DOI: 10.4149/BLL_2023_056

Bratisl Med J 2023; 124 (5)

368 – 372

CLINICAL STUDY

Plasmatic apelin shows a promising potential as a screening biomarker for atrial fibrillation

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ABSTRACT

OBJECTIVES: Purpose of this study was to evaluate properties of apelin, a peptide detectable in peripheral blood, for atrial fibrillation (AF) detection in a diverse population of patients covering a broad spectrum from healthy to polymorbid patients.

BACKGROUND: AF is the most common cardiac arrhythmia with constantly increasing incidence and prevalence. Currently available diagnostic tools do not provide sufficient detection rate. Large proportion of patients with AF remains undiagnosed and the possibility of screening at-risk groups would be significantly beneficial.

METHODS: We designed this study as a multi-centre retrospective study. Study population included 183 patients. 64 in non-AF and 119 in AF group.

RESULTS: Apelin plasma concentration was significantly lower in AF group compared to non-AF group ($p < 0.001$). Receiver operating characteristic analysis of apelin as a predictor of AF scored area under the curve of 0.79, sensitivity = 0.941 and specificity = 0.578. Multivariate analysis using logistic regression adjusted for age, BMI, apelin, dilated LV, dilated LA, arterial hypertension, and gender showed only apelin and age to be statistically significant contributors for AF.

CONCLUSION: Apelin might be a promising biomarker for detecting AF in our study population. These results suggest promising potential of apelin as a screening biomarker for AF *(Tab. 2, Fig. 1, Ref. 46)*. Text in PDF *www.elis.sk*

KEY WORDS: biomarker, apelin, arrhythmia, atrial fibrillation.

Abbreviations: ACE2 – angiotensin-converting enzyme 2, AF – atrial fibrillation, APJ – apelin receptor, BMI – body mass index, CI – confidence interval, ECG – electrocardiography, LV – left ventricle, LA – left atrium, ROC – receiver operating characteristic, SD – standard deviation

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Acknowledgements: This work was supported by the independent research grants provided by the Ministry of Education, Science, Research and Sport of the Slovak Republic VEGA under grant number 1/0563/21.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with constantly increasing incidence, affecting approximately 3 % of the adult population (1, 2) and the incidence of AF recurrence is around 45 % despite therapy (3). The number of people affected by AF in Europe is expected to double in 50 years (4). Despite substantial progress in prevention, diagnostics and treatment, AF remains associated with high morbidity, mortality and health care costs (5, 6). As an independent risk factor, AF increases mortality two-fold in women and 1.5-fold in men and 5-fold the risk of ischemic stroke (2, 6). Appropriate therapy significantly reduces these risks; however, it must be preceded by correct and timely diagnosis (6–8).

ECG-based diagnostic methods are considered "golden standard" for AF detection (9, 10). However, they do not provide sufficient detection rate in the setting of paroxysmal asymptomatic AF. Prolonged monitoring is more accurate compared to standard 12-lead ECG. On the other hand, it is associated with higher cost, inconvenience and sometimes limited availability (11, 12). Accurate, simple, cost-effective and widely available diagnostic tool,

such as a biomarker detectable in peripheral blood, would be significantly beneficial in the management of AF patients and several biomarkers have already been investigated in this context (13–17). Based on available literature and our prior research apelin shows promising results (18–21).

Apelin is an endogenous peptide with a wide range of effects on cardiovascular system, including several processes directly or indirectly linked with AF. Among other effects, it increases atrial conduction velocity, refractoriness, prevents the inducibility of AF, modulates cardiac sodium current, shortens action potential duration in atrial myocytes via its effects on multiple ionic channels, affects the renin-angiotensin-aldosterone signalling pathway and acts as a second catalytic substrate for angiotensin-converting enzyme 2 (ACE2) (22–26).

Our previous research included two studies in patients with low risk of stroke and one in patients with high risk (18, 19, 21). In this study we pooled all patients from previous studies including previously unreported patients excluded in patient matching, forming a large heterogenous study population with a goal to further investigate apelin's predictive value for AF.

Materials and methods

The study was approved by the Ethics Committee of the National Cardiovascular Institute, Bratislava, Slovakia and a written informed consent was obtained from all patients.

