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ORIGINAL RESEARCH

Apelinergic System in the Left Ventricle Adverse Remodeling After Myocardial Infarction: A Preliminary Study

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Background: Despite a growing evidence from the animal models of the cardioprotective function of the apelinergic system in the setting of myocardial infarction, little is known on the role of apelinergic system in the development of post- infarction adverse left ventricle remodeling in humans.

Methods: The study group consisted of 49 patients with first-time ST-segment elevation myocardial infarction of anterior wall treated invasively. Echocardiography was performed on index hospitalization and on one-year check-up, with categorizing the study population into group with adverse LV remodeling defined as an increase of LV end diastolic volume by >20% (n = 12) and the group without adverse remodeling (n = 29). ELA, AP-17, AP-13 and APJ receptor levels were measured on one-year follow-up.

Results: Patients with adverse LV remodeling presented significantly higher plasma level of apelin-13 (85.63 [75.43–96.13] vs 65.43 [57.35–69.35], p = 0.001) and apelin-17 (69.36 [42.61–77.04] vs 30.04 [25.97–41.95], p = 0.004). In a univariable logistic regression analysis, higher LVEDV and LVEDV1, higher LVESV and LVESVi, lower LVEF, higher WMSI score, higher SYNTAX score, higher levels of hs-CRP during index hospitalization and higher levels of AP-13 and AP-17 on the one-year check-up were associated with adverse LV remodeling. In multivariable logistic regression analysis, only AP-17 level was independently associated with adverse LV remodeling (p = 0.050).

Conclusion: Apelinergic system may be involved in the development of post- infarction adverse left ventricle remodeling.

Keywords: apelin, myocardial infarction, adverse remodeling

Introduction

Prevalence of heart failure (HF) is rising over the last decades and coronary artery disease (CAD) remains its most common cause. Invasive treatment of myocardial infarction (MI) has significantly reduced mortality in the early phase and has also contributed to reducing the incidence of major left ventricular (LV) damage. However, despite timely implementation of an invasive strategy and optimal pharmacological prevention, in some patients a progression of post-infarction adverse LV remodeling with symptomatic HF developing over time is observed.[1,2]

Cardiac remodeling is a change in cardiac size, architecture and histology secondary to cardiac injury.[3] It develops in 30% of patients after ST-segment elevation myocardial infarction (STEMI) and has a deleterious impact on prognosis demonstrated in numerous studies.[4,5] Adverse LV remodeling following MI is more pronounced in men, patients with larger infarct size and late or unsuccessful reperfusion.[6] It is a complex pathophysiological process, and the underlying mechanisms are not entirely understood. Due to a growing evidence of the role of the apelinergic system in the pathogenesis of cardiovascular diseases and its cardioprotective function, its potential role in preventing adverse LV remodeling following MI is a subject of a rising interest of the researchers.

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Apelinergic system consists of the apelin receptor (APJ) and its two endogenous ligands – apelin and ELABELA.[7] Apelin, synthesized as a 77-amino acid prepropeptide is next processed into fragments denoted by their lengths as Apelin-36, Apelin-19, Apelin-17 and Apelin-13.[8,9] Expressed predominantly in the endocardial and vascular endothelial cells, APJ ligands exert vast autocrine and paracrine effects due to APJ receptor being localized in endothelial and smooth muscle cells as well as cardiomyocytes.[10] The apelin/ELABELA/APJ system, a broad regulator of physiology, has an important role in maintaining cardiovascular system in health. It regulates the vascular tone – activation of the apelin receptor on vascular endothelial cells promotes nitric oxide production and causes vasodilatation.[11,12] In the setting of MI, apelinergic system which expression is induced by hypoxia promotes new vessel formation and diminishes ischaemic injury.[13–15] In animal models, lack of apelin increased susceptibility to ischaemia – reperfusion injury with larger infarct sizes and more significant ventricular impairment.[16] The beneficial effect of apelin and ELABELA in MI are likely due to their proangiogenic, anti-fibrotic and antiplatelet actions.[17]

The apelinergic system is also implicated in HF pathogenesis, with plasma apelin concentration increase in the early HF and down-regulation with the disease progression.[18–21] APJ ligands have protective role in HF, improving cardiac contractility, preventing hypertrophy and reducing mortality.[16,22,23] To date, apelin is the most potent inotrope discovered in isolated human heart tissue.[24] Traditional inotropes increase intracellular calcium and subsequently oxygen demand, leading to hypertrophy and promoting arrhythmias, however apelin's inotropic effect is probably mediated by enhanced calcium sensitivity. Combination of inotropic and vasodilative actions has been proved to improve haemodynamics in acute HF.[25]

However, data on the role of apelin/ELABELA/APJ system in the development of adverse LV remodeling and subsequent post-infarct HF are scarce. Thus, the objective of this prospective study was a comprehensive analysis of the relationship between the newly discovered apelinergic system components and the development of adverse LV remodeling after myocardial infarction.

Materials and Methods

Study Design and Patients Characteristics

This is a single-center, prospective, observational study that included 49 patients admitted with first-time STEMI of anterior wall to Tadeusz Marciniak Lower Silesia Specialist Hospital – Emergency Medicine Center, Department of Cardiology (Wroclaw, Poland).

