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Paraoxonase 1 and atrial fibrillation

Is there a relationship?

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Abstract

Atrial fibrillation (AF) is associated with oxidative stress and inflammation. Paraoxonase-1 (PON1), circulates in blood bound to high-density lipoproteins and reduces systemic oxidative stress. The aim of this study was to evaluate PON1 serum concentration and PON1 arylesterase activity (AREase) in patients with AF. We studied a group of 67 patients with symptomatic paroxysmal or persistent AF admitted for cardioversion and a control group of 59 patients without AF. Clinical parameters, lipid profile, PON1 concentration and AREase were evaluated. A significant difference in serum PON1 concentration and in AREase was found among the two groups. In a multivariate linear regression model, the presence of AF was associated with low PON1 concentration ($P = .022$). The body mass index was also independently associated with PON1 values ($P < .001$). Only the high-density lipoproteins-cholesterol level was independently associated with AREase ($P = .002$). PON1 serum concentrations and AREase were diminished in patients with AF, and the presence of AF was independently associated with low PON1 values.

Abbreviations: AF = atrial fibrillation, AREase = arylesterase activity, BMI = body mass index, HDL = high-density lipoproteins, HDL-C = HDL cholesterol, IHD = ischemic heart disease, LDL = low density lipoproteins, LDL-C = LDL cholesterol, PON1 = paroxonase 1, TG = triglycerides.

Keywords: atrial fibrillation, oxidative stress, paraoxonase-1

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with increased mortality and morbidity. Besides AF association with increased age, obesity, diabetes, hypertension or coronary heart disease, increasing evidence suggests that enhanced oxidative stress and inflammation, play a predominant role in the initiation and perpetuation of AF.[1,2] PON1 (paroxonase-1) is a calcium-dependent hydrolytic enzyme, primarily generated in the liver and found in the circulation bound to high-density lipoproteins (HDL).[3] PON1 has been linked to three separate catalytic activities, paraoxonase, arylesterase, and lactonase. Arylesterase activity is thought to be a superior surrogate of PON1 concentration, as it shows minimal interindividual variability.[4] Aviram et al[5] demonstrated for the first time that HDL-associated PON1 protects not only low density lipoproteins (LDL), but also HDL from oxidation. PON1 achieves its antioxidant activity by first inhibiting the buildup of oxidized lipids during induced oxidation, then by consuming and thereby removing preexisting oxidized lipoproteins.

PON1 may also play an anti-inflammatory role through a variety of mechanisms, including shielding HDL and LDL from oxidation, minimizing monocyte chemotaxis and adhesion to endothelium, or preventing monocytes from transforming into macrophages, that results in decreased vascular inflammation response.[6,7] Aharoni et al[8] discovered that in INFy/lipopolysaccharide -stimulated macrophages, PON1 significantly reduced the synthesis and release of the pro-inflammatory cytokines TNF-alpha and IL-6, which further supports the anti-inflammatory effect of PON1. Moreover, a recent study showed that AREase was directly proportional to the levels of proinflammatory markers (interleukin 6, C-reactive protein, and leptin), until higher levels of inflammation when the enzyme's activity reached a plateau or even decreased.[9] These substantial investigations suggest high levels of inflammation may decrease PON1 activity, rendering HDL dysfunctional and leading to an increased risk of cardiometabolic diseases.

Evolving knowledge that HDL becomes dysfunctional during cardiovascular disease development, has fueled a search for additional HDL characteristics, which may be used as risk biomarkers of cardiovascular disease.[10,11] Currently, PON1 is

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

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known to have decreased AREase activity in a variety of disorders associated with high oxidative stress and chronic inflammation, such as dyslipidemia, obesity, atherosclerosis or chronic kidney disease.[12–14] In addition, through its multiple functions, the PON1 status may be an early biomarker for predicting the evolution of cardiovascular disease.[15,16] Given that oxidative stress and inflammation, as well as metabolic syndrome components are involved in AF pathogenesis and might have an additive effect on AF risk, we hypothesized an association between PON1 and AF. To the best of our knowledge, previous studies have not evaluated the role of PON1 in AF. In this study, we analyzed the relationship of PON1 concentration and the antioxidant activity of HDL, represented by the arylesterase activity of PON1, to AF.

2. Materials and methods

Between December 2019 and December 2020, 67 consecutive patients with symptomatic paroxysmal or persistent AF admitted at Cardiology Department of the Rehabilitation Hospital from Cluj-Napoca for cardioversion were enrolled. Main exclusion criteria were designed to avoid any other disease that might influence PON1 activity (e.g., malignancies, autoimmune diseases, and psychiatric disorders). A control group of 59 participants age and gender matched were selected from patients attending the same clinic for non-arrhythmia related symptoms. Exclusion criteria were similar, a history of AF, other prolonged atrial arrhythmias, or unexplained palpitations were added. The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee; all patients provided written informed consent.

General data of patients were collected, including age, gender, body mass index (BMI), and the following comorbidities: obesity, ischemic heart disease (IHD), hypertension, and diabetes mellitus. Obesity was defined as a BMI of 30 or higher. IHD was considered in adults with known stable angina, unstable angina, or with a history of myocardial infarction, as well as in asymptomatic patients who were diagnosed through non-invasive methods, Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or a diastolic blood pressure ≥ 90 mm Hg or current antihypertensive drugs. Diabetes mellitus was defined as fasting glucose ≥ 7.0 mmol/L, 2-hours glucose ≥ 11.1 mmol/L, or using diabetes medication. Intravenous blood samples after overnight fasting was withdrawn for, total cholesterol, LDL cholesterol (LDL-C), HDL-C, triglycerides (TG), aspartate transaminase, alanine aminotransferase. All patients with AF underwent transthoracic echocardiography and the following parameters were performed according to the American Society of Echocardiography guidelines: anteroposterior left atrium diameter, left atrium area, left atrium volume, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular ejection fraction, and right ventricle diameter.

Human serum arylesterase/paraoxonase was determined using a colorimetric method according to manufacturer instruction (Arylesterase/paraoxonase assay kit; ZeptoMetrix LLC, Buffalo, NY). The principle of the assay is based on arylesterase/paraoxonase property to catalyze the phenyl acetate cleavage, resulting in phenol formation. The phenol rate formation was measured by analyzing the absorbance increase as measured at 270 nm and 25°C, using a BioDrop Duo UV-VIS spectrophotometer. The working reagents were 20 mM Tris/HCl buffer at pH 8.0 which contained 4 mM phenyl acetate and 1 mM CaCl2 as substrate. It was considered that one unit of arylesterase activity equals to 1 μM of phenol formed in one minute. The activity was expressed in kU/L. Blank samples containing water were used to correct the non-enzymatic hydrolysis. A purified PON standard was included in the kit.

Serum PON1 was measured using ELISA technique (Stat Fax 303 Plus Microstrip Reader, Minneapolis, MN). The detection and concertation of PON1 enzyme was performed using commercially available Human PON1 ELISA Kit (Elabscience, Houston, TX). The results were expressed in ng/mL.

Statistical analysis was performed using MedCalc Statistical Software version 19.7 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org). Continuous data were evaluated for normality of distribution using the Shapiro–Wilk test and expressed as the median and 25th to 75th percentiles. Qualitative data were characterized by frequency and percentage. Comparisons between groups were performed using the Mann–Whitney of chi-square tests, whenever appropriate. Multivariate linear regression was used in order to determine which parameters were associated with PON1 serum concentration and arylesterase activity. A P-value < .05 was considered statistically significant. The sample size was calculated using the first 10 patients from each group (AF and controls). For AREase we calculated a mean difference of 10.9 kU/L between the two groups. For a type 1 (alpha) error of 0.05 and a type 2 (beta) error of 0.15, we calculated a sample size of 58 patients in AF group and 51 patients in controls.

3. Results

Study groups characteristics can be found Table 1. There were statistically significant differences between patients with AF and controls regarding BMI, PON1 and AREase, lipid profile and presence of IHD, myocardial infarction, heart failure or stroke.

