Prevalence and determinants of permanent atrial fibrillation in post-menopausal hypertensive women

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ABSTRACT

Objective. We studied the prevalence and major predisposing factors of permanent atrial fibrillation (PAF) in a population of hypertensive post-menopausal (HPMW) women. Materials and Methods. We enrolled 125 consecutive HPMW with PAF, 125 HPMW in sinus rhythm were the control group (CG). Women with valvular heart disease, coronary artery disease, WPW syndrome, left ventricular (LV) ejection fraction <45% and thyroid disorders were excluded. The mean age was similar: 53±3 years for women on PAF and 51±6 for women with sinus rhythm (P<0.45). All women who underwent M-B mode echocardiography, LV mass, function, and left atrial (LA) volume were assessed according to American Society of Echocardiography guidelines. Diabetes was assessed according to American Diabetes Association guidelines. Results. In a population of 8945 consecutive women, 4497 were hypertensive (50.2%) and 125 were on PAF (0.3%). We observed a highly significant difference between the two groups in relation to obesity: 31 (24.8%) in the AF-group and 15 (12%) in CG, Chi-squared 10, P<0.0016, OR 2.8, 95%; to increased LA volume: 37 (29.6%) in AF-group and 13 (10.4%) in CG, Chi-squared 14.4, P<0.0001, OR 3.62, 95%. No difference in diabetes: 30 (24%) in AF-group and 28 (22.4%) in CG, Chi-squared 0.09, P<0.76, OR 1.09, 95%, and LV diastolic dysfunction (LVDD): 24 (19.2%) in AF-group and 20 (16%) in CG, Chi-squared 0.44, P<0.5, OR 1.25, 95%. In contrast to what was expected LV hypertrophy had a lower incidence of 59 (47.2%) in AF-group than in CG 84 (67.2%), Chi-squared 10.21, P<0.0014, OR 0.44, 95%. Conclusions. The prevalence of PAF in HPMW is not elevated, obesity and increased LA volume are strong determinants of PAF, not depending on age. LVDD, LV hypertrophy, and diabetes status seem not to play a relevant role as PAF determinants.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in women, the incidence of which increases with age and it seems that it will double by 2050.[1] Although the age-adjusted incidence and prevalence of AF are lower in women, the risk of death in women with AF is similar to or even higher than in men.[2] Women with AF, especially in the presence of additional risk factors such as older age, tend to be more symptomatic and they have a higher risk of stroke than men, even in the presence of anticoagulation therapy,[3] so it is mandatory to identify women with increased risk to develop AF early. There is a lively scientific debate on the identification of the risk factors and pathogenetic mechanisms related to the development of this arrhythmia, to identify effective

preventive therapy.[4] Hypertension is a recognized predisposing factor for AF,[5] and it has been proved that high blood pressure may increase the risk of stroke, bleeding complications, and recurrence of AF. The incidence of AF increases with age and in the presence of arterial hypertension, the prevalence of AF in postmenopausal women is controversial.[4,6]

Our study aimed to evaluate the prevalence and the major predisposing factors of permanent atrial fibrillation (PAF) in a large population of hypertensive post-menopausal (HPMW) women.

Materials and Methods

Patients

We enrolled 125 consecutive HPMW affected by PAF, between January 2021 and December 2021. 125 HPMW consecutive in sinus rhythm were enrolled as the control group (CG), from out-patients. PAF was diagnosed when continuous AF had lasted for at least 12 months and the presence of AF had been accepted by the patient and physician, and no more attempts would be made to restore or maintain sinus rhythm, according to the current guidelines.[7] Post-menopause was defined as the absence of menstruation for at least the preceding 12 months. All the women were identified in our outpatient clinic, the recruitment started on January 1, 2021, and lasted one year. All of them were Caucasian, and hypertensive from 1-10 years, mean 7, all on antihypertensive therapy, and many of them were also on antidiabetic treatment, so they represented prevalent cases. The study was approved by the ethics committee. Women with valvular heart disease, including severe mitral regurgitation, all kinds of coronary artery disease, pre-excitation syndrome, left ventricular ejection fraction <45%, and severe or end-stage renal disease were excluded. All participants gave informed consent for the analysis, and all women completed a questionnaire that included questions about demographic characteristics, menopause status, smoking status, alcohol intake, physical activity, education, family history of medical diseases, residential area, and drug history under the supervision of a trained nurse. The main characteristics of our population are described in Table 1. All women underwent: clinical evaluation with a complete history, 12 lead electrocardiogram (ECG), transthoracic echocardiogram (TTE) comprehensive mono and bