (by 1.3 times) and histidine (by 1.2 times) compared to the men with pLVEF (Table 2).

Groups with pAHF and without pAHF in STEMI cohort with pLVEF (including female and male)

There were significantly higher levels of majority of PAA in patients with pLVEF and pAHF in comparison with the control group: total aminoacidemia (by 1.7 times) with increased levels of glutamic acid (by 3.4 times), ornithine (by 3.2 times), alanine (by 2.8 times), phenylalanine (by 2.5 times), glycine (by 2.4 times), leucine (by 2.2 times), serine (by 2.0 times), proline (by 2.0 times), lysine (by 1.9 times), aspartic acid (by 1,9 times), methionine (by 1.9 times), glutamine (by 1.9 times), valine (by 1.6 times), tyrosine (by 1.6 times), homocysteine (by 1.5 times), histidine (by 1.5 times), threonine (by 1.2 times) and isoleucine (by 1,1 times) (Table 2).

In the group without pAHF with pLVEF, significantly higher levels of glutamic acid (by 1.7 times), alanine (by 1.4 times) and significantly lower level of arginine (by 2.0 times) were revealed in comparison with control group (Table 2).

There were significantly differences in the levels of all PAA, except homocysteine and cysteine, between groups with pAHF and without pAHF. The patients with pAHF had higher levels of total aminoacidemia (by 1.6 times) with increased levels of phenylalanine (by 2.7 times), proline (by 2.3 times), alanine (by 2.1 times), methionine (by 2.1 times), glutamic acid (by 2.0 times), aspartic acid (by 1,9 times), glycine (by 1.9 times), leucine (by 1.8 times), lysine (by 1.7 times), ornithine (by 1.7 times), arginine (by 1.6 times), serine (by 1.6 times), valine (by 1.6 times), tyrosine (by 1.6 times), glutamine (by 1.6 times), threonine (by 1.4 times), histidine (by 1.3 times) and isoleucine (by 1,3 times) (Table 2).

Logistic regression analysis

Univariable logistic regression models with pAHF and comorbidities, demographic, clinical variables

The significant association between female sex, stable angina, CHF, AHF Killip II–III on admission, sinus tachycardia more than 80/min on admission, number of ECG leads with elevation and depression ST more than 1 mm, ESR, plasma urea and eGFR on admission as predictors and pAHF development were revealed by univariable logistic regression in general STEMI cohort as well as in STEMI cohort with pLVEF (including women and men) (Table 3). In STEMI cohort with pLVEF, the highest strength of association with pAHF was revealed for female sex (OR 11.4, $p = 0.0001$), type 2 diabetes mellitus (OR 9.45, $p = 0.012$) and AHF on admission (OR 6.61, $p = 0.002$) (Table 3).

Univariable logistic regression models with pAHF and PAA variables

As shown in Table 4, significant associations between PAA variables and pAHF in STEMI cohort with pLVEF (including female and male) were revealed by univariable logistic regression for all PAA, except homocysteine, arginine, proline and isoleucine. The most prominent associations of pAHF have been revealed with methionine (OR 375.2, $p < 0.0001$), aspartic acid (OR 10.3, $p < 0.0001$), tyrosine (OR 4.34, $p < 0.0001$), histidine (OR 3.41, $p = 0.0001$), threonine (OR 3.32, $p = 0.002$), serine (OR 3.20, $p < 0.0001$),

Table 3 Univariable logistic regression analysis including comorbidities, demographic and clinical variables in general STEMI cohort and STEMI cohort with pLVEF (including female and male patients) for prediction of pAHF