Correlations between PON1 and other continuous variables can be observed in Table 2. PON1 was weakly correlated with age and TG, moderately correlated with HDL-c and strongly correlated with BMI. AREase was strongly correlated with HDL-cholesterol.

There were no significant correlations between PON1 or AREase and echocardiographic parameters in AF patients (Table 3).

Lower PON1 levels were observed in obese patients or in those with hypertension (Table 4).

Multivariate analysis for variables associated with PON1 levels was performed using linear regression (Table 5). Patients with AF independently influenced the levels of PON1. The BMI were independently associated with PON1 values.

There was no statistically significant association between AREase and variables from Table 6.

Multivariate analysis for variables associated with AREase was performed using linear regression (Table 7). Only the HDL-C values were independently associated with arylesterase activity.

4. Discussion

The findings of the present study revealed an association between AF and arylesterase activity of PON1 and PON1 concentration. Also, the study reconfirms the relationship between PON1 and obesity and lipid profile.

We found statistically significant differences between the AF group and the control group regarding the clinical parameters. The AF patients presented higher BMIs and higher TG, with lower level of HDL-C and they were more prone to having arterial hypertension. It is well known that AF associates with obesity, and other comorbidities including diabetes, hypertension, or coronary heart disease.

Although dyslipidemia is a well-known risk factor for cardiovascular disease, the exact role of blood lipids in the AF development, is still debated.[17] HDL-C and TG, but not LDL-C or total cholesterol, were linked to the incidence of AF in two community-based cohorts.[18] Similar to these observations, a post hoc analysis of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack trial found that a low level of baseline HDL-C was associated with an increased risk of AF.[19]

Table 1

Characteristics of patients with and without atrial fibrillation.

Variables		Patients with AF	Controls	*P*
Age (yr)*		60 (55; 65)	60 (54; 63)	.287
Gender†	Male	50 (74.6)	40 (67.8)	.397
	Female	17 (25.4)	19 (32.2)	
Body mass index (kg/m^2)*		31 (27.65; 33.9)	23.45 (21.6; 25.23)	<.001
PON1* (ng/mL)		6 (2.81; 12.08)	15.31 (13.9; 16.3)	<.001
AREase* (kU/L)		67.04 (53.24; 84.41)	77.7 (61.07; 89.78)	.012
LDL-C* (mg/dL)		113 (87; 137)	137.80 (104.4; 159.6)	.003
HDL-C* (mg/dL)		41 (34; 47.5)	52 (45; 62)	<.001
TC* (mg/dL)		182 (149; 221.5)	217 (178; 238)	.003
TG* (mg/dL)		126 (100.5; 178)	117 (77; 146)	.01
AST* (UI/L)		22 (19; 29.5)	22 (19; 30)	.782
ALT* (UI/L)		23 (16.5; 40.5)	22 (19; 27)	.48
Obesity†		40 (59.7)	4 (6.8)	<.001
Heart failure†		11 (16.4)	4 (6.8)	.108
IHD†		5 (7.5)	10 (16.9)	.172
HTN†		45 (67.2)	20 (33.9)	<.001
DM†		10 (14.9)	2 (3.4)	.058
Myocardial infarction†		3 (4.5)	1 (1.7)	.622
Stroke/TIA†		8 (11.9)	3 (5.1)	.296
Statins†		36 (53.7)	28 (47.5)	.6
LVEDD* (mm)		50 (46; 55)	48 (45; 52)	.088
LVESD* (mm)		34 (29.7; 40.2)	34 (26; 39)	.379
LVEF* (%)		55 (50; 60)	60 (55; 60)	.085

AF = atrial fibrillation, ALT = alanine aminotransferase, AREase = arylesterase activity, AST = aspartate transaminare, DM = diabetes mellitus, HDL-C = high-density lipoproteins cholesterol, HTN = hypertension, IHD = ischemic heart disease, LDL-C = low-density lipoproteins cholesterol, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, PON1 = paroxonase 1, TC = total cholesterol, TG = triglycerides, TIA = transient ischemic attack.

*Expressed as median and 25–75 percentiles.

†Expressed as frequency and percentage fibrillation.

Table 2

Correlations between PON1, AREase and demographic, anthropometric and laboratory data.

