



## Endothelial dysfunction in patients with lone atrial fibrillation

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### Original Article

#### Abstract

**BACKGROUND:** Atrial fibrillation (AF) is the most common tachyarrhythmia in patients with cardiovascular diseases (CVDs) and may have significant complications such as stroke. The present study aims to evaluate endothelial dysfunction in patients with lone atrial fibrillation (LAF) through flow-mediated dilation (FMD) in the brachial artery, as a non-invasive method for evaluating functional and structural markers of endothelial dysfunction.

**METHODS:** In this case-control study, 43 patients with LAF were selected. 51 age and sex-matched healthy individuals were selected as the control group. The brachial artery diameter of the subjects in both groups was measured through FMD. The obtained data were analyzed by SPSS software.

**RESULTS:** Patients with LAF and healthy subjects did not have any difference in terms of gender, heart rate (HR), and systolic blood pressure (SBP) ( $P > 0.05$  for all). FMD of the patients with AF was significantly lower ( $P = 0.04$ ) than FMD of the healthy controls.

**CONCLUSION:** Our findings showed that LAF was associated with systemic endothelial dysfunction. AF plays an important and independent role in reducing FMD.

**Keywords:** Atrial Fibrillation; Arrhythmia; Dysfunction

*Date of submission:* 30 Dec. 2019, *Date of acceptance:* 28 Apr. 2020

#### Introduction

Atrial fibrillation (AF) is the most frequent tachyarrhythmia which affects more than 5% of people over 65 years. It is a progressive arrhythmia with an increasing rate of prevalence with age. Although AF is not an independent factor for predicting mortality in patients with cardiovascular diseases (CVDs), its complications and morbidity, such as stroke, are significant.<sup>1,2</sup> In 80% of cases, AF is associated with some conditions and CVDs. These underlying causes include ischemic heart failure (IHF), heart failure, valvular heart disease (VHD), hypertension, diabetes mellitus (DM), alcohol consumption, thyroid, and pulmonary diseases. Based on the study population, about 2-10% and in some studies, up to 30% of patients have no specific cause for AF.<sup>3-5</sup> Lone atrial fibrillation (LAF) has a different pathophysiology process and develops in patients younger than 60 years with no evidence of

hypertension or structural heart disease.<sup>6</sup>

Several demographic, genetic, and anthropometric factors have been suggested as the risk factors for AF. Although the prevalence of AF increases with age, LAF can occur in younger patients.<sup>7</sup> Indeed, LAF appears due to physiological changes associated with the autonomic system tone, especially the parasympathetic pathway (vagal AF), insulin sensitivity, and imbalance between serum electrolytes at the cell level with a short refractory period.<sup>7</sup>

On the other hand, some studies have shown that endothelium is not just a barrier between intracellular and intravascular components; instead,

**How to cite this article:** Heshmat-Ghahdarjani K, Jangjoo S, Amirpour A, Najafian J, Khosravi A, Heidarpour M, et al. **Endothelial dysfunction in patients with lone atrial fibrillation.** ARYA Atheroscler 2020; 16(6): ???.

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it is an extensive organ with many essential tasks that play a crucial role in tissue oxygenation, vasomotor control, homeostasis, inflammation, and immune response.<sup>8</sup>

Sometimes the endothelium suffers some injury and an abnormal activity called endothelial dysfunction (ED). Indeed, ED is a clinical syndrome described by impaired reactivity of the vasculature.<sup>9</sup>

Given that endothelial dysfunction is involved in the clinical manifestations of many diseases, its evaluation has a potential diagnostic and prognostic role.<sup>10</sup> Besides, it has recently been shown that endothelial dysfunction can be reversible. This could be important because reversibility at an early stage can increase the disease treatment chance, and even changes in endothelial dysfunction in advanced diseases may be effective in reducing progression and complications of them.<sup>8,11-15</sup> In arrhythmia, there is a cause-effect relationship between conditions that impair endothelial function and metabolic activity. The relationship between these two functions and basal mechanisms has not been investigated so far. The present study is intended to investigate endothelial dysfunction in patients with LAF through flow-mediated dilation (FMD) in the brachial artery as a non-invasive technique for evaluating the functional and structural markers of endothelial dysfunction. We aimed to help identify the functional and structural markers of LAF and decrease its complications or exacerbation through the administration of inhibitory drugs in clinical trials.

## Materials and Methods

In this case-control study, 43 patients who fulfilled diagnostic criteria of LAF were enrolled in this study through the non-randomized convenience sampling method from patients who visited the Shahid Chamran Hospital in Isfahan, Iran, from January 2017 to August 2017. 51 age- and gender-matched healthy subjects according to medical history, physical examination, and routine laboratory tests without a history of palpitation or AF were also enrolled as a control group. The control group were mainly selected from patients' relatives who fulfilled the study inclusion criteria.

AF was considered lone in patients younger than 60 years of age if there were no known associated CVDs or precipitating factors for AF. Lone AF was confirmed by 12-lead electrocardiogram (ECG).

Subjects with a history of hypertension, DM, coronary artery disease (CAD), heart failure, peripheral artery disease (PAD), stroke, infectious diseases, known liver or kidney disorders, hypercholesterolemia,

hypertriglyceridemia, gynecologic disorders (such as polymenorrhea, cystic ovary diseases), morbid obesity [body mass index (BMI) > 35], abuse of substances, anemia (hemoglobin < 12 mg/dl), sinusitis, known lung disorder, recent body trauma or surgery, and migraine were not included in the study for both case and control groups.

The study exclusion criteria were using any drugs, pregnancy, and lactation. Furthermore, all participants had not used hormonal contraceptives or vasoactive drugs in the last three months before the study. All cases were in AF rhythm at the time of the study, but after ventricular rate control (less than 90 beats/minute) and if sinus rhythm was achieved before FMD measurement, they would be excluded. The ventricular rates in all patients with AF were controlled with beta-blockers or calcium channel blockers.

Informed consent was obtained from all participants, and the study protocol was approved by the ethics committee of Isfahan University of Medical Sciences with ID IR.396.3.540. This article was the result of a thesis on residency course with number 396540.

In the beginning, all subjects underwent a complete examination that included physical examination, blood sampling for routine biochemistry measurements, echocardiography, and ECG. Then, forearm FMD was performed under fasting conditions or consumption of low-fat meals before testing.

A high-resolution B-mode ultrasonographic system (ATL Ultrasound, HDI 5000, Bothell, Washington, USA) with a linear transducer mid-frequency of 7.5 MHz was used to determine FMD of the brachial artery. FMD was performed between 8 AM and 9 AM in a room with a controlled temperature by an expert cardiologist who was utterly blind to the study. FMD was not measured during the menstrual phase in female patients.

All subjects were fasting at least 4 hours before the study. They were instructed not to eat, drink caffeinated beverages, or take vitamin C supplements at least 12 hours before the study. After 10 minutes of rest at the supine position, heart rate and blood pressure were measured, and the baseline brachial artery diameter was determined from 3-4 cm above the non-dominant elbow pit. When the 2D long-axis image of the vessel was identified and recorded digitally, the ultrasound probe position was kept constant and remained intact throughout the test. Artery diameters were determined with ultrasonic calipers from the leading edge of the anterior wall to the leading edge of the

posterior wall of the brachial artery at the end of the diastole (the beginning of R wave on ECG). External ECG monitoring during echocardiography and FMD studies ensures the proper timing of images regarding the cardiac cycle. To adapt the heart beat rate to changes with that of patients with AF, the mean artery diameter was obtained from 5 consecutive cardiac cycles. The same method was applied to healthy subjects. After determining the base diameter (Dbase), the sphygmomanometer cuff was placed on the arm and inflated to 300 mmHg for 5 minutes. The cuff was then released, and the second scan was taken every 10 seconds during 120 seconds after the cuff deflation at the end of the diastolic period. The highest 10 second averaged interval throughout the 2-minute post-occlusion collection period represented the peak hyperemic diameter. This measurement determined the endothelium-dependent dilation diameter (Dafter). Changes in the diameter were computed as a percentage relative to the baseline diameter. FMD was calculated using the following formula:

$$\text{FMD} = [(\text{Dafter}-\text{Dbase})/\text{Dbase}] \times 100$$

Two other observers supervised the procedures.

The obtained data were gathered in the checklist and entered SPSS software (version 22, IBM Corporation, Armonk, NY, USA) for analysis. The continuous variables were expressed as mean  $\pm$  standard deviation (SD). Normal distribution of

data was evaluated with Kolmogorov-Smirnov (K-S) test. Differences in continuous variables between the case and control groups were analyzed using the independent-sample t-test in normal distribution variables. If the data distribution was not normal, the Mann-Whitney U test was used. Categorical variables were presented as absolute numbers (%). These variables were analyzed between groups using the chi-square test. P-value of less than 0.05 was considered as the level of significance. All of the statistical analyses were performed by a blind analyzer about the details of the study.