Variables[a]	All STEMI patients ($n=92$)[b]			STEMI with pLVEF ($n=69$)[b]		
	OR	95% CI	p[c]	OR	95% CI	p[c]
Age	1.68*$^{\#\#}$	1.01–1.13	0.009	1.03	0.97–1.10	0.338
Female sex	3.72**$^{\#\#\#}$	1.47–9.43	0.004	11.4***$^{\#\#\#}$	2.73–47.6	0.0001
Stable angina	3.92**$^{\#\#\#}$	1.50–10.3	0.003	4.02*$^{\#\#\#}$	1.10–14.5	0.024
Previous MI	6.33*$^{\#\#\#}$	1.52–26.4	0.006	6.51$^{\#\#\#}$	0.94–44.8	0.053
CHF	8.69***$^{\#\#\#}$	2.89–26.1	0.00001	3.68*$^{\#\#\#}$	1.07–12.6	0.029
Type 2 diabetes mellitus	2.00$^{\#\#}$	0.46–8.77	0.355	9.45*$^{\#\#\#}$	1.48–60.2	0.012
AHF Killip II-III on admission	11.9***$^{\#\#\#}$	4.08–34.8	< 0.00001	6.61**$^{\#\#\#}$	1.86–23.3	0.002
Sinus tachycardia > 80/min (on admission)	5.73***$^{\#\#\#}$	2.17–15.1	0.0002	4.46*$^{\#\#\#}$	1.30–15.3	0.015
Sum of elevation and depression ST in 12-ECG leads (mm) (on admission)	1.03$^{\#\#}$	0.99–1.07	0.139	1.02$^{\#\#}$	0.97–1.07	0.431
Number of ECG leads with elevation and depression ST > = 1 mm (on admission)	1.29**$^{\#\#\#}$	1.08–1.54	0.002	1.31*$^{\#\#}$	1.02–1.67	0.022
rLVEF	10.2***$^{\#\#\#}$	3.37–30.9	0.00001	–	–	–
WMSI (on admission)	5.33**$^{\#\#}$	1.67–17.0	0.001	1.16	0.16–8.19	0.881
V_E/V_A (on admission)	0.74	0.08–7.04	0.788	0.90	0.06–13.7	0.937
$AccRate_E$, m/sec^2 (on admission)	1.67*$^{\#\#}$	1.04–2.69	0.001	1.65$^{\#}$	0.86–3.16	0.093
$DecRate_E$, m/sec^2 (on admission)	1.66**$^{\#\#\#}$	1.15–2.40	0.004	1.12	0.63–1.99	0.690
$DecT_E$, msec (on admission)	0.98*	0.97–0.99	0.016	1.00	0.98–1.03	0.701
ESR, mm/h (on admission)	1.05*$^{\#\#\#}$	1.01–1.11	0.012	1.07*$^{\#\#\#}$	1.01–1.12	0.004
Plasma urea, mmol/L (on admission)	1.36**$^{\#\#\#}$	1.10–1.68	0.002	1.30*$^{\#\#}$	1.02–1.66	0.026
Plasma creatinine, mcmol/L (on admission)	1.03*$^{\#\#}$	1.01–1.06	0.006	1.02$^{\#}$	0.99–1.05	0.089
eGFR, mL/min (on admission)	0.96***$^{\#\#}$	0.93–0.98	< 0.00001	0.96**$^{\#}$	0.93–0.99	0.0003

AHF acute heart failure, $AccRate_E$ acceleration rate of early mitral diastolic inflow velocity, *CHF* chronic heart failure, $DecRate_E$ deceleration rate of early mitral diastolic inflow velocity, $DecT_E$ deceleration time of early mitral diastolic inflow velocity, *ESR* erythrocyte sedimentation rate, *eGFR* estimated glomerular filtration rate, *MI* myocardial infarction, *pAHF* persistent/late AHF after 48 h of admission, *pLVEF* preserved left-ventricular ejection fraction, *rLVEF* reduced left-ventricular ejection fraction, *STEMI* ST-elevation myocardial infarction, V_E/V_A ratio of the peak early (V_E) to peak late atrial (V_A) of mitral diastolic inflow velocity, *WMSI* wall motion score index

[a]Variables that were statistically significant for both cohorts are presented in bold

[b]*OR* odds ratio, *CI* confidence interval; *$p<0.05$, **$p<0.01$, ***$p<0.001$—significance of proper coefficient of variable in univariable logistic regression model; $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$—significance of constant B0 in univariable logistic regression model

[c]Significance of coefficient χ^2 in univariable logistic regression model

ornithine (OR 2.78, $p<0.0001$), glycine (OR 2.49, $p<0.0001$), leucine (OR 2.29, $p=0.0003$), phenylalanine (OR 2.26, $p=0.0003$) and lysine (OR 2.17, $p=0.0002$) (Table 4).

