ORIGINAL ARTICLE

The role of flow-mediated dilatation and high sensitive C-reactive protein in paroxysmal atrial fibrillation

Ahmed A. Wafa *, Eid M. Daoud, Gamal F. Gomaa

Department of Cardiology, Faculty of Medicine, Specialized Medicine Hospital, Mansoura University, Mansoura City, Egypt

Received 15 January 2012; accepted 15 May 2012
Available online 30 June 2012

Keywords
Paroxysmal atrial fibrillation;
Brachial flow-mediated dilatation;
C-reactive protein

Abstract
Background: Atrial fibrillation (AF) is the most common type of arrhythmia and recognized as a risk factor for thromboembolism. Endothelial damage or dysfunction may contribute to increase the risk of thromboembolism via the mediation of a prothrombotic or hypercoagulable state.

Objectives: The aim of the current study is to investigate endothelial dysfunction (represented by brachial flow-mediated dilatation “FMD”) and inflammation (represented by hs-CRP) in patients with paroxysmal atrial fibrillation.

Subjects and methods: Forty-two patients with AF taken from the Cardiology Department and Outpatients Clinic, Specialized Medical Hospital, Mansoura University, in the period between February 2011 and May 2011 were enrolled in our study, the patients were then subsequently divided according to the clinical type of AF into Group I: comprised 20 patients with paroxysmal AF (PAF) with mean age 57.35y. Group II: comprised 22 patients with chronic AF (CAF) with mean age 57.68y. Twenty control subjects without AF were enrolled in this study (Group III).

Patients and control groups were subjected to clinical evaluation, electrocardiography (ECG), echocardiography and brachial FMD (using external brachial ultrasonography. Serum level of hs-CRP was assessed in all subjects. The diameter change induced by FMD was expressed as the percent change relative to that at the initial scan (FMD%) according to the following equation:

\[
FMD\% = \frac{\text{Maximum diameter} - \text{baseline diameter}}{\text{Baseline diameter}} \times 100.
\]

Results: Left atrial diameter was significantly increased when compared either GI or GII with control group (3.96 ± 0.27; 4.7 ± 0.48 vs 3.05 ± 0.35 cm) (\(P < 0.001\)). Brachial flow-mediated dilatation difference and percentage change of FMD were significantly lower in groups I and II in comparison to group III (0.09 ± 0.05; 0.09 ± 0.04 vs 0.79 ± 0.07 mm) and (1.96 ± 0.98; 1.99 ± 0.89 vs...

* Corresponding author. Tel.: +20 12 2393 7098.
E-mail address: abomaryam2002@yahoo.com (A.A. Wafa).
Peer review under responsibility of Egyptian Society of Cardiology.
1. Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia and recognized as a risk factor for thromboembolism, but the pathogenesis of thrombus formation remains unclear. Previous reports have suggested that loss of atrial contraction in AF is associated with thrombogenesis.

The risk of ischemic stroke increases by three- to fourfold in patients with non-valvular AF and anticoagulant therapy reduces this risk by two-thirds.

In patients with chronic AF there is an increased activation of platelets and the coagulation system in peripheral venous blood. In the patients with paroxysmal AF, atrial fibrillation itself enhances platelet aggregation and coagulation and these processes are influenced by the duration of AF.

Interestingly, however, ischemic stroke occurs in the patients with paroxysmal AF even during sinus rhythm.

Endothelial damage or dysfunction may contribute to the increased risk of thromboembolism via the mediation of a prothrombotic or hypercoagulable state. However, the precise pathophysiological mechanisms relating endothelial dysfunction to AF and thromboembolism are yet to be fully elucidated.

C-reactive protein (CRP), a sensitive marker of inflammation, is known to be associated with vascular dysfunction.

Endothelial dysfunction is one of the initial pathological processes of atherosclerosis and has been associated with increased cardiovascular risk. Brachial artery flow-mediated dilatation (FMD) is a validated non-invasive physiological measure widely used as a research method to quantify endothelial function. Brachial FMD has been shown to be an independent predictor of cardiovascular outcomes.

The dilatation response with increased blood flow is mainly mediated by nitric oxide released from arterial endothelial cells.

2. Objectives

The aim of the current study is to investigate endothelial dysfunction (represented by brachial FMD) and inflammation (represented by hs-CRP) in patients with paroxysmal atrial fibrillation.

3. Subjects and methods

Fifty selected patients with AF were taken from the Cardiology Department and Outpatients Clinic, Specialized Medical Hospital, Mansoura University, Egypt, in period between February 2011 and May 2011 and enrolled in our study, the patients were then subsequently divided according to the clinical type of AF into Group I: comprised 22 patients with paroxysmal AF (PAF) with mean age 57.35y (two patients did not agree to go for the study protocol). Group II: comprised 28 patients with chronic AF (CAF) with mean age 57.68y (six patients did not agree to go for the study protocol). Twenty control subjects without AF were enrolled in this study (Group III).