## Results

The present study included 43 patients with LAF (24-57 years, 72.1% male), and 51 healthy subjects (23-56 years, 70.6% male). The clinical characteristics of the patients with LAF and healthy subjects are shown in table 1. There were no differences between the two groups in demographic characteristics. Seven patients in the LAF group and six participants from the healthy subjects were someday smokers (P = 0.52).

FMD parameters of the case and control groups have been demonstrated in table 2. As shown in this table, the mean of FMD in the control group (healthy subjects) was significantly higher than that of the patients with LAF (P = 0.04).

**Table 1.** Demographic and clinical characteristics of the study participants

Clinical characteristics	Patients with LAF (n = 43)	Healthy subjects (n = 51)	P
Age (years)	41.95 $\pm$ 8.25	39.11 $\pm$ 8.47	0.10*
Resting HR (beats/minutes)	79.48 $\pm$ 8.53	77.25 $\pm$ 6.82	0.16*
SBP (mmHg)	109.09 $\pm$ 11.31	112.78 $\pm$ 10.94	0.09*
DBP (mmHg)	68.39 $\pm$ 6.70	68.90 $\pm$ 6.18	0.65*
Weight (Kg)	73.04 $\pm$ 9.98	72.64 $\pm$ 8.74	0.78*
Height (cm)	169.90 $\pm$ 8.46	169.47 $\pm$ 8.01	0.79*
BMI (Kg/m <sup>2</sup> )	25.23 $\pm$ 2.34	25.28 $\pm$ 2.50	0.96*
FBS (mg/dl)	87.79 $\pm$ 6.97	86.27 $\pm$ 7.00	0.29*
TG (mg/dl)	104.79 $\pm$ 23.76	108.43 $\pm$ 24.19	0.48 <sup>s</sup>
LDL (mg/dl)	83.83 $\pm$ 20.02	88.96 $\pm$ 22.77	0.31*
HDL (mg/dl)	53.76 $\pm$ 8.71	51.09 $\pm$ 9.48	0.11*
Uric acid (mg/dl)	5.32 $\pm$ 0.83	5.20 $\pm$ 0.78	0.45 <sup>s</sup>
Creatinine (mg/dl)	0.86 $\pm$ 0.20	0.89 $\pm$ 0.18	0.36 <sup>s</sup>
ALT (U/l)	29.76 $\pm$ 6.79	27.84 $\pm$ 7.32	0.28*
TSH (mIU/l)	1.41 $\pm$ 0.75	1.49 $\pm$ 0.66	0.68 <sup>s</sup>
Hemoglobin (g/dl)	14.38 $\pm$ 1.02	14.10 $\pm$ 1.02	0.16*
Platelet count (per $\mu$ l)	198.25 $\pm$ 33.40	197.60 $\pm$ 27.86	0.71*
GFR (ml/min/1.73m <sup>2</sup> )	121.23 $\pm$ 33.11	118.26 $\pm$ 28.43	0.70*
Smoker [n (%)]	7 (16.3)	6 (11.8)	0.52**

LAF: Lone atrial fibrillation; HR: Hear rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; FBS: Fasting blood sugar; TG: Triglycerides; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; ALT: Alanine aminotransferase; TSH: thyroid-stimulating hormone; GFR: Glomerular filtration rate

Data are reported as mean  $\pm$  standard division (SD) or [n (%)].

\* Results from independent t-test, \*\* Results from chi-square analysis, <sup>s</sup> Results from Mann-Whitney U test

**Table 2.** Lone atrial fibrillation (FMD) parameters between case and control

Parameter	Patients with LAF (n = 43)	Healthy subjects (n = 51)	P*
BBD (mm)	4.21 ± 0.74	4.06 ± 0.67	0.29
PAD (mm)	4.45 ± 0.75	4.35 ± 0.66	0.57
FMD (%)	5.79 ± 3.85	7.56 ± 4.38	0.04

LAF: Lone atrial fibrillation; BBD: Basal brachial diameter; FMD: Flow Mediated Dilation; PAD: Peripheral arterial diameter; Data are reported as mean ± standard deviation (SD).

\* Results from Mann-Whitney U test

## Discussion

The present study showed that endothelial function, which was evaluated with FMD of the brachial artery, was significantly impaired in patients with LAF compared to the healthy subjects. This result suggests that endothelial dysfunction plays a role in the pathogenesis of AF.