Multivariable logistic regression models

Multivariable logistic regression analysis, including significant comorbidities, demographic and clinical predictors (presented in Table 3) and significant PAA predictors (presented in Table 4) of pAHF in STEMI cohort with pLVEF (including female and male), revealed that only plasma level of glycine, not other PAA, remained a significant independent predictor of pAHF in all five multivariable logistic regression models (Table 5).

As shown in Table 4 and Fig. 2, good accuracy of logistic regression model including plasma glycine and pAHF in STEMI cohort with pLVEF (including female and male) was revealed using ROC analysis (AUC 0.84 [95% CI 0.73–0.92], $p<0.0001$; sensitivity 86.7%/specificity 77.8% for plasma level of glycine > 2.58 (95% CI 2.16–3.34) mg/dL).

Discussion

Although there are many risk factors (high blood pressure, high cholesterol and glucose level, etc.) for developing heart disease in female and male, in female, other factors may be more meaningful. In our study, the female plasma levels of phenylalanine and glycine were significantly higher

Table 4 Univariable logistic regression analysis including PAA variables in STEMI cohort with pLVEF (including female and male patients) for prediction of pAHF

PAA. mg/dL	OR (95% CI)[a]	AUC ± SE (95% CI)[b]	p^c
Hcy	0.52 (0.001–470.3)	0.65 ± 0.07 (0.52–0.77)	0.0295
Lys	2.17 (1.29–3.64) $^{**\#\#}$	0.76 ± 0.07 (0.64–0.85)	0.0002
His	3.41 (1.39–8.38)$^{**\#\#}$	0.75 ± 0.07 (0.63–0.85)	0.0001
Arg	1.76 (0.93–3.34)	0.68 ± 0.08 (0.55–0.78)	0.0219
Orn	2.78 (1.39–5.56)$^{**\#\#}$	0.77 ± 0.06 (0.65–0.86)	< 0.0001
Asp	10.3 (2.03–52.3)$^{**\#\#}$	0.79 ± 0.07 (0.68–0.88)	< 0.0001
Thr	3.32 (1.16–9.53)$^{*\#}$	0.71 ± 0.07 (0.59–0.81)	0.002
Ser	3.20 (1.50–6.84)$^{**\#\#}$	0.79 ± 0.07 (0.67–0.88)	< 0.0001
Glu	1.46 (1.15–1.87) $^{**\#\#}$	0.77 ± 0.07 (0.66–0.87)	< 0.0001
Pro	1.69 (0.99–2.84)	0.69 ± 0.08 (0.57–0.80)	0.0114
Gly	2.49 (1.51–4.11)$^{****\#\#\#}$	0.84 ± 0.05 (0.73–0.92)	< 0.0001
Ala	1.58 (1.20–2.09)$^{***\#\#}$	0.79 ± 0.07 (0.68–0.88)	0.0001
Val	1.99 (1.24–3.20)$^{**\#\#}$	0.76 ± 0.07 (0.65–0.86)	0.0002
Met	375.2 (7.91–17,789.5)$^{***\#\#}$	0.80 ± 0.07 (0.69–0.89)	< 0.0001
Ile	3.07 (0.84–11.2)	0.68 ± 0.08 (0.56–0.79)	0.0169
Leu	2.29 (1.30–4.03)$^{**\#\#}$	0.76 ± 0.07 (0.64–0.85)	0.0003
Tyr	4.34 (1.52–12.4)$^{**\#\#}$	0.79 ± 0.06 (0.68–0.88)	< 0.0001
Phe	2.26 (1.39–3.66)$^{***\#\#\#}$	0.79 ± 0.08 (0.67–0.88)	0.0003
Gln	1.25 (1.004–1.54)$^{*\#}$	0.68 ± 0.07 (0.56–0.79)	0.0126
Total PPA	1.06 (1.02–1.10)$^{***\#\#}$	0.78 ± 0.07 (0.66–0.87)	< 0.0001

