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The association between apelin-12 levels and paroxysmal supraventricular tachycardia

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Aims **Our aim was to investigate the apelin-12 levels in patients with atrioventricular tachyarrhythmias and compare with those in patients with lone atrial fibrillation.**

Methods **Forty four patients with supraventricular tachycardia as atrial fibrillation, 44 patients with paroxysmal supraventricular tachycardia (P-SVT) as atrioventricular tachyarrhythmias, including atrioventricular nodal reentrant tachycardia or atrioventricular reentrant tachycardia, and 30 age- and sex-matched healthy individuals were included in the study.**

Results **The apelin-12 levels were significantly lower in both atrial fibrillation and P-SVT groups than control group. In post-hoc analysis, there was no significant difference in apelin-12 levels between atrial fibrillation and P-SVT groups ($P = 0.9$). Patients in atrial fibrillation group and patients in P-SVT group had significantly lower apelin-12 levels than control group, separately ($P<0.001$ and $P<0.001$, respectively). The sensitivity and specificity values of the apelin-12 levels for predicting SVT, including both atrial fibrillation and atrioventricular reentrant tachycardia or atrioventricular nodal reentrant tachycardia were 64.77 and 90%, respectively (cut-off value was 0.87). The area under the receiver operator characteristic curve was 0.834 for the apelin-12 levels ($P = 0.0001$).**

Conclusion **Apelin-12 levels are lower in patients with atrial fibrillation and P-SVT than control groups. Lower apelin levels in patients with atrial fibrillation and P-SVT would be expected to result in a decrease in the conduction velocity.**

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Introduction

The peptide apelin and the apelin receptors are present in the heart,[1,2] the systemic and pulmonary vasculature, and there were studies that showed the changes of plasma apelin levels in myocardial infarction,[3] heart failure,[4–8] and pulmonary hypertension.[4,9] In heart failure patients, the concentration of apelin was 200-fold higher in atrial tissue than in left ventricular tissue. Plasma apelin concentrations correlated to atrial apelin levels, and it was thought that atrial apelin might be an important source of apelin in plasma.[5] Apelin protein levels were upregulated in left ventricular tissue, but were lower in atrial tissue from patients with heart failure compared with healthy controls.[5] The other studies researching the plasma levels of apelin in heart failure patients have reported the downregulation of the apelin system.[4,7,8]

Paroxysmal supraventricular tachycardia (SVT) is episodic, with an abrupt onset and termination. Manifestations of SVT are quite variable; patients may be asymptomatic or they have minor palpitations or more severe symptoms. SVTs may be classified as an atrial or atrioventricular tachyarrhythmia. Atrial fibrillation is an extremely common arrhythmia arising from chaotic atrial depolarization. The most common cause of paroxysmal SVT is atrioventricular nodal reentrant tachycardia (AVNRT).

Previously, the relation between atrial fibrillation and apelin levels was shown in a few studies.[10–12] All of these studies showed that lower levels of apelin levels were associated with atrial fibrillation and were related to the recurrence of arrhythmia.[11]

No published data exist to date about the level of apelin-12 in patients with paroxysmal SVT. So, we aimed to investigate the apelin-12 levels in patients with atrioventricular tachyarrhythmias and compare with those in patients with lone atrial fibrillation.

Participants and methods

Patient population

From March 2011 to March 2012, 88 consecutive patients with SVT who were admitted to our emergency room with palpitations were included in the study. These participants were matched on the basis of age, sex, and

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ethnicity with 30 controls recruited from a healthy population. Forty four patients with SVT had atrial fibrillation and the other 44 of them had atrioventricular tachyarrhythmias, including AVNRT or atrioventricular reentrant tachycardia (AVRT). All participants provided written informed consent. The protocol was approved by the local ethics committee. Individuals were considered eligible for enrollment if they had persistent atrial fibrillation and had a structurally normal heart on echocardiography. Other individuals were considered eligible for enrollment if they had AVNRT or AVRT on admission to emergency and had a structurally normal heart on echocardiography.

Exclusion criteria were as follows: history of coronary artery disease and heart failure, suspected myocarditis or pericarditis, diabetes mellitus, unstable angina pectoris, ST and non-ST-segment elevation myocardial infarction, impaired renal function (creatinine $\geq$1.4 mg/dl), unstable endocrine or metabolic diseases, patients with concomitant inflammatory diseases such as infections and autoimmune disorders, acute/chronic hepatic or hepatobiliary disease, pulmonary hypertension, and malignancy.

All participants underwent standard 12-lead electrocardiogram at enrollment and were evaluated by a cardiology specialist in the emergency room. A standardized echocardiogram was also obtained from each individual. The echocardiograms were carried out by a cardiology specialist in the echocardiography laboratory in our cardiology department. The echocardiography was performed by Vivid 3 instruments (GE Medical Systems, Milwaukee, Wisconsin, USA), with a 2.5-MHz transducer and harmonic imaging. Left ventricular ejection fraction was assessed using the modified biplane Simpson's method.

Blood sampling and laboratory methods

Blood samples of all individuals were taken from an antecubital vein following an electrocardiogram. Plasma was extracted, aliquoted, and stored at -70°C until analysis. Plasma apelin-12 levels were determined using a commercially available enzyme immunoassay without extraction (Phoenix Pharmaceuticals, Belmont, California, USA) according to the manufacturer's instructions.

Statistical analysis

Categorical variables were presented as counts and percentages and were compared with the χ^2 test. Continuous variables were expressed as means and SD. Student's *t*-test or Mann–Whitney *U*-test (as appropriate) has been used for continuous variables between two groups. Comparisons among three groups were carried out using one-way analysis of variance and Tukey's post-hoc test. Correlation analyses were performed using the Pearson or Spearman's coefficient of correlation. Sensitivity and specificity values of apelin-12 levels for predicting SVT were estimated using receiver operator characteristic (ROC) curve analysis. The cut-off level of apelin-12 levels was determined using MedCalc 9.2.0.1 (MedCalc Software, Mariakerke, Belgium). A trial version of (demo) SPSS 15.0 software was used for basic statistical analysis (Version 15; SPSS Inc., Chicago, Illinois, USA). A value of $P<0.05$ was accepted as statistically significant.

Results

The baseline characteristic properties of study patients are summarized in Table 1. There were no significant differences among the three groups with respect to sex distribution, age, frequencies of major coronary risk factors (i.e., diabetes mellitus, hypertension, dyslipidemia, smoking, family history of coronary artery disease), serum creatinine, calcium, potassium, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, left ventricular ejection fraction, left atrial diameter, SBP, and DBP ($P>0.05$ for all). The heart rate of control group was significantly low as compared with atrial fibrillation and SVT groups.

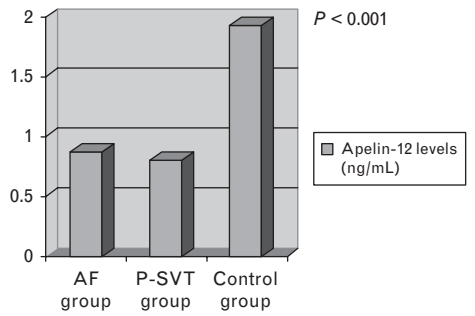
The apelin-12 levels were significantly lower both in atrial fibrillation and SVT groups than the control group (Fig. 1). In post-hoc analysis, there was no significant difference in apelin-12 levels between atrial fibrillation and SVT groups ($P=0.9$). Patients in the atrial fibrillation group and patients in the SVT group had significantly

Table 1 The characteristics of study participants

	Lone AF group ($n=44$)	PSVT group ($n=44$)	Control group ($n=30$)	*P*
Age (years)	45 ± 7	42 ± 9	40 ± 8	0.3
Women (%)	60.5	55.6	56.7	0.8
History of (%)				
Diabetes mellitus	11.6	13.3	10	0.6
Hypertension	18.6	24.4	13.3	0.2
Smoke	20.9	17.8	16.7	0.9
Creatinine (mg/dl)	0.90 ± 0.20	0.86 ± 0.19	0.89 ± 0.20	0.5
Hemoglobin (mg/dl)	13.5 ± 1.8	13.6 ± 1.7	13.9 ± 1.4	0.6
White blood cell count	10 ± 3	10.3 ± 3	8.9 ± 2.7	0.1
Troponin I	0.04 ± 0.04	0.03 ± 0.04	0.02 ± 0.02	0.1
SBP (mmHg)	131 ± 18	137 ± 22	130 ± 18	0.2
DBP (mmHg)	76 ± 11	78 ± 14	77 ± 12	0.8
Heart rate (beat/min)	142 ± 21	146 ± 27	84 ± 14	<0.001

Data expressed as mean ± SD or percentage. AF, atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia. $P<0.05$ was accepted as statistically significant.