This finding is consistent with the results obtained in previous studies. For the first time, Takahashi et al. reported the systemic endothelial dysfunction in patients with AF.<sup>16</sup> This study showed endothelium-dependent dilation in a group of patients with AF using venous occlusion plethysmography. This study drew attention to the non-invasive evaluation of systemic endothelial function in patients with AF and led to numerous trials which showed that FMD could be used to evaluate endothelial function in patients with AF. These trials show that patients with AF always have an impaired FMD, and their endothelial function can improve upon sinus rhythm restoration.<sup>17-20</sup>

However, most of these studies have been conducted on patients with underlying conditions, including hypertension, CAD, and DM, which are known as risk factors for endothelial dysfunction. A number of studies also confirmed that sustained AF is associated with systemic endothelial dysfunction, even in relatively young patients with no CVDs or risk factors.<sup>21,22</sup> It has been shown that AF is an independent contributor to lower FMD, and a prolonged arrhythmia duration may confer the risk for more profound endothelial damage.<sup>21</sup>

It seems that the relation between AF and ED is in a vicious cycle. In this way, not only AF could cause ED, but ED could also provoke AF. Pathophysiologic mechanisms behind systemic endothelial dysfunction in AF could be explained in these three theories as below:

1. In patients with AF, irregular heartbeats produce turbulent blood flow and oscillating shear stress in systemic vessels. This decreases NO production, and thus endothelial NO synthase expression could be changed and finally cause ED.<sup>23</sup>

This theory has been supported by findings of reduced plasma nitrite/nitrate levels in AF.<sup>24</sup>

2. AF could induce damage to the endocardium of the left atrium, which could reduce circulating nitroso-compounds serving as endogenous NO donors to systemic vessels and then cause endothelial dysfunction.<sup>25</sup>

3. Activation of the renin-angiotensin system,<sup>26</sup> neurohumoral activation,<sup>27</sup> and oxidative stress could be also implicated in the development of endothelial dysfunction in AF, particularly with longer arrhythmia duration.<sup>28</sup>

On the other hand, ED could cause AF, and this could be explained in three different categories as below:

1. ED results in the down-regulation of NO and the up-regulation of adhesion molecules that promote increased levels of inflammation and oxidative stress. Consequently, the generation of reactive oxygen species and oxidative injury leads to the electrophysiological remodeling observed in AF.<sup>29</sup> Additionally, it has been shown that NO reduces spontaneous electrical activity in cardiomyocytes isolated from the pulmonary vein. Therefore, NO could be as a regulator of AF arrhythmogenesis, and down-regulation of that could provoke AF.<sup>30</sup>

2. Inflammation could result in atrial ectopy in discharging cells near the pulmonary veins.<sup>31</sup> Thus, patients with ED, who are associated with an increased level of inflammation, are at higher risk of developing AF. Moreover, FMD can potentially identify persons with abnormal vascular biological profiles that precede this arrhythmia.<sup>32</sup>

3. Many shared risk factors for AF, such as hypertension, increasing age, DM, and smoking, have been associated with endothelial dysfunction.<sup>33</sup> These conditions can lead to an increase in the level of vascular endothelial dysfunction and predispose individuals to AF.

## Conclusion

Our findings proved that LAF was associated with systemic endothelial dysfunction. Actually, AF plays an important and independent role in reducing FMD.

These findings may be important for further studies to identify the clinical relevance and potential therapeutic outcomes, especially in categorizing thromboembolic risks and preventing AF-induced thromboembolism.

**Limitations:** The current study is one of the first studies to show FMD in relatively young LAF patients (mean age of 41 years), which is highly important and can negatively affect endothelial



function due to aging and the presence of atherosclerosis risk factors. The first limitation of the study was a relatively small sample size. However, both patient and control groups were sufficiently homogenous, and the differences in the main findings between the groups were substantial. The second limitation was the lack of use of other markers of endothelial function in the study to better evaluate ED beside FMD to show the higher strength of ED in patients with LAF. On the other hand, in the present study, physical activity was not assessed, which could affect endothelial function. However, there were no reports on the negative effects of beta-blockers and calcium channel blockers on endothelial function, but they were not controlled in our investigation.

### Acknowledgments

The authors would like to appreciate Isfahan Cardiovascular Research Institute. This article is the result of a thesis of residency course with number 396540 in Isfahan University of Medical Sciences.

### Conflict of Interests

Authors have no conflict of interests.

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