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Flow-mediated dilation is associated with cardiovascular events in non-valvular atrial fibrillation patients

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ABSTRACT

Background: Atrial fibrillation is associated with multiple atherosclerotic risk factors and predisposes to cardiovascular events (CVE). Endothelial dysfunction is associated with atherosclerosis and independently predicts CVE. The aim of the study was to evaluate the association between endothelial dysfunction, as assessed by flow-mediated dilation (FMD), and CVE in AF patients.

Methods: We prospectively measured FMD in 514 non-valvular AF patients on anticoagulant treatment with vitamin K antagonists. Patients were followed-up for a mean time of 23.5 months. The main composite outcome of the study was the occurrence of stroke/TIA, myocardial infarction, urgent revascularization and cardiovascular death.

Results: Median value of FMD was 4.6% [IQR 1.46–8.00]. A CVE occurred in 44 patients (8.56%):non-fatal myocardial infarction (MI) in 7, fatal MI in 2, stent/coronary artery by-pass graft (CABG) in 10, ischemic non-fatal stroke in 10, fatal stroke in 3, transient ischemic attack (TIA) in 1, and cardiovascular death in 11 patients. Patients who experienced a CVE showed significantly reduced FMD compared to those who did not (3.06% [IQR 0.00–6.00] vs 4.67% [IQR 1.58–8.22], $p = 0.027$). During a mean follow-up of 23.5 months, the rate of CVE was significantly higher in subjects with FMD below median (<4.6%) than in those with FMD above median (27 vs 17, log-rank test $p = 0.006$). COX analysis demonstrated that low FMD (below median) (HR: 2.20, CI 95%:1.13–4.28, $p = 0.020$), age (HR: 1.08, CI 95%: 1.03–1.12, $p < 0.001$), smoking (HR: 4.15, CI 95%: 1.63–10.6, $p = 0.003$) and history of stroke/TIA (HR: 2.38, CI 95%: 1.13–5.04, $p = 0.023$) independently predicted CVE.

Conclusions: In AF patients low FMD is associated with increased risk of CVE suggesting that impaired artery dilatation predisposes to atherosclerotic complications.

1. Introduction

Atrial fibrillation (AF), the most common arrhythmia encountered in clinical practice in Western countries, accounts for approximately one third of all hospitalizations for cardiac rhythm disorders [1]. AF predisposes to an increased risk of thromboembolic events such as arterial embolism and stroke [2,3]. Ischemic stroke associated with AF was nearly doubled as likely to be fatal as non-AF stroke [4].

AF patients are also characterized by an atherosclerotic burden [5], with a high prevalence of atherosclerotic risk factors such as arterial hypertension, diabetes, obesity and dyslipidemia [5]. The presence of multiple atherosclerotic risk factors is common in AF patients and may predispose to the occurrence of AF itself [5]. In fact, prospective studies demonstrated that patients with risk factors for atherosclerosis are more prone to experiencing this arrhythmia [6,7]. Furthermore, the coexistence of atherosclerotic risk factors may explain why patients with AF may suffer from coronary events with a rate of ischemic heart disease [8] twice than people without AF [8,9].

Normal function of arterial endothelium is crucial for maintaining vascular homeostasis [10].

Endothelial dysfunction represents one of the major determinants for the development of atherosclerosis and its complications [10,11]. Since atherosclerosis is a systemic process, endothelial function can be assessed both in the coronary tree and in the peripheral circulation. Flow-mediated dilation (FMD) of the brachial artery is commonly used to quantify peripheral endothelial function [12,13].

Impaired FMD is a mirror of endothelial dysfunction in a wide variety of cardiovascular (CV) diseases [14–17]. A meta-analysis demonstrated that 1% increase of FMD is associated with 13% reduction of experiencing a cardiovascular event [18].

Few studies demonstrated the presence of endothelial dysfunction in AF [19,20]. FMD was significantly impaired in 40 permanent AF patients compared to healthy controls, concomitantly with an enhanced level of soluble E-selectin and von Willebrand factor [21] and was improved by restoration of sinus rhythm [22].

The relation between endothelial dysfunction and CV events in patients with AF has never been explored. Thus, the aim of this study is

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to evaluate if the impaired FMD in patients with AF could be a predictor of future CV events.

2. Methods

2.1. Study design and patient selection

This was a prospective single-centre observational cohort study, including 550 consecutive AF patients, who referred to the Atherothrombosis Center of the Department of Internal Medicine and Medical Specialties of "Sapienza" University of Rome.

All patients were receiving an anticoagulant treatment with vitamin K antagonists, such as warfarin/acenocumarol, after risk stratification according to the CHA_2DS_2-VASc score [23]. Anticoagulation therapy was periodically monitored by the use of the International Normalized Ratio, maintained in an intended therapeutic range of 2.0–3.0. The following were exclusion criteria: prosthetic heart valves, severe valve disease, severe cognitive impairment, chronic infectious diseases, autoimmune systemic diseases and active cancer. Moreover, we excluded patients taking nitrates.

Based on above criteria, 36 (6.5%) patients were excluded and 514 participated at the study.

At baseline, all patients provided a written informed consent. During the first visit, patient's medical history and anthropometric data were recorded. A standard 12-lead electrocardiogram was also performed. A sample of urine was collected from all patients. The presence of CV risk factors such as arterial hypertension, diabetes mellitus and heart failure, was assessed using international definitions [24–26].

2.2. Flow-mediated dilation

Ultrasound assessment of basal brachial diameter and endothelial dependent FMD of brachial artery were investigated according to current guidelines [27] and as previously described [28,29].