PAA plasma amino acids, *pAHF* persistent/late AHF after 48 h of admission, *pLVEF* preserved left-ventricular ejection fraction, *STEMI* ST-elevation myocardial infarction

[a]*OR* odds ratio, *CI* confidence interval; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$ significance of coefficient χ^2 of univariable logistic regression model; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ significance of proper coefficient of PAA variable in univariable logistic regression model

[b]*AUC* area under curve, *SE* standart error, *CI* confidence interval

[c]Significance of difference between AUC value of univariable logistic regression model and AUC value 0.5

in general STEMI cohort and, especially, in STEMI cohort with pLVEF. Also in our study, the significant associations between female sex, plasma level of glycine and pAHF have been revealed by logistic regression analysis.

Glycine is the well-known key component of several metabolic pathways such as glutathione synthesis and folate cycle of one-carbon metabolism (Locasale 2013; Weinberg et al. 2016). Previously, our special attention was deserved to alterations of free glycine level in blood serum of diabetic rats due to its involvement also into glutathione biosynthesis (Kuchmerovska et al. 2008). In the numerous studies in vivo, the glycine cytoprotection against necrosis resulted from the immunomodulation, but not from the neuronal signaling effects of glycine; and an apoptosis as a result of hypoxia under experimental condition was possible due to the use of glycine to prevent cell necrosis. Although the effect of glycine to shift necrotic to apoptotic cell death has not been completely studied and can vary, depending on the types of cells (Weinberg et al. 2016). If we talk about neuronal signaling effects of glycine trying to explain the high predictive value of glycinemia in our study, it should be noted that glycine is the one of endogenous agonists of *N*-methyl-D-aspartate receptors (NMDA) of the hypothalamic paraaortic and paraventricular nuclei. These receptors are responsible for autonomous and neuroendocrine regulation of the cardiovascular system (Kc and Dick 2010; Ouattara et al. 2013; Arora et al. 2014). In the experimental study, administration of glycine to animals in contrast to the expected renal cytoprotection was associated with an increase in acute ischemic–reperfusion renal injury as a result of NMDA activation (Arora et al. 2014). It has been demonstrated that NMDA activation is associated with increased intracellular calcium, impairment of nitric oxide synthesis, and increased production of reactive oxygen species, and is the one of the key causes in pathogenesis of heart failure (Kang et al. 2009; Seminotti et al. 2011; Martins-Pinge et al. 2013; Stern and Potapenko 2013; Moura et al. 2014). The role of NMDA activation in the pathogenesis of ischemic/reperfusion injury has been confirmed by the cytoprotective effect of the NMDA inhibition, especially, in pre- and postconditioning of the isolated rat heart (Weinberg et al. 2016; Govoruskina et al. 2019).

In our study, we have observed higher PAA levels in all female groups of STEMI patients compared to the respective male groups. Taking into account the mentioned

Table 5 Multivariable logistic regression analysis including plasma level of glycine, comorbidities, demographic and clinical variables in STEMI cohort with pLVEF (including female and male patients) for prediction of pAHF

Regression models	Odds ratio	95% Confidence Interval	p^a	p^b
Model 1[c]	2.49	1.51–4.11	< 0.0001	–
Model 2[d]	1.91	1.18–3.09	0.001	0.006
Model 3[e]	1.91	(1.12–3.23)	< 0.0001	< 0.05
Model 4[f]	2.70	1.68–4.62	< 0.0001	0.0003
Model 5[g]	2.31	1.38–3.85	0.0003	0.001
Model 6[h]	2.48	1.43–4.28	< 0.0001	0.001