Study population

We designed a multicentre retrospective study. The population consisted of two study groups: a group of patients with AF (AF group, 119 patients) and a group without AF (non-AF group, 64 patients) composed of patients without AF and healthy blood donors. AF was excluded based on the history and 12-lead ECG at the time of enrolment. Patients were pooled from our previous apelin study populations (18, 19, 21). Inclusion criteria for each study are available in the supplementary material.

Seven-day ECG monitoring was performed using a QardioCore device and ECG event recording was performed using a Hartmann Veroval.

Exclusion criteria for both groups were: electrical cardioversion less than 7 days prior to inclusion, acute coronary syndrome less than 1 month prior to inclusion, cardiac surgery less than 3 months prior to inclusion, acute or decompensated heart failure at the time of inclusion, pregnancy, cardiomyopathy, alcoholism (≥ 8 drinks/week), thyrotoxicosis, renal disease (dialysis/ transplant/ CrCl < 0.5 ml/s), liver disease (cirrhosis/ transaminase > 3x ULT/ bilirubin > 2x ULT), mechanical prosthetic valve, severe mitral stenosis, class I and IV antiarrhythmic drugs usage in the last month, class III antiarrhythmic drugs usage in the last 3 months.

Data collection and biochemical analysis

In AF and non-AF groups, baseline clinical data were obtained during out-patient visits or during a hospitalization and recorded into an electronic online case report form. Peripheral fasting blood was taken in the morning using K3EDTA tubes. In the control group, baseline clinical data and fasting blood samples were collected at the time of blood donation. The blood was centrifuged at 2700 g for 5 minutes and the obtained plasma samples were stored at –80 °C. The apelin-12 concentration was measured using a commercially available ELISA kit (Phoenix Pharmaceutical, Karlsruhe, Germany) in plasma samples. Fifty microliters of plasma samples were used for measurement according to the manufacturer's protocol.

Statistical methods

Continuous variables are presented as means and standard deviations, whereas categorical variables are presented as percentages. Normality of data was tested using a Shapiro-Wilk test. Unpaired Student t-test and Mann-Whitney test were used to compare continuous variables as appropriate. Chi-squared and Fisher's exact test were used to compare categorical variables as appropriate. Receiver operating characteristic (ROC) curves together with respective values of sensitivity, specificity, and accuracy at various cut-off levels of the selected parameter were calculated to evaluate

Tab. 1. Patient data.

	AF group (n = 119)	non-AF group (n = 64)	p
Age (years)	64.28±11.31	54.8±17.19	< 0.001
Male gender (%)	81 (68.07%)	32 (50%)	0.025
Weight (kg)	85.39±15.51	84.4±12.36	0.668
Height (cm)	170.99±17.76	170.1±8.5	0.299
BMI (kg/m2)	31.23±20.54	29.12±3.27	0.362
Dilated LV (%)	9 (7.56%)	2 (3.13%)	0.334
Dilated LA (%)	87 (73.11%)	19 (29.69%)	1
Ischemic stroke / TIA (%)	25 (21%)	7 (10.94%)	0.132
STEMI	0.06±0.27	0.09±0.34	0.45
NSTEMI	0.12±0.85	0.06±0.3	0.62
Diastolic dysfunction	46 (38.66%)	21 (32.81%)	0.534
Smoking (> 5 cigarettes per day) (%)	4 (3.36%)	2 (3.13%)	1
Ventricular tachycardia / ventricular fibrillation (%)	3 (2.5%)	1 (1.56%)	1
Arterial hypertension (%)	99 (83.19%)	29 (45.31%)	< 0.001
Diabetes Mellitus (%)	0 (0%)	0 (0%)	NA
Pulmonary embolism (%)	2 (1.68%)	0 (0%)	0.543
Deep vein thrombosis (%)	3 (2.5%)	0 (0%)	0.553
Peripheral arterial disease / aortic plaque (%)	22 (18.49%)	10 (15.62%)	0.778
Left ventricular hypertrophy (%)	30 (25.21%)	13 (20.31%)	0.574
Stable coronary artery disease (%)	26 (21.85%)	8 (12.5%)	0.177
Chronic obstructive pulmonary disease (COPD) (%)	9 (7.56%)	1 (1.56%)	0.169
Obstructive sleep apnea (OSA) (%)	0 (0%)	1 (1.56%)	0.35
Severe valvulopathy (%)	0 (0%)	0 (0%)	NA
Electrical cardioversion (%)	3 (2.5%)	0 (0%)	0.119
Pharmacological cardioversion (%)	5 (4.2%)	0 (0%)	0.028
Apelin (ng/ml)	0.74±0.15	0.98±0.31	< 0.001