	PON		AREase	
Variables	***r***	***P***	***r***	***P***
Age	0.195	.029	0.069	.443
BMI	–0.517	<.001	0.033	.71
LDL-C	0.099	.270	0.156	.082
HDL-C	0.242	.006	0.333	<.001
TC	0.102	.256	0.152	.09
TG	0.185	.038	0.048	.597
AST	0.155	.102	0.061	.520
ALT	0.148	.119	0.086	.366

ALT = alanine aminotransferase, AREase = arylesterase activity, AST = aspartate transaminare, BMI = body mass index, HDL-C = high-density lipoproteins cholesterol, LDL-C = low-density lipoproteins cholesterol, PON1 = paroxonase 1, TC = total cholesterol, TG = triglycerides.

In contrast, other research has found that AF patients have a normal lipid profile.[20] However, literature is inconsistent, and the exact role of blood lipids in the development of AF, if any, remains to be determined.

Both PON1 and arylesterase activity were also significantly lower in the AF group, while patients with AF independently influenced the levels of PON, but not the arylesterase activity.

Human paraoxonase 1, which exhibits PON, arylesterase, and diazoxonase activity, is exclusively linked to HDL-C. PON1 activity has been shown to be inversely related to the risk of cardiovascular disease due to its antioxidant and anti-atherogenic properties that protect both LDL-C and HDL-C against lipid peroxidation.[21] When compared to people with high PON1 activity, low PON1 activity has been linked to "poor-quality" HDL-C, implying a higher risk of developing disorders where oxidative stress is involved. A decrease in PON1 activity has been observed in states of high oxidative stress including metabolic syndrome, obesity, uncontrolled diabetes, and dyslipidemia, all of which are known risk factors for AF.[22]

Zhao et al[23] conducted a meta-analysis of 43 studies and determined that reduced activity of PON1 is associated with a higher susceptibility for cardiovascular diseases. PON1 activity has also been linked to a greater risk of severe adverse cardiac events, and low PON1 serum concentrations have been shown to be an independent predictor of cardiovascular mortality.[3] Lipid peroxidation is thought to be a crucial stage in the development of atherosclerosis. In addition, oxidation of lipoproteins also causes cell damage and electrophysiologic changes in cardiomyocytes, a pathophysiological mechanism present in AF. Thus, reduced antioxidative function, has been proposed as an AF predisposing substrate. Trieb et al[24] were the first to provide evidence that indices of HDL function, including cholesterol efflux capacity, lecithin-cholesterol acyltransferase activity, and HDL-particle number are markedly reduced in AF patients. Furthermore, this reduction was partially correlated with AF progression stage characterized by a switch from paroxysmal to persistent AF. Importantly, restoration of sinus rhythm ameliorated HDL dysfunction in AF patients after catheter ablation. However, in their study the paraoxonase-mediated arylesterase activity was not influenced by AF.

Our study showed that the BMI was independently associated with PON1 values. Due to inconclusive data, there is a paucity of data on alterations in PON1 status in obesity. Following the first findings on decreased PON1 activity and increased lipid peroxidation levels in isolated HDL from adult obesity, lower serum AREase has been consistently documented in obese individuals.[25,26] On the other hand, investigations on PON activity in obesity have shown mixed results; some have found a decreased PON activity,[27] while others have found no significant alterations.[28]

It has been demonstrated an increase in oxidative stress in obese individuals, the LDL-C isolated from obese patients being more susceptible to lipid peroxidation than the LDL-C isolated from healthy control group.[25] Thus obesity is associated with

Table 3

Correlations between PON, AREase and echocardiographic parameters in AF patients.

	PON		AREase	
Variables	***r***	***P***	***r***	***P***
LAD	0.042	0.763	−0.200	0.147
LAA	−0.075	0.670	−0.255	0.139
LAVOL	−0.036	0.848	−0.155	0.414
LVEDD	−0.110	0.439	−0.201	0.153
LVESD	0.022	0.878	−0.215	0.126
LVEF	−0.125	0.378	0.046	0.747
RV	−0.180	0.281	−0.244	0.140

AF = atrial fibrillation, AREase = arylesterase activity, LAA = left atrium area, LAD = left atrium diameter, LAVOL = left atrium volume, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, PON1 = paroxonase 1, RV = right ventricle diameter.