MI was diagnosed in accordance with the criteria of the 4th universal definition according to the Guidelines of the European Society of Cardiology.[26] All patients underwent primary percutaneous coronary intervention (PCI) within 12 h from the onset of symptoms. The exclusion criteria were as follows: the history of previous MI or PCI, history of HF with LVEF < 50%, MI treated conservatively or type II MI, moderate to severe valvular disease, hypertrophic cardiomyopathy, lack of informed consent and poor acoustic window limiting the ability of the accurate assessment of cardiac structures and function in echocardiography. Demographic, standard laboratory data, vital parameters (blood pressure and heart rate), and medical history were gathered on admission, and transthoracic echocardiography was performed during the index hospitalization for the MI. SYNTAX score was assessed based on baseline coronary angiogram, before flow restoration, by an experienced interventional cardiologist. Data regarding pharmacotherapy was collected on the day of discharge from the hospital. An echocardiographic and laboratory check-up was performed after one year with categorizing the study population into the group of patients with adverse LV remodeling (defined as the increase of LV end diastolic volume (LVEDV) by ≥20%) and the group of patients without adverse LV remodeling (Figure 1).

All patients included in the study provided their written informed consent to participate. The protocol of the study complied with the Declaration of Helsinki and was approved by the Local Bioethics Committee of Wroclaw Medical University, Poland, signature number KB-749/2020.

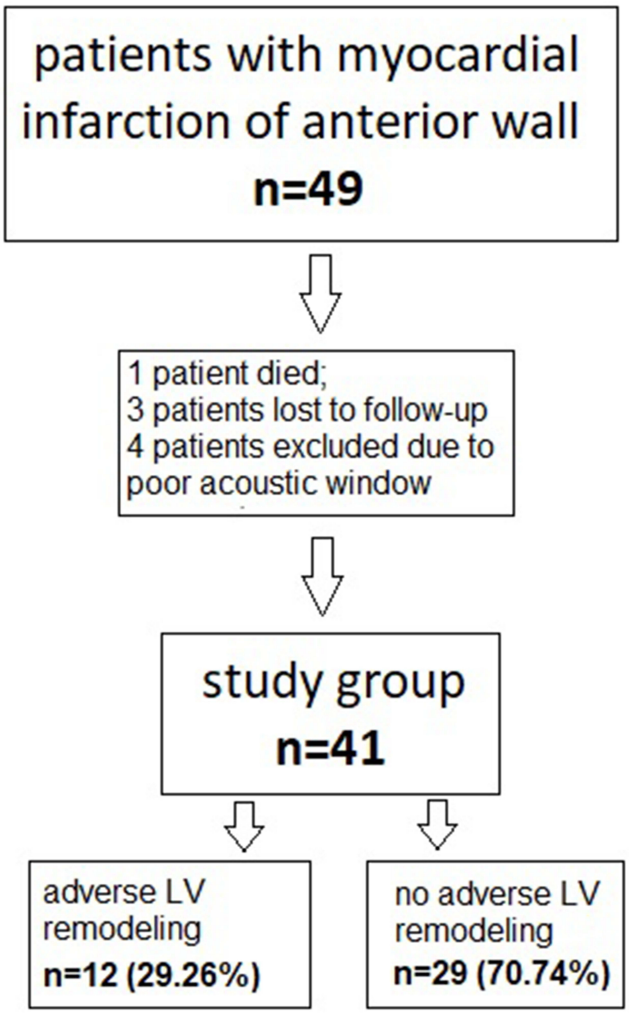

Figure 1 Study diagram.

Echocardiography

The study was performed in left decubital position, by 2 experienced operators, using Vivid E95 or Vivid E9 system, 48–72 h from admission (after the transfer from intensive care unit). Off-line analysis was performed on an Echopac station. The following structural measurements were assessed: left ventricular septal and posterior wall thickness (IVS and LVPW), left ventricular end-diastolic and end-systolic diameter and Simpson's biplane volumetric measurements: left ventricle end-diastolic volume (LVEDV) and end-systolic volume (LVESV). LVEF was calculated as LVEF = (LVEDV-LVESV)/LVEDVx100%. The LV mass was estimated by Devereux method.[27] The measures were indexed for body surface area (BSA) in accordance with the formula of DuBois and DuBois.[28] Wall motion score index (WMSI) was calculated with the 17-segment model, contractility of each segment was scored as follows: 1 – normal or hypercontractile, 2 – hypokinesia; 3 – akinesia; 4 – dyskinesia. The WMSI was calculated by dividing the sum of the score of each segment by the number of segments.

Biochemical Determinations of Apelinergic System Elements

Venous blood samples (2 mL) were collected during one-year follow-up, using a vacuum system and stored in EDTA tubes, then coagulated for 30 minutes at room temperature and after that centrifugated at 3000 × g (centrifuge MPW 260R, MPW Med. Instruments, Warsaw, Poland) for 15 min at room temperature – method described before.[29] The samples were stored at −20°C. ELA, apelin-13 (AP-13), apelin-17 (AP-17), and apelin receptor (APLNR) concentrations

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were measured using ELISA sets (MyBioSource Inc., San Diego, CA, USA) in accordance with the manufacturer's instructions. The sensitivity of the ELA test was 10.0 pg/mL, of the APLNR test was 7.4pg/mL, while the intra- and intra-assay CV values were <8.0% and <10.0%, respectively. The sensitivity of the AP-13 assay was less than 33.0pg/mL, and intra- and inter-assay CVs were <4% and <6.5%, respectively. The minimum detectable dose of AP-17 was less than 72.0 pg/mL, and intra- and inter-assay CVs were <10.0% and <12.0%, respectively.