BMI – Body Mass Index; LV – left ventricle; LA – left atrium; TIA – transient ischemic attack; STEMI – ST elevation myocardial infarction; NSTEMI – non-ST elevation myocardial infarction

Tab. 2. Logistic regression model for AF detection.

	Estimate	Standard error	z	Wald Test			95% Confidence interval (odds ratio scale)	
				Wald statistic	df	p	Lower bound	Upper bound
(Intercept)	–8.396	2.119	–3.962	15.700	1	< 0.001	0.000	0.014
Age (years)	0.063	0.025	2.519	6.346	1	0.012	1.014	1.119
BMI (kg/m2)	–0.012	0.018	–0.635	0.403	1	0.526	0.954	1.024
Apelin (ng/ml)	3.301	0.905	3.648	13.310	1	< 0.001	4.608	159.975
Dilated LV	–0.045	0.445	–0.101	0.010	1	0.919	0.400	2.287
Dilated LA	–0.209	0.245	–0.855	0.731	1	0.393	0.502	1.311
Arterial hypertension (%)	–0.519	0.547	–0.949	0.901	1	0.342	0.204	1.738
Male gender (%)	0.043	0.252	0.170	0.029	1	0.865	0.636	1.712

BMI – body mass index; LV – left ventricle; LA – left atrium

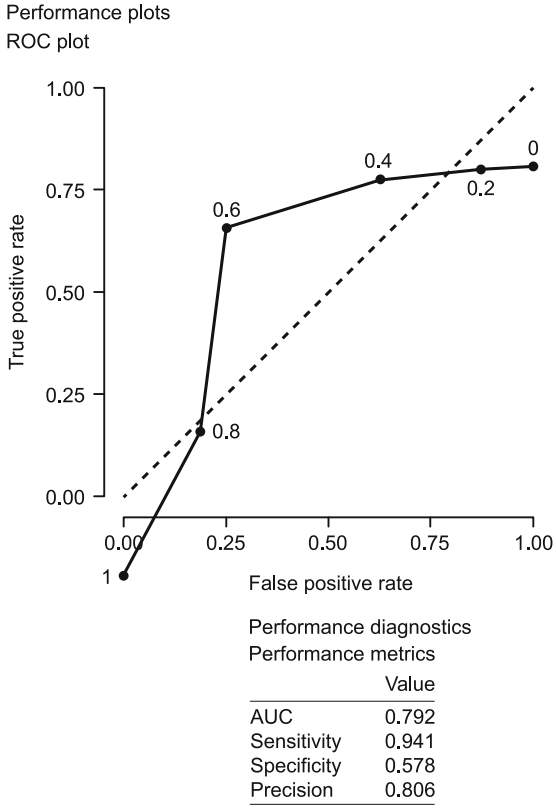

Fig. 1. ROC analysis of apelin for detection of AF.

the diagnostic performance. The effect of explanatory variables on the outcome was evaluated using logistic regression analysis. The estimates are presented together with the 95% confidence interval (CI). $p < 0.05$ was considered statistically significant. Data were analysed using StatsDirect statistical software version 3.2.10 (http://www.statsdirect.com) and JASP statistical software (Version 0.14.1, JASP Team 2020 (https://jasp-stats.org).

Results

Our study was composed of two groups. AF group (n = 119) included 81 males and 38 females with mean age of 64.28 (SD ± 11.31) and non-AF group which included 32 males and 32 females with mean age of 54.8 (SD ± 17.19). All collected variables with their corresponding p-values are presented in Table 1.