Fig. 1



The difference in apelin levels among three groups [0.87 ± 0.43 in the atrial fibrillation group, 0.81 ± 0.28 in the paroxysmal supraventricular tachycardia (P-SVT) group, and 1.94 ± 1.55 in the control group, $P<0.001$].

lower apelin-12 levels than the control group, separately ($P<0.001$ and $P<0.001$, respectively).

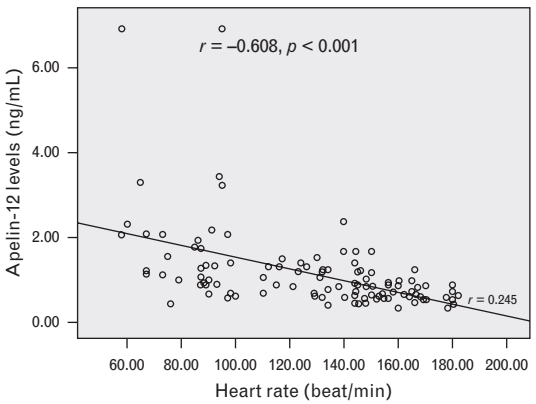
Figure 2 shows the Pearson correlation analysis of apelin-12 levels and heart rate. Apelin-12 levels were highly negatively correlated with the heart rate of the study participants ($r=-0.608$ and $P<0.001$).

ROC analysis was used to identify the ability of apelin-12 levels to predict the SVT and is shown in Fig. 3. We accepted both patients with atrial fibrillation and P-SVT groups as SVT Group for this analysis. The area under the ROC curve was 0.834 for the apelin-12 levels ($P=0.0001$). The sensitivity and specificity values of the apelin-12 levels were 64.77 and 90%, respectively (cut-off value was 0.87).

Discussion

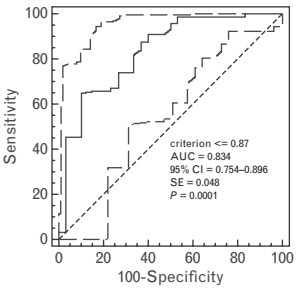
We have demonstrated that the apelin-12 levels were significantly lower both in the atrial fibrillation and paroxysmal SVT groups than the control group.

Fig. 2



The correlation analysis of apelin-12 levels and heart rate in all study patients.

Fig. 3



Receiver operator characteristic curve of apelin-12 levels in study patients for predicting supraventricular tachycardia. AUC, area under curve; CI, confidence interval.

Apelin is a peptide that is the ligand for the APJ (angiotensin receptor like-1) receptor.[8,13] Apelin and APJ are widely distributed in the vasculature of organs.[8] Apelin mRNA expression was found in the gastrointestinal tract, adipose tissue, brain (corpus callosum, amygdala, substantia nigra, and pituitary), spinal cord, lung, kidney, liver, skeletal muscle, and cardiovascular system.[14,15] In the cardiovascular system, apelin has been detected in endothelial cells of large conduit arteries, coronary vessels, and endocardium of the right atrium.[14]

Apelin–APJ system plays a role in regulation of fluid[16] and glucose homeostasis, feeding behavior, vessel formation, cell proliferation and immunity.[17]

In the cardiovascular system, apelin is a potent vasodilator[14,18,19] with a strong positive inotropic effect.[8,13,17] The vasodilatation effect of apelin is connected with nitric oxide and it may also be because of the fact that APJ receptors counteract the pressure effect of angiotensin II.[14] Apelin is a coronary vasodilator and reduces peripheral vascular resistance. Intravenous apelin administration in rodents reduces mean arterial pressure and systemic venous tone.[18]