AF atrial fibrillation, *AHF* acute heart failure, *CHF* chronic heart failure, *eGFR* estimated glomerular filtration rate, *ESR* erythrocyte sedimentation rate, *PAA* plasma amino acids, *pAHF* persistent/late AHF after 48 h of admission, *pLVEF* preserved left-ventricular ejection fraction, *STEMI* ST-elevation myocardial infarction, *T2DM* type 2 diabetes mellitus, V_E/V_A ratio of the peak early (V_E) to peak late atrial (V_A) of mitral diastolic inflow velocity

[a]Significance of coefficient χ^2 of logistic regression model

[b]Significance of coefficient of glycine in multivariable logistic regression model

[c]Univariable logistic regression model including plasma level of glycine (mg/dL)

[d]Multivariable logistic regression model (1) including plasma level of glycine (mg/dL), AHF Killip II–III on admission, number of ECG leads with elevation and depression ST more than 1 mm, ratio V_E/V_A by EchoCG on admission

[e]Multivariable logistic regression model (2) including plasma level of glycine (mg/dL), age (years), female sex, stable angina, CHF, smoking

[f]Multivariable logistic regression model (3) including plasma level of glycine (mg/dL), sex, CHF, T2DM, obesity

[g]Multivariable logistic regression model (4) including plasma level of glycine (mg/dL), sinus tachycardia (> 80/min), paroxysmal AF, ESR, eGFR (ml/min), plasma urea (mmol/L) on admission

[h]Multivariable logistic regression model (5) including plasma level of glycine (mg/dL), T2DM, AHF Killip II–III on admission and eGFR (ml/min) on admission

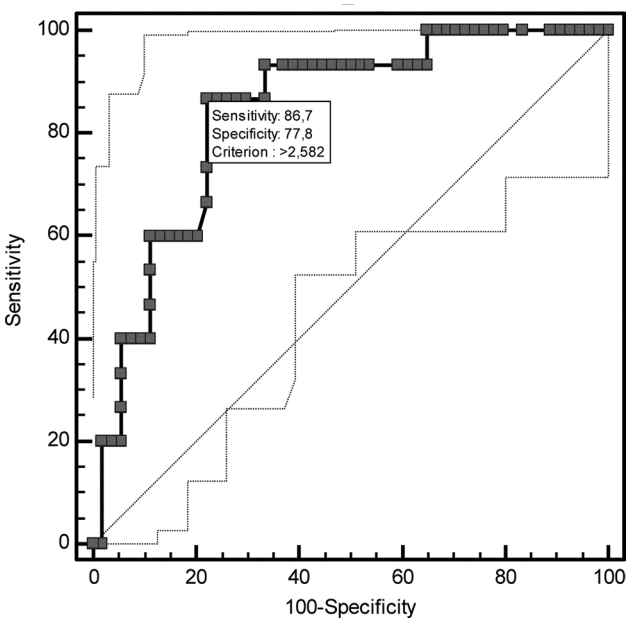

Fig. 2 ROC curve of plasma glycine level for prediction of pAHF in patients with STEMI and pLVEF ($n = 69$) (AUC 0.84 ± SE 0.05 [95% CI 0.73–0.92], $p < 0.0001$). *AUC* area under curve, *CI* confidence interval, *pAHF* persistent/late AHF more than 48 h after admission, *pLVEF* preserved left-ventricular ejection fraction, *ROC* receiver-operator characteristic, *SE* standard error, *STEMI* ST-elevation myocardial infarction