The study was approved by the Ethics Committee of Mansoura Faculty of Medicine and all patients gave the written informed consent to participate in the study.

The patients with valvular heart disease, hyperthyroidism, diabetes mellitus, malignancy and hepatic or renal impairment were excluded from our study. We also exclude the patients with acute cardiovascular or cerebrovascular events.

In patients with chronic AF we did not exclude patients with hypertension or chronic stable angina.

Hypertension was considered when systolic blood pressure over 140 mmHg and/or diastolic blood pressure over 90 mmHg, and/or taking antihypertensive.

Dyslipidemia was defined as total cholesterol over 220 mg/dL and/or current treatment with statins.

4. Clinical evaluation

Complete history and physical examination were done for all patients and control subjects. Past electrocardiography tracings were reviewed. Paroxysmal AF was defined when no more than two consecutive ECGs of AF and confirmed intercession by documented sinus rhythm.

Chronic AF was defined as AF documented electrocardiographically on at least two occasions at least 2 months apart.

5. Echocardiographic measurements

M-mode, 2D and Doppler transthoracic echocardiography were performed for patients and control subjects. LA and LV dimensions and LV fractional shortening were measured by M-mode echocardiography.

6. Endothelial measurements

The subjects were kept in the supine position in a quiet, dark, and air-conditioned room (with a constant temperature of 23–26 °C throughout the study). After 20 min of rest, the basal brachial artery diameter was measured. Endothelium-dependent and endothelium-independent vasodilatations were examined in the brachial artery using external ultrasound. Measurement was done by the same operator.

The right brachial artery was scanned in the longitudinal section 3–5 cm above the antecubital fossa using a high-resolu-
tion external ultrasound (Vivid 3 model) with a 10-MHz linear-array transducer. Forearm blood flow was altered by inflating the blood pressure tourniquet placed around the forearm. The cuff was inflated to 20 mmHg higher than the systolic blood pressure for 5 min. Endothelium-dependent FMD was assessed as the percent change in the arterial diameter in response to reactive hyperemia associated with 5 min of ischemia.

The diameter change induced by FMD was expressed as the percent change relative to that at the initial scan (FMD%) according to the following equation 11:

\[
FMD\% = \frac{\text{Maximum diameter} - \text{baseline diameter}}{\text{Baseline diameter}} \times 100
\]

7. Laboratory measurements

All patients and control subjects were subjected to:

- Routine laboratory profile: including fasting and 2 h post prandial blood sugar.
- Fasting serum lipid profile: using enzymatic colorimetric methods (Human, Wiesbaden, Germany).
- Estimation of serum level of hs-CRP using ELISA technique (DiaSys Lab Inc., Webster, USA).

8. Statistical analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences) version 15. Qualitative data were presented as number and percent. Comparison between groups was done by Chi-square test. Quantitative data were tested for normality by Kolmogrov–Smirnov test. Normally distributed data were presented as mean ± SD. Student t-test was used to compare between two groups. F-test (one way Anova) was used to compare between more than two groups. Pearson’s correlation

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics and medications of study groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (PAF) (n = 20)</td>
<td>GII (CAF) (n = 22)</td>
</tr>
<tr>
<td>Age</td>
<td>57.35 ± 3.9</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>7 (35%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>ACF-I/ARBs</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>CCB</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>Antiarhythmic</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Statins</td>
<td>4 (20%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Echocardiographic data of study groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (PAF) (n = 20)</td>
<td>GII (CAF) (n = 22)</td>
</tr>
<tr>
<td>ESD</td>
<td>2.94 ± 0.34</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>EDD</td>
<td>4.63 ± 0.41</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>IVST</td>
<td>1.21 ± 0.18</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>PWT</td>
<td>1.14 ± 0.15</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>FS%</td>
<td>34.25 ± 1.89</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>3.96 ± 0.27</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ESD = end systolic diameter, EDD = end diastolic diameter, IVST = interventricular septal thickness, PWT = posterior wall thickness, FS% = fractional shortening, LAD = left atrial diameter.
P1: GI vs GII (PAF vs CAF), P2: GI vs GIII (PAF vs control), P3: GII vs GIII (CAF vs control).
coefficient was used to test correlation between variables. $P < 0.05$ was considered to be statistically significant.

9. Results

Clinical characteristics and medications are reviewed in Table 1.

In Table 2 there was a significant increase of EDD when compared patients with CAF with control group ($P = 0.04$). Also, there was a significant decrease of FS% when compared either GI or GII with control group ($P < 0.001$ and $P = 0.003$, respectively).

Left atrial diameter was significantly increased when compared either GI or GII with control group ($P < 0.001$). Also, LAD significantly increased when compared the patients with CAF with the patients with PAF ($P < 0.001$).