The levels of creatinine, glucose, high-sensitivity C-reactive protein (CRP), high-sensitivity troponin T, creatinine kinase-MB isoenzyme (CK-MB), N-terminal pro-B-type natriuretic peptide (NT-proBNP), total cholesterol (TCh), HDL and LDL cholesterol, triglycerides (TG) and hematological variables were assayed by routine automatic analysis on the index hospitalization.

Coronary Angiography

All patients were managed invasively with urgent coronary angiography and primary PCI of the infarct-related artery (LAD) with drug-eluting stent implantation and TIMI III after the procedure. The SYNTAX score was calculated to define the severity of CAD, based on the SYNTAX score calculator (syntaxscore.org/index.php).

Statistical Analysis

Distribution of data was tested with the Shapiro–Wilk normality test. Data were presented as mean and standard deviation (+ SD) or median (interquartile range Q1-Q3), depending on their distribution. The qualitative variables were showed as number of observation (percent). Student-*t* test, Mann–Whitney test, chi-square test or Fisher's exact test was used for groups comparison. Univariable and multivariable logistic regression analyses were performed to identify predictors of post-infarction remodeling of the left ventricle in the patients after anterior wall infarction. P-values less than 0.05 were considered as significant. Statistical analyses were conducted using Statistica 13.3 software (Tibco Inc., Palo Alto, CA, USA).

Results

Study Group

The study included 49 patients with STEMI of anterior wall, the mean age was 61 [51–66], there was predominance of men (71.43%). One patient died, 3 patients were lost to follow-up and 4 patients were excluded due to poor acoustic window. On the check-up visit after one year, 17 patients presented with HF symptoms (5 patients with NYHA 1; 11 patients with NYHA II; 1 patient with NYHA III).

The clinical, laboratory and echocardiographic characteristics of patients with STEMI of anterior wall divided into the groups according to the occurrence of adverse LV remodeling are presented in Table 1. Adverse LV remodeling at one year follow-up occurred in 29.26% (12 out of 41) of patients. The group of patients with adverse LV remodeling and the control group did not differ in terms of demographic data, medical history, pharmacological treatment or participation in the cardiac rehabilitation program. Patients with adverse LV remodeling presented with significantly higher BMI (30.33 [4.14] vs 27.59 [3.09], p = 0.049) than the control group. Demographic and clinical parameters are presented in Table 1.

Echocardiographic Parameters

In terms of volumetric parameters, the group of patients with adverse LV remodeling was characterized by significantly higher baseline LVEDV (128.37 [27.79] vs 98.66 [21.01], p = 0.003) and LVEDVi (63.92 [15.38] vs 50.19 [10.46], p = 0.006), significantly higher baseline LVESV (77.25 [22.19] vs 48.0 [15.39], p < 0.001), and LVEDVi (38.67 [12.67] vs 24.51 [8.00], p < 0.001) and significantly lower LVEF (40.62 [6.73] vs 52.4 [7.92], p < 0.001) than the control group. Patients with adverse LV remodeling were also characterized by significantly higher baseline wall motion score index than the control group (2.02 [0.17] vs 1.63 [0.27], p < 0.001). Echocardiographic data are presented in Table 2.

Table 1 Demographic and Clinical Parameters in the Patients with Anterior Wall Infarction. Descriptive Data Were Presented as Mean [SD], Median [Interquartile Range, Q1–Q3] or Number of Observation (%).

		Anterior Wall Infarction (N = 49)		Anterior Wall Infarction		p-value
				Post-Infarction Remodeling (N = 12)	Non-Post-Infarction Remodeling (N = 29)	
Male sex		N (%)	35 (71.43)	9 (75.00)	20 (68.97)	0.696
Age (years)		Me [Q1-Q3]	61.00 [51.00–66.00]	65.00 [53.00–68.50]	59.00 [51.00–65.00]	0.479
BMI (kg/m^2)		M (SD)	27.75 [4.14]	30.33 [5.54]	27.59 [3.09]	0.049*
Obesity		N (%)	12 (24.49)	4 (33.33)	7 (24.14)	0.701
CHA_2DS_2-VASc score:	0	N (%)	2 (6.06)	0 (0.00)	1 (5.88)	0.586
	1	N (%)	2 (6.06)	1 (10.00)	1 (5.88)	
	≥2	N (%)	29 (87.88)	9 (90.00)	15 (88.24)	
Hypertension:		N (%)	32 (65.31)	7 (58.33)	20 (68.97)	0.513
Diabetes mellitus type II:		N (%)	10 (20.41)	4 (33.33)	5 (17.24)	0.407
Post-infarction rehabilitation		N (%)	32 (65.31)	8 (66.67)	20 (68.97)	1.000
AF		N (%)	6 (12.24)	2 (16.67)	4 (13.79)	1.000
SBP (mmHg)		M [SD]	132.62 [21.67]	130.00 [19.23]	133.40 [24.00]	0.678
HR (bpm)		M [SD]	72.50 [9.21]	71.09 [9.11]	72.82 [8.81]	0.587
ACEi		N (%)	49 (100.00)	12 (100.00)	28 (96.55)	1.000
ARB		N (%)	49 (100.00)	12 (100.00)	29 (100.00)	1.000
Beta-blockers		N (%)	42 (85.71)	11 (91.67)	24 (82.76)	0.651
MRA		N (%)	16 (32.65)	4 (33.33)	10 (34.48)	1.000
Statins		N (%)	47 (95.91)	11 (91.67)	28 (96.55)	0.504
Antiplatelet agents		N (%)	49 (100.00)	12 (100.00)	29 (100.00)	1.000
Anticoagulant agents		N (%)	6 (12.24)	0 (0.00)	5 (17.24)	0.297
Diuretics		N (%)	8 (16.32)	4 (33.33)	4 (13.79)	0.202
ASA		N (%)	47 (95.91)	12 (100.00)	27 (93.10)	1.000
Flozins		N (%)	5 (10.20)	0 (0.00)	4 (13.79)	0.302