There was statistically significant difference between AF and non-AF group in age (64.28 ± 11.31 vs 54.8 ± 17.19 respectively, $p < 0.001$), arterial hypertension (83.19 % vs 45.31% respectively, $p < 0.001$), gender (male gender 68.07 % vs 50 % respectively, $p = 0.025$) and apelin plasmatic levels (0.74 ± 0.15 vs 0.98 ± 0.31 respectively, $p < 0.001$).

Multivariate analysis using logistic regression adjusted for age, BMI, apelin, dilated LV, dilated LA, arterial hypertension, and gender showed only apelin and age to be statistically significant contributors for AF (Tab. 2).

ROC analysis of apelin for detection of AF scored area under the curve (AUC) of 0.79, sensitivity = 0.941 and specificity = 0.578 (Fig. 1).

Discussion

In our study apelin showed good properties for detection of AF. This study builds on our previous research on apelin in which we analyzed patient groups with different risk profiles (18, 19, 21). In this study we pooled all patients from our previous research on apelin, including previously unpublished patients, who were excluded in propensity matching, forming a large diverse cohort of patients covering a broad spectrum from healthy to polymorbid patients. We believe that such a composition of patients is closer to real clinical conditions and that this larger cohort offers more robust results.

Besides apelin plasmatic levels, age, male gender, and arterial hypertension showed statistically significant difference between the two groups. Multivariate analysis showed only apelin and age to be statistically significant contributors for AF. These results are consistent with previously published data on arterial fibrillation and are known risk factors (6, 27).

Apelin is an endogenous peptide acting as a ligand for G-protein coupled APJ receptor. This system is involved in many physiological and pathophysiological processes including a wide range of effects on cardiovascular system. Apelin has already been studied as a potential candidate for treatment of heart failure and prevention of postischemic reperfusion (I/R) injury (28, 29) and now growing evidence supports its potential use as a biomarker for

AF detection (18–21, 30, 31). The pathophysiological basis for this strong relationship between apelin and AF is the fact that apelin directly or indirectly affects many processes and pathways associated with AF. Among other effects, it increases atrial conduction velocity and refractoriness, prevents the inducibility of AF, modulates cardiac sodium current, shortens action potential duration in atrial myocytes via its effects on multiple ionic channels, affects the renin-angiotensin-aldosterone signalling pathway and acts as a second catalytic substrate for ACE2 (22–25). Whether the change in plasmatic levels of apelin is caused by atrial stretch (32) or is rather a reflection of electrical remodelling of atria as suggested by our previous study (21) merits further research.

ECG recorded during fibrillation is an unparalalled diagnostic tool for AF detection offering almost 100 % specificity and sensitivity (33). The only downside is the fact that in many patients AF is often paroxysmal and asymptomatic. In this setting standard 12-lead ECG, 24h or even 48h Holter monitoring does not provide sufficient detection rate (34, 35) resulting in a large number of untreated patients with a high risk of stroke. Moreover, evidence shows that this subclinical AF is associated with an even higher risk of stroke (36). The need for a new widely-available, accurate, cost-effective and simple diagnostic tool, such as a biomarker detectable in peripheral blood, is further underscored by data showing tremendous benefits of potential AF screening (37, 38).

Our patient population did not include patients with severe valvulopathy, diabetes mellitus or heart failure. This is a significant limiting factor since valvular disease such as severe aortic stenosis (39) and diabetes mellitus have been shown to alter apelin plasmatic levels (40). In the setting of heart failure, assessment of apelin is even more complex. Some authors have reported decreased, unaltered, or even increased concentrations in these patients (25, 41, 42). On the other hand, other factors such as coronary atherosclerosis (43), arterial hypertension (44, 45) and left ventricular hypertrophy (46) have also been shown to alter plasmatic levels and despite these factors being present, apelin performed very well in detecting AF.

Our study had several limitations. Our study population did not include patients with severe valvulopathy, diabetes mellitus or heart failure. Therefore, the findings of our study cannot be generalized to the entire AF population. There was a statistically significant difference in age, a known risk factor for AF, between the two studied groups. Lastly the study was designed as a multicentre retrospective study.

In conclusion, our results suggest that apelin might be a promising biomarker for detecting AF. Additional research on different independent cohorts of patients with AF is however needed to confirm and further investigate our findings.

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Received November 27, 2022
Accepted December 8, 2022.