above, we tried to answer the question of primary or secondary nature of such metabolic PAA differences between women and men, based on the recent genetic research results. The highly sex-specific effect of single-nucleotide polymorphism (SNPs) in the carbamoyl-phosphate synthase 1 (CPS1) gene locus on free plasma level of glycine has been revealed by genome-wide association study (GWAS) (Mittelstrass et al. 2011). The fourfold stronger association between SNP rs715 in CPS1 gene and plasma glycine in women than in men has been demonstrated in RISC study. The RISK study researchers suggested that the polymorphism of CPS1 gene may cause excess ammonia, which may then lead to an increase in the production of glycine and tetrahydrofolate under condition of the glycine cleavage (Xie et al. 2013). The glycine-associated risk of AMI in patients with stable angina has been revealed in WENBIT study (Ding et al. 2016a, b). This risk can be modulated by the methylene-tetrahydrofolate-dehydrogenase-1 (MTHFD1) gene polymorphism, and was assessed by plasma levels of serine and glycine (Ding et al. 2016a, b). According to the authors of this study, increased levels of intracellular glycine were associated with impaired formation of 5,10-methylene-tetrahydrofolate, presumably due to backflow through serine-hydroxymethyl-transferase. Thus, the interaction observed between the rs1076991 polymorphism of MTHFD1 and the plasma level of glycine indicates the role of the shift of MTHFD1 from sufficient to deficient in the regulation of purine synthesis and the reverse flow between serine and glycine (Ding et al. 2016a, b).

Consequently, there are convincing evidences of the genetic predisposition of a certain type of PAA profile in women, especially concerning higher level of glycine despite of the fact that this amino acid can exert its influence on non-genetic level. That is why, we can suppose that hyperglycinemia in female patients with STEMI may have primary genetic-associated nature and can be associated with initiating development of secondary hemodynamic preconditions for pAHF in STEMI with pLVEF.

Limitations

We have conducted a single-center prospective cohort study, so the generalizability of our results may be limited. The STEMI cohort was relatively small, that may have influenced the power of our study. Due to our STEMI cohort did not receive RT, we are limited in the ability to extend our study results to patients receiving RT. The further investigations may provide insights into the predictive role of plasma amino acids in the development of pAHF in STEMI patients after PCI.

Taking into account 12-h fasting period before collection of blood sample, we had approximately 15–24 h of this period in the main group of study population. Based on the literature data, we believe that some plateau in amino acid levels should be present more than 12 h after the onset of STEMI symptoms in the plasma of patients not receiving RT. We understand that the difference in time periods from symptom onset to blood sample collection may affect the results of PAA tests and can be methodological limitation of the study.

Conclusion

According to the results of our prospective cohort study, including STEMI patients not receiving RT, we can suppose that women have significantly higher levels of majority of PAA than men in general STEMI cohort as well as in STEMI cohort with pLVEF. In STEMI cohort with pLVEF, the plasma levels of phenylalanine and glycine are the most significantly increased in female group as well as in the group with pAHF (including female and male). Female sex (OR 11.4) and plasma level of glycine (OR 2.49) are significant predictors of pAHF in STEMI cohort with pLVEF (including female and male). Such relation may be due to genetically determined higher level of glycine in women, unlike men. Plasma level of glycine remains an independent predictor of pAHF in STEMI cohort with pLVEF in multivariable logistic regression models adjusting for comorbidities, demographic and clinical variables. In our study, the glycine level > 2.58 [95% CI 2.16–3.34] mg/dL was characterized by sensitivity 86.7% and specificity 77.8% (AUC 0.84 [95% CI 0.73–0.92], $p < 0.0001$) for prediction of pAHF in STEMI patients with pLVEF (including female and male) not receiving RT. Thus, glycine in relation to female sex could be useful predictor of pAHF development in STEMI patients with pLVEF.

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Data availability statement All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethics approval The research was conducted in accordance with the World Medical Association Declaration of Helsinki. The study protocol was reviewed and approved by the local ethics committee of Bogomolets National Medical University (Kyiv, Ukraine)

Informed consent Informed consent was obtained from all participants.

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