Note: *statistically significant.

Abbreviations: AF, atrial fibrillation; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; ASA, acetylsalicylic acid; BMI, body mass index; HR, heart rate; MI, myocardial infarction; MRA, antagonists of mineralocorticoid receptors; SBP, systolic blood pressure.

Angiographic Data

Patients with adverse LV remodeling were characterized by significantly more complex CAD expressed by higher SYNTAX score (23.08 [5.44] vs 17.39 [8.13], p = 0.032) than the control group. The group with adverse LV remodeling and the control group did not differ in terms of prevalence of multivessel CAD. Angiographic data are presented in Table 2.

Table 2 Echocardiographic and Angiographic Parameters in the Patients with Anterior Wall Infarction. Descriptive Data Were Presented as Mean [SD] or Median [Interquartile Range, Q1-Q3].

			Anterior Wall Infarction (N = 49)	Anterior Wall Infarction		p-value
				Post-Infarction Remodeling (N = 12)	Non-Post-Infarction Remodeling (N = 29)	
Echocardiographic parameters						
LVEDV (mL)		M [SD]	105.52 [25.26]	128.37 [27.79]	98.66 [21.01]	0.003*
LVEDVi (mL/m^2)		M [SD]	53.32 [12.91]	63.92 [15.38]	50.19 [10.46]	0.006*
LVESV (mL)		M [SD]	54.52 [20.65]	77.25 [22.19]	48.00 [15.39]	<0.001*
LVESVi (mL/m^2)		M [SD]	27.75 [10.88]	38.67 [12.67]	24.51 [8.00]	<0.001*
LVEF (%)		M [SD]	49.83 [8.98]	40.62 [6.73]	52.40 [7.92]	<0.001*
LVEF ≤ 50% after 1 year		N (%)	17 (40.48)	12 (100.00)	5 (17.24)	<0.0001*
Wall motion score index		M [SD]	1.71 [0.29]	2.02 [0.17]	1.63 [0.27]	<0.001*
Interventricular septum thickness (mm)		M [SD]	13.37 [2.71]	13.00 [1.82]	13.48 [2.96]	0.686
Posterior wall thickness (mm)		M [SD]	10.13 [2.11]	9.42 [1.98]	10.51 [1.84]	0.179
Left ventricular mass index (g/m^2)		M [SD]	224.19 [57.51]	235.66 [31.24]	219.49 [64.37]	0.529
Hypertrophy		N (%)	16 (53.33)	4 (57.14)	12 (52.17)	1.000
Concentric hypertrophy		N (%)	5 (22.73)	1 (25.00)	4 (22.22)	1.000
Eccentric hypertrophy		N (%)	11 (52.38)	3 (75.00)	8 (47.06)	0.586
E (cm/s)		M [SD]	0.71 ± 0.18	0.80 ± 0.21	0.69 ± 0.18	0.201
E/e'		M [SD]	11.02 ± 3.89	12.46 ± 4.03	10.57 ± 3.86	0.354
Restrictive inflow		N (%)	3 (9.37)	2 (28.57)	1 (4.17)	0.119
LA a-p		M [SD]	40.15 [4.16]	41.09 [4.18]	40.07 [3.40]	0.430
LA area		M [SD]	21.11 [2.77]	22.00 [2.86]	20.80 [2.67]	0.256
Type of CAD:	1-vessel	N (%)	19 (57.57)	4 (40.00)	11 (64.71)	0.382
	2-vessels	N (%)	9 (27.27)	4 (40.00)	3 (17.65)	
	3-vessels	N (%)	5 (15.15)	2 (20.00)	3 (17.65)	
Post-infarction artery:	LAD	N (%)	46 (93.88)	12 (100.00)	26 (89.66)	0.542
	No-LAD	N (%)	3 (6.12)	0 (0.00)	3 (10.34)	
STB	<4h	N (%)	24 (48.98)	6 (50.00)	15 (51.72)	0.919
	>4h	N (%)	25 (51.02)	6 (50.00)	14 (48.28)	
SYNTAX scale		M [SD]	18.51 ± 7.81	23.08 ± 5.44	17.39 ± 8.13	0.032*
CTO:		N (%)	2 (4.08)	1 (8.33)	1 (3.45)	0.504

Note: *statistically significant.

Abbreviations: CAD, coronary artery disease; CTO, chronic total occlusion; LA, left atrium; LAD, left anterior descendant; M, mean; Me, Median; N, number; STB, Symptom-to-balloon time.