Briefly, the study was performed in a temperature-controlled room (22 °C) with the subjects in a resting, supine state between 8 a.m. and 10 a.m. after at least an 8-hour fasting. Brachial artery diameter was imaged using a 7.5-Mhz linear array transducer ultrasound system (GE Vivid S6) equipped with electronic callipers, vascular software for two-dimensional imaging, colour and spectral Doppler, and internal electrocardiogram; the brachial artery was imaged at a location 3–7 cm above the antecubital crease. To create a flow stimulus in the brachial artery, a sphygmomanometric cuff was placed on the forearm; the cuff was inflated at least 50 mm Hg above systolic pressure to occlude artery inflow for 5 min.

The brachial artery diameter was measured as the distance from the near wall intima–media interface to the far wall luminal–intima interface and expressed as millimetre. FMD was expressed as a change in post-stimulus diameter evaluated as a percentage of the baseline diameter. Because of beat-to-beat variation in flow velocity and cycle length in patients with AF, FMD was expressed as percent change in the brachial artery diameter measured at end of the diastole, coincident with the R wave on the electrocardiogram and 600 ms after the R wave [22]. The average of 5 cardiac cycles with cycle length >600 ms was used for calculations. FMD was performed in all patients by the same operator. To evaluate the reproducibility of FMD twenty patients with AF underwent FMD measurement on 2 separate occasions (baseline AND after 1 week). Variability of different measurements was assessed by using intra-class correlation coefficient (ICC).

ICC for brachial diameter at rest and FMD was 0.98 and 0.89, respectively.

2.3. Outcome events

All major CV events were considered the end points of the study. CV events included fatal and nonfatal ischemic strokes, fatal and nonfatal myocardial infarctions (MI), cardiac revascularization/coronary artery bypass surgery, transient ischemic attack (TIA) and CV death. Diagnosis of MI was made according to the universal definition proposed by the Joint ESC/ACCF/AHA/WHF Task Force [30]. The occurrence of stroke was determined on clinical manifestations and confirmed by radiological findings. Transient ischemic attack was defined according to the Classification of Cerebrovascular Diseases III [31]. If a patient died within 4 weeks from the occurrence of stroke or myocardial infarction, this event was recorded as a fatal stroke or fatal myocardial infarction. CV death was defined unless an unequivocal non-CV cause of death was confirmed by a central adjudication committee. Adjudication of events was performed by a committee (FV, PP) who did not participate to the enrollment of patients and was unaware of the clinical and laboratory characteristics of patients.

The study protocol was approved by the Sapienza University ethical committee (ref. 1306) and was conducted in accordance to the declaration of Helsinki [32]. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

3. Statistical analysis

Categorical variables were reported as counts (percentages) and continuous variables as means +/− standard deviation (SD) or median and interquartile range (IQR) unless otherwise indicated. Independence of categorical variables was tested by χ^2 test. Normal distribution of parameters was assessed by Kolmogorov–Smirnov test. Student unpaired *t* test and Pearson product–moment correlation analysis were used for normally distributed continuous variables. Group comparisons were performed using analysis of variance (ANOVA). Appropriate nonparametric tests (Mann–Whitney *U* test, Kruskal–Wallis test, Spearman rank correlation test [rS]) were employed for all the other variables.

After dividing the AF population in two groups according to the median value of FMD, the cumulative incidence was estimated using a Kaplan–Meier product–limit estimator. Survival curves were formally compared using the log-rank test. Cox proportional hazards analysis was used to calculate the adjusted relative hazards of outcome events by each clinical variable. The multivariate analysis was determined with a forward stepwise variable selection procedure including variables that could potentially affect FMD. In addition to FMD, the following variables were considered: arterial hypertension, diabetes, history

Table 1
Baseline characteristics of study population.

	Whole cohort (n = 514)	Low FMD[a] (<4.6%) (n = 256)	High FMD[a] (≥4.6%) (n = 258)	p value
Age (years)	72.9 ± 8.7	73.6 ± 8.5	72.1 ± 8.8	0.064
Heart rate (beats/min)	70 [60.0–86.0]	70.0 [60.0–82.0]	70.0 [61.5–87.5]	0.232
Female gender n. (%)	42.0	39.5	44.6	0.247
Body mass index (kg/m^2)	27.2 ± 4.5	27.1 ± 4.6	27.3 ± 4.4	0.506
Smoking habit (%)	9.6	8.3	11.0	0.184
CHA_2DS_2-VASc score	3.3 ± 1.5	3.4 ± 1.5	3.3 ± 1.5	0.416
Time in therapeutic range	64.8 ± 16.4	65.1 ± 15.4	64.9 ± 16.9	0.938
Hypertension (%)	87.8	90.6	84.9	0.032
Systolic blood pressure (mm Hg)	135.0 [120.0–150.0]	130.0 [120.0–145.0]	135.0 [120.0–150.0]	0.602
Diabetes mellitus (%)	18.5	19.9	17.1	0.235
Heart failure (%)	12.5	14.8	10.1	0.066
Ejection fraction (%)	53.9 ± 7.5	53.6 ± 7.4	54.6 ± 4.4	0.153
History of stroke/TIA[a] (%)	12.1	11.3	12.8	0.355
History of MI[a] (%)	19.3	19.1	19.4	0.517
Anti-platelets (%)	14.2	13.5	14.8	0.386
ACE[a] inhibitor/ARBs[a] (%)	72.1	73.7	70.6	0.247
β blockers (%)	41.3	37.5	45.1	0.049
Calcium channel blockers (%)	33.0	34.3	31.8	0.571
Statins (%)	45.2	45.7	44.7	0.859

[a] FMD: flow-mediated dilation, AF: atrial fibrillation, TIA: transient ischemic attack, ACE: angiotensin-converting-enzyme, ARBs: angiotensin receptor blockers, MI: myocardial Infarction.