In Table 3 brachial flow-mediated dilatation difference and percentage change of FMD were significantly lower in groups I and II in comparison to group III ($P < 0.001$) (Figs. 2-4). No significant difference in these parameters when compared the patients with PAF and CAF.

High sensitive CRP was significantly higher when compared either group I or group II with the control group. Also hs-CRP has significantly increased when compared group II with group I ($P < 0.001$). There was a negative correlation between high sensitive C-reactive protein and percent change of FMD (Fig. 1).

10. Discussion

Atrial fibrillation is associated with an increased thromboembolic risk and prothrombotic state. Endothelial dysfunction is a contributory factor to the prothrombotic state seen in many cardiovascular disorders: including AF. Indeed, endothelial dysfunction has been identified in many disease states and has been associated with worse outcomes and cardiovascular risk in the patients with hypertension, atheroscle-
rosis, diabetes mellitus and many other conditions. While the data in AF patients are more limited.

Brachial artery FMD is a validated, non-invasive tool to quantify endothelial function. It has been very much used in recent years, and there are numerous studies on FMD and cardiovascular disease, vascular risk factors, or endothelial dysfunction therapy. In contrast, there are few studies on FMD in atrial fibrillation.

Our results show that the percentage change of FMD is significantly lower in patients with AF (paroxysmal or chronic) in comparison to control subjects (Figs. 2–4). These results suggest that endothelial dysfunction and activation predominate in the patients with AF which may be contributory to the thrombotic state seen in these patients. Of note, FMD did not differ significantly among the subgroups of AF patient, indicating that endothelial dysfunction exists whether the AF is paroxysmal or permanent. These results are similar to the results of Freestone et al. who found endothelial dysfunction in both paroxysmal and chronic AF.

However, Freestone et al. evaluated the plasma level of vWF as an index of endothelial dysfunction, which is affected by many known cardiovascular risk factors. It is frequently argued that abnormalities in markers of endothelial function in AF patients could be due to some known cardiovascular risks that often coexist with AF. For example, elevated plasma level of vWF is associated with established cardiovascular risk factors such as age, smoking, diabetes mellitus, cholesterol, and hypertension. Although serum levels of vWF in AF patients were compared to control in this study, control subjects had few or no cardiovascular risk factors and this may influence the serum level of vWF.

The study conducted by Matsue et al. suggested that patients with paroxysmal AF, even outside the AF period, are comparable in the degree of endothelial dysfunction (measured by digital reactive hyperemia pulse amplitude tonometry) to persistent AF patients. This impairment of endothelial function is caused by the presence of paroxysmal AF itself, independent of other coexisting comorbidities.

Figure 2  Longitudinal section of brachial artery before and after cuff inflation in patient.

Figure 3  Longitudinal section of brachial artery before and after cuff inflation in patient with CAF.

Figure 4  Longitudinal section of brachial artery before and after cuff inflation in normal subject.
There have been numerous clinical studies that have investigated the relationship between inflammation (using known serum or plasma vascular inflammatory markers) and AF. hs-CRP has evolved as the most robust and reproducible marker of vascular inflammation.

Our study shows that the level of hs-CRP was higher among patients with AF compared with control in sinus rhythm. Also, persistent AF patients have higher hs-CRP levels than paroxysmal AF patients and both have higher levels than control suggesting that CRP may be a marker for inflammatory states that may promote the persistence of AF, potentially by inducing structural and/or electrical remodeling of the atria. These pathways may represent a novel mechanism by which structural changes resulting from inflammation perpetuate AF.

The precise, mechanism for the increased circulating hs-CRP in AF is uncertain but might reflect active participation of CRP in the local inflammatory response within the atrial myocardium.

In AF, inflammation might not only result in endothelial damage, dysfunction or activation but also be linked directly to thrombogenesis.

Our results are similar to numerous studies who had reported specifically on the association of CRP with the development and maintenance of AF.

Currently, it remains unclear whether inflammation is a cause of AF or merely a consequence. Sata et al. attempted to establish causality between inflammation and onset of AF in 15 patients with paroxysmal AF. The study provided an insight into the role of inflammatory process in AF and suggested that inflammation might be an independent risk factor for AF.

11. Conclusions

The findings of our study suggested that the patients with PAF are comparable in the degree of endothelial dysfunction to CAF patients. This may explain why the risk of thromboembolism in PAF is comparable with that in CAF patients. Also, our study suggested that CRP may be a marker for inflammatory states in AF patients that may promote the persistence of AF. These findings require further testing and confirmation in a larger trial. Nevertheless, these pathways may provide a potential target for pharmacological approaches for treating AF. Randomized trials of agents such as anti-inflammatory and/or other CRP lowering drugs may be warranted.

References