Biochemical Data

Patients who presented adverse LV remodeling as opposed to control group presented significantly higher plasma levels of hsCRP (5.55 [2.95–57.55] vs 2.4 [0.9–3.7], p = 0.009) and troponin T (6217.0 [1864.0–10,569.0] vs 1723 [1401.0-–3426.0], p = 0.007) determined on the index hospitalization.

In terms of plasma level of apelinergic system components determined on the one-year check-up, patients who developed LV adverse remodeling presented significantly higher plasma levels of apelin-13 (85.63 [75.43–96.13] vs 65.43 [57.35–69.35], p = 0.001) and apelin-17 (69.36 [42.61–77.04] vs 30.04 [25.97–41.95], p = 0.004), but did not differ significantly in the plasma level of ELA and APLNR. Biochemical data are presented in Table 3.

Determinants of the Left Ventricle Adverse Remodeling

In order to define determinants of the adverse LV remodeling, a univariable logistic regression analysis was performed. Among echocardiographic parameters, higher LVEDV and LVEDV1, higher LVESV and LVESVi, lower LVEF and higher WMSI score were associated with the occurrence of the adverse LV remodeling, while in terms of angiography – higher SYNTAX score. Among biochemical data, higher levels of hs-CRP during index hospitalization and higher levels of AP-13 I AP-17 on the one-year check-up were associated with adverse LV remodeling. The results of the logistic regression analysis are presented in Figure 2 in the form of a forest plot diagram.

In multivariable logistic regression analysis, after checking the conditions for conducting this analysis and removing co-correlated variables, the final model of predictors of post-infarction remodeling was obtained. Only AP-17 level was

Table 3 Laboratory Parameters in the Patients with Anterior Wall Infarction. Descriptive Data Were Presented as Mean [SD] or Median [Interquartile Range, Q1-Q3]

		Anterior Wall Infarction (N = 49)	Anterior Wall Infarction		p-value
			Post-Infarction Remodeling (N = 12)	Non-Post-Infarction Remodeling (N = 29)	
Hemoglobin (g/dL)	M [SD]	14.68 [2.18]	14.61 [1.19]	14.65 [2.56]	0.964
TCh (mg/dL)	Me [Q1-Q3]	192.5 [162.50–230.00]	230.00 [149.00–256.00]	191.00 [162.00–215.00]	0.530
HDL (mg/dL)	Me [Q1-Q3]	46.25 [39.70–56.45]	55.00 [44.00–62.00]	47.00 [41.80–57.70]	0.307
LDL (mg/dL)	Me [Q1-Q3]	116.00 [87.30–151.00]	116.00 [67.00–185.00]	114.00 [87.15–148.00]	0.746
TG (mg/dL)	Me [Q1-Q3]	121.00 [98.00–147.50]	112.00 [87.00–154.00]	128.00 [112.00–146.00]	0.282
CRP (mg/L)	Me [Q1-Q3]	3.00 [1.00–6.73]	5.55 [2.95–57.55]	2.40 [0.90–3.70]	0.009*
Creatinine (mg/dL)	M [SD]	0.91 [0.20]	0.99 [0.26]	0.87 [0.17]	0.107
Troponin (pg/mL)	Me [Q1-Q3]	2284.50 [1427.50–5408.50]	6217.00 [1864.00–10,569.00]	1723.00 [1401.00–3426.00]	0.007*
NT-proBNP (pg/mL)	Me [Q1-Q3]	232.00 [88.00–975.20]	395.50 [124.50–1533.50]	138.00 [78.80–766.00]	0.269
CK-MB (IU/L)	Me [Q1-Q3]	101.00 [46.00–161.00]	136.50 [64.50–213.50]	101.00 [61.00–135.00]	0.276
eGFR (mL/min/1.73 m^2)	M [SD]	87.65 [17.41]	83.25 [21.49]	90.17 [17.45]	0.287
ELA (pg/mL)	Me [Q1-Q3]	516.87 [428.75–833.33]	464.58 [430.83–935.41]	564.17 [425.00–833.33]	0.779
AP-13 (pg/mL)	Me [Q1-Q3]	68.56 [59.64–82.10]	85.63 [75.43–96.13]	65.43 [57.35–69.35]	0.001*
AP-17 (pg/mL)	Me [Q1-Q3]	37.38 [27.59–57.26]	69.36 [42.61–77.04]	30.04 [25.97–41.95]	0.004*
APLNR (ng/mL)	Me [Q1-Q3]	8.69 [4.03–12.02]	5.01 [4.18–10.61]	10.07 [4.00–12.78]	0.294

Note: *: statistically significant.

Abbreviations: AP-13, apelin-13; AP-17, apelin-17; CK-MB, creatine kinase MB; CRP, C-reactive protein; e-GFR, glomerular filtration rate; ELA, elabela peptide; APLNR, apelin receptor; HDL, high density lipoprotein; LDL, low density lipoprotein; M, mean, Me, median; NT-proBNP, N-terminal pro-brain natriuretic peptide; TCh, total cholesterol; TG, triglycerides.