Table 4

Association between PON1 concentration and nominal variables.

	Variables	PON concentration	*P*
Gender	Female	12.46 (5.20; 15.44)	.133
	Male	13.63 (5.94; 16.68)	
Obesity	Yes	5.41 (2.46; 11.32)	<.001
	No	14.83 (12.33; 16.26)	
IHD	Yes	14.75 (10.01; 16.85)	.339
	No	12.99 (5.69; 16.04)	
HTN	Yes	11.67 (4.14; 15.58)	.032
	No	14.71 (9.58; 16.25)	
DM	Yes	6.66 (3.42;15.38)	.136
	No	13.79 (6.38; 16.13)	
Statins	Yes	12.93 (6.15; 16.48)	.516
	No	13.61 (5.62; 15.95)	

DM = diabetes mellitus, HTN = hypertension, IHD = ischemic heart disease, PON1 = paroxonase 1.

Table 5

Multivariate linear regression for PON1 concentration.

	Unstandardized coefficients			95% CI for B	
Variables	**B**	***t***	***P***	**Min**	**Max**
(Constant)	2.163	6.757	0.000	1.529	2.797
AF	−0.185	−2.321	0.022	−0.343	−0.027
Age	−0.005	−1.283	0.202	−0.013	0.003
BMI	−0.028	−3.970	<0.001	−0.042	−0.014
HDL-C	−0.001	−0.239	0.812	−0.005	0.004

AF = atrial fibrillation, BMI = body mass index, CI = confidence interval, HDL-C = high-density lipoproteins cholesterol, PON1 = paroxonase 1.

alterations of lipid profile, in terms of both composition and level, which in turn carries a higher risk of cardiovascular disease, including AF.

Despite the documented association between low levels of serum PON1 and coronary artery disease and obesity, to the best of our knowledge no data are available on the levels of serum PON1 and ARE activity in patients with AF.

However, since the study population was small, extrapolation of our findings to other populations should be done with caution. Our findings are observational, do not indicate causality, and may be influenced by unmeasured variables. Nonetheless, given the scarcity of data on this subject, our findings constitute an important addition to the literature.

Further research should be directed to measurement of PON1 activity in combination with the lipid profile, as well as inclusion of these parameters into scores for improving the prediction and evolution of AF. Deeper understanding of PON1 role in AF might provide novel interventions in AF treatment, including PON1 targeted pharmacological agent.

Table 6

Association between AREase and nominal variables.

	Variables	AREase	*P* value
Gender	Female	75.48 (62.15; 86.95)	.284
	Male	70.77 (51.95; 85.69)	
Obesity	Yes	70.89 (59.05; 86.36)	.709
	No	75.72 (54.65; 86.13)	
IHD	Yes	75.69 (56.46; 91.59)	.778
	No	72.45 (55.31; 86)	
HTN	Yes	71.99 (58.76; 86.42)	.901
	No	72.94 (54.26; 85.87)	
DM	Yes	69.35 (47.66; 85.38)	.417
	No	73.78 (57.12; 86.33)	
Statins	Yes	72.75 (55.91; 86.1)	.573
	No	70.38 (55.24; 86.33)	

AREase = arylesterase activity, DM = diabetes mellitus, HTN = hypertension, IHD = ischemic heart disease.

Table 7

Multivariate linear regression for arylesterase activity.

	Unstandardized coefficients			95% CI for B	
Variables	**B**	***t***	***P***	**Min**	**Max**
(Constant)	1.656	25.666	<.001	1.529	1.784
AF	−0.016	−0.517	.606	−0.075	0.044
HDL-C	0.004	3.185	.002	0.001	0.006

AF = atrial fibrillation, CI = confidence interval, HDL-C = high-density lipoproteins cholesterol.

5. Conclusions

The study shows that there might be an association between AF and the arylesterase activity of PON1 or PON1 concentration. Although the results are preliminary, they add important information regarding the conundrum of AF and oxidative stress.

Author contributions

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