Apelin has been shown to exert potent positive inotropic effects on both normal and failing myocardium[20] by increasing intracellular calcium rather than enhancing the calcium sensitivity of the myofilaments.[13,21] The inotropic response to apelin may involve activation of phospholipase C, protein kinase C, and sarcolemmal sodium hydrogen exchange, and sodium calcium exchange.[21] In humans, apelin was reduced in patients with left ventricular dysfunction secondary to ischemic heart disease, congestive heart failure, and dyslipidemia.[13,21,22]

Paroxysmal SVT is a common cardiac arrhythmia presenting to emergency departments.[23] It can be benign and self-limiting. Patients may present with distressing symptoms of palpitations, dizziness, fatigue, and weakness; however, patients may also experience serious complaints or symptoms, including angina, dyspnea, hypotension, or congestive heart failure.[24,25]

There are three accepted mechanisms for tachyarrhythmias: increased automaticity in a normal or ectopic site, reentry in a normal or accessory pathway, and after depolarizations causing triggered rhythms. About 60% of patients with SVT have reentry within the atrioventricular node (AVNRT), and 20% have reentry involving a bypass tract (AVRT). The remaining have reentry in other sites.[25] Reentry can occur in atrioventricular node, in atrium, and between atrioventricular node and accessory pathways. Paroxysmal SVT can occur by reentry in atrioventricular node or between atrioventricular node and the accessory pathway.[26] The underlying mechanism of atrial fibrillation is still debated. Cellular proarrhythmic mechanisms (automaticity and triggered activity) and reentrant mechanisms might underlie atrial fibrillation. Shortening of atrial refractoriness and reentrant wavelength or local conduction heterogeneities and changes in ion channel function may occur in patients with atrial fibrillation.[27]

Low levels of the regulatory peptide apelin have been reported in patients with lone atrial fibrillation.[10–12] Kallergis *et al.*[10] demonstrated that apelin levels are lower in patients with persistent, long-lasting, lone atrial fibrillation and they found that successful cardioversion of atrial fibrillation led to a significant increase in plasma apelin levels. Similarly, Falcone *et al.*[11] demonstrated that significantly lower apelin plasma levels were found in patients with atrial fibrillation recurrence with respect to population with persistence of sinus rhythm during a 6-month follow-up. These studies show that apelin may play an important role in intercellular communication. In the present study, we showed the relationship between apelin and patients with atrial fibrillation and paroxysmal SVT like other studies. We showed high negative correlation between heart rate and serum apelin levels in our study. This result supports the finding of study by Kallergis *et al.* because they found an increase in apelin levels when they supplied sinus rhythm in atrial fibrillation patients. After conversion of atrial fibrillation to sinus rhythm, the heart rate will decrease and become regular. So our study first shows the relation between heart rate and serum apelin levels.

The function of individual cells in the conductive and contractile tissues of the heart depends on an intact resting membrane potential. Na^+, K^+, and Ca^{++} ions have a primary role in creating the membrane potential and regulating conduction and contraction. Disturbances in intracellular and extracellular ion concentrations can alter the membrane potential and produce abnormalities of impulse generation, conduction, and myofibril contraction.[26] Apelin significantly activated the sarcolemmal Na^+/H^+ exchanger, increased intracellular pH, and increased conduction velocity in monolayers of cultured neonatal rat cardiac myocytes.[28] Cheng *et al.*[29] demonstrated that apelin increased sodium current, ultrarapid potassium currents and reverse mode of sodium-calcium exchanger current, but decreased late sodium current and L-type calcium currents and did not change transient outward current or inward rectifier potassium currents in rabbit left atrial myocytes, so apelin affected the electrophysiology of left atrial myocytes and hence led to a shortening of axion potential duration via regulation of various ionic currents.

Lower apelin levels in patients with atrial fibrillation and PSVT would be expected to result in a decrease of the conduction velocity. Slowing conduction leads to a shorter wavelength, facilitates conduction block, and permits a larger number of re-entering wavelets to coexist in the atria and atrioventricular node.

The arrhythmogenic role of apelin needs to be investigated further. In conclusion, our results demonstrate that apelin levels are lower in patients with atrial fibrillation and PSVT than control groups and highly correlated with heart rate.

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