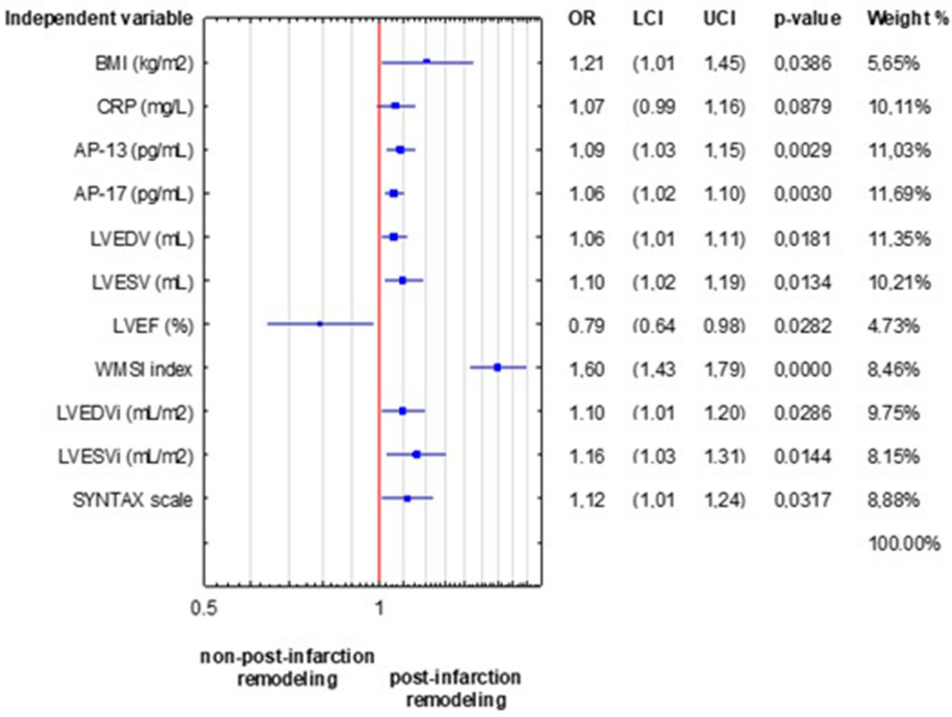

Figure 2 Forrest plot showing the odds ratios calculated in univariable logistic regression analysis for risk of post-infarction remodeling in the patients with anterior wall infarction.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; AP-13, apelin-13; AP-17, apelin-17; LVEDV, left ventricle end-diastolic volume; LVESV, left ventricle end-systolic volume; LVEF, left ventricle ejection fraction; WMSI, Wall motion score index; LVEDVi, indexed left ventricle end-diastolic volume; LVESVi, indexed left ventricle end-systolic volume; OR, odds ratio; LCI, lower confidence interval; UCI, upper confidence interval.

independently associated with adverse LV remodeling (p = 0.050). The model explains 47.7% of adverse LV remodeling cases (Figure 3).

Discussion

The population of patients after MI represents a high-risk group for HF development, associated mostly with an adverse LV remodeling. That underscores a need to screen that population on discharge from hospitalization due to MI in terms of risk factors for the development of adverse LV remodeling and to closely monitor this population during the first months after the hospitalization, in order to enable a timely diagnosis and a proper treatment implementation. Understanding the pathophysiological mechanisms of post-MI adverse LV remodeling is also important in search for new potential therapeutic targets.[30] Despite growing evidence for an important role of the apelin/ELABELA/APJ system in pathophysiology of the cardiovascular system, little is known of its role in the development of post-infarct HF.

In our study population, apelin-17 was the only determinant of post-MI adverse LV remodeling identified in multivariable logistic regression analysis. It is worth emphasizing that our study is the first to identify the apelin as a determinant of adverse LV remodeling after MI.

Data on the influence of apelinergic study on adverse post-MI remodeling is very limited in the literature. In the study by Weir et al, part of clinical study investigating the effects of eplerenone on LV remodeling following myocardial infarction in patients with LV dysfunction (LVEF < 40%), plasma apelin-12, -13, -16 level, cardiac morphology and function on MRI were assessed during hospitalization due to myocardial infarction and on follow-up 24 weeks after discharge. The researchers investigated the influence of apelinergic system on cardiac remodeling and found no relationship between baseline apelin level and the change in LVEDVi, infarct volume and LVEF over 24 weeks.[31] However, in the trial, the association of apelin level and adverse remodeling defined as an increase in LVEDV by 20%

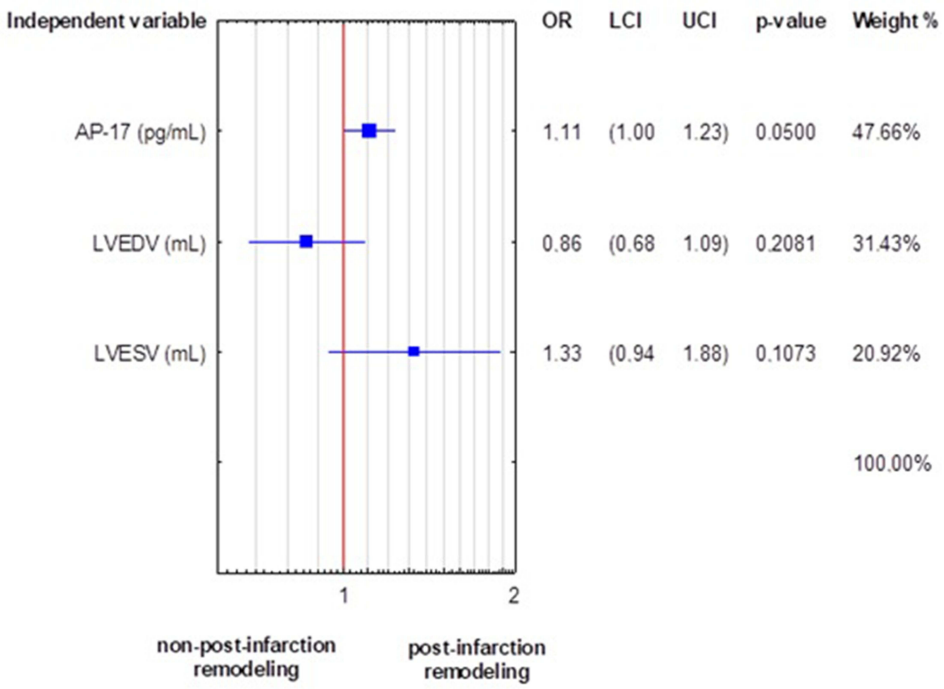

Figure 3 Forrest plot showing the odds ratios calculated in final model of multivariable logistic regression analysis for risk of post-infarction remodeling in the patients with anterior wall infarction.

Abbreviations: LVEDV, left ventricle end-diastolic volume; LVESV, left ventricle end-systolic volume; AP-17, apelin-17; OR, odds ratio; LCI, lower confidence interval; UCI, upper confidence interval.

were not examined and what is more, the other members of apelin family (apelin-17 in particular) were not measured which could influence the study results given the data on apelin-17 relationship with cardiac remodeling from our study.

Association of classic biomarkers including BNPs, marker of cardiomyocyte injury (cardiac troponin) and marker of inflammatory response (CRP) with post-myocardial adverse infarction remodeling is well documented, and a positive correlation was also found in our population, however not in the multiple analysis. In the literature, also extracellular matrix turnover markers (like most frequently analyzed MMP-9) level positively correlated with cardiac remodeling.[32] MicroRNAs, participating in cardiovascular processes through post-transcriptional regulation of gene expression, take part in regulation of cardiomyocyte apoptosis and fibrosis.[33] However, the role of microRNAs in adverse remodeling prediction is unclear to date.[34]

In our study, the level of apelin was measured during the follow-up (after one year from index hospitalization). The level of a biomarker measured in the acute phase of myocardial infarction would be of greatest clinical usefulness as a predictor of adverse cardiac remodeling, however the follow-up level can also be regarded clinically significant in a potential biomarker -guided therapy.[34] Additionally, from the pathophysiological point of view, the biomarkers evaluated in the acute phase reflect mostly the severity of the MI and not the chronic, persistent unfavorable neurohumoral environment contributing to adverse LV remodeling.

Hence, Reinstadler et al studied the prognostic utility of serial biomarker measurement and multi marker approach after myocardial infarction – they measured several biomarkers (aspartate and alanine aminotransferases, troponin T, NT-proBNP, lactate dehydrogenase, CRP) daily for 4 days after admission due to myocardial infarction. They proved the peak and not the admission value of level of the biomarkers to be associated with cardiac remodeling. It indicates that not only the selection of biomarker but also the timing of the measurement might be of importance in post-MI adverse LV remodeling prediction.[35,36]

The data on the dynamics of plasma concentrations of apelin/ELABELA/APJ system in patients with MI are scarce. In the study by Diakowska et al, plasma level of ELABELA, apelin-13 and apelin-17 level measured on the first day of the hospitalization were significantly increased compared to healthy controls.[37] However, in the study by Weir et al,

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plasma apelin concentrations measured 2 days after MI were lower than in controls, then rose significantly over time, but after 24 weeks remained lower than in controls. It could be speculated that plasma apelin level increases in the early phase of MI than is exhausted and subsequently rebuilt, but this phenomenon needs further studies.[31]

Adverse LV remodeling following MI is a complex phenomenon characterized by a delicate interplay between cellular and extracellular components. Data from the literature, based mainly on animal models, indicate that apelin/ELABELA/APJ system may play an important role in this process.

According to literature, an increase in plasma apelin level that is observed in the early phase of MI[37,38] is associated with improved prognosis in patients with MI,[39] which indicates an important cardioprotective role of the apelinergic system following MI.

The protective effect of the apelin/ELABELA/APJ system in an injured heart consists of affecting most pathological mechanisms involved in the adverse LV remodeling, like the excessive fibrosis and inflammation. Following MI, a replacement fibrosis is needed for scar formation, but in excess, it stiffens the heart and impairs oxygen diffusion.[1] Afterwards, inflammation, being a critical component of tissue healing in injured myocardium, when not modulated properly after MI, can contribute to adverse LV remodeling.[2] In animal model, apelin-13 administration attenuated MI-induced fibrosis via inhibition of NF-kB signaling,[40] preventing cardiac fibroblast activation, reducing the levels of TNFalfa and IL1beta proinflammatory mediators in the ischaemic heart.[41] Also in animal model, apelin-13 inhibited collagen synthesis by mouse cardiac fibroblasts.[42] Other investigators found that apelin-13 administration has angiogenic and anti-fibrotic effects via an enhancement of the expression of VEGFA, Kdr, Ang-1 and eNOS in the infarcted myocardium.[43] However, primary PCI leads to a substantial myocardial salvage and infarct size reduction, reperfusion itself causes a second wave of injury – succinate accumulation during ischaemia is suddenly oxidized, which mediates the production of reactive oxygen species (ROS). Chronically elevated ROS induces a vicious cycle of cardiac hypertrophy, myocyte death and cardiac adverse remodeling.[1] In animal model, apelin knockout mice presented an enhanced susceptibility to ischemia-reperfusion injury with greater infarct size and increased myocardial inflammation, while apelin analogue administration at the time of reperfusion showed a protective effect in vivo.[13] The cardioprotective effect of apelin/ELABELA/APJ system against ischemia/reperfusion injury consists mainly of limitation of infarct size and myocardial contracture and improvement of post-ischaemic contractile recovery.[44] Overactivation of the renin-angiotensin system plays an important role in adverse left ventricle remodeling. If the apelin system opposes the actions of the renin-angiotensin system, the systems may also reciprocally regulate each other.[7] In animal models, loss of apelin potentiates angiotensin-II – induced myocardial injury and apelin treatment reverses these changes.[45,46]

In this study, the group of patients with an adverse LV remodeling showed an increased level of apelin-13 and apelin-17 after one year compared to the control group (patients without adverse LV remodelling).

Considering the adverse LV remodeling being one of the main causes of post-MI HF, this result is in accordance with the data from the literature indicating a close relationship between apelin/ELABELA/APJ system and the pathogenesis of HF. According to the literature, apelin and ELABELA take part in regulating cardiovascular homeostasis by increasing contractile reserve, cardiorenal protective actions and decreasing preload and afterload.[47] A study by Liu et al, investigating potential diagnostic value of plasma ELABELA and apelin in HF in a population of 335 patients, demonstrated that plasma ELABELA was significantly reduced in patients with HF and correlated with increasing NYHA grade, and that plasma apelin level was significantly elevated in patients with HF but was not affected by NYHA grade. What is more, plasma apelin level in the study positively correlated to BNP level, LVEDd and negatively correlated to LVEF.[48] In a study by Han et al, an increased level of plasma apelin in HF patients, but also a gradual decrease of plasma level of apelin with increasing NYHA grade was noted, with plasma apelin level in NYHA IV patients even lower than in patients without HF.[49] A range of data from the literature indicates that during the development of HF, the plasma apelin-13 level rises in the initial phase and decreases along with the progression of the disease.[24] In a study by Goidescu et al on a population of 53 patients with HFrEF (either dilatative cardiomyopathy or ischemic heart disease), patients with NYHA IV HF had significantly higher level of NT-proBNP and significantly lower serum level of apelin-13 compared to the patients with NYHA II heart failure.[50] Also in this study, a significant negative correlation between left ventricle end-systolic volume and the serum apelin-13 level and in patients with NYHA IV a positive correlation between values of RWT and serum apelin-13 level was found. In a multivariate analysis in this

study, the decrease of serum apelin-13 level was associated with a significant increase of adverse events (death, heart failure decompensation).[50] It would seem that the increase of apelinergic system elements at the onset of the disease is compensatory, however with the progression of the remodeling, widening and eccentric hypertrophy of the failing heart, its compensatory mechanisms are exhausted, which is expressed also by a decrease in the concentrations of apelin. It is worth emphasizing that in our study population patients presented mostly with mild symptoms of heart failure: NYHA I or II grade and relatively low levels of NT-proBNP level, which indicates that heart failure was not advanced.

Conclusion

To conclude, in our study population the serum levels of apelin-17 and apelin-13 after one year post-MI were significantly increased in patients with adverse LV remodeling compared with the patients without adverse LV remodeling and in multivariable logistic regression analysis, the serum level of apelin-17 on follow -up was the only independent parameter associated with the occurrence of adverse LV remodeling. Thus, apelinergic system may be involved in the pathophysiology of post- infarction adverse left ventricle (LV) remodeling; however, due to the limited sample size of the study, further studies are needed to better consolidate the results. Our study should be an incentive for further research on the involvement of the apelinergic system in post-MI cardiac adverse remodeling and HF pathophysiology.

Study Strength and Limitations

The major strength of the study was the innovative nature of the analysis over the influence of recently discovered apelinergic system on left ventricular adverse remodeling after myocardial infarction.

However, the main limitation of the study is a small sample of patients. Therefore, the results are to be considered indicative and preliminary, and further research on larger group is needed to better consolidate the results. The study was single-center and included exclusively Caucasians, therefore extrapolating the results in other populations should be considered with caution. Women were underrepresented in the study group. The ischemia time was defined as a dichotomous variable (<4 h or >4 h) and not as a continuous variable expressed in minutes.

Future Directions

Despite the results of our study being preliminary and requiring confirmation, they may indicate a role of the apelinergic system in post-infarction left ventricular remodeling. However, the molecular mechanism of the influence of the apelinergic system on the development of left ventricular remodeling is unclear and therefore its associations with the markers of inflammation, fibrosis and endothelial function in patients with myocardial infarction need further research. Furthermore, the apelinergic system could constitute a potential therapeutic target in patients at risk of developing post-infarction left ventricular remodeling.

Disclosure

The authors report no conflicts of interest in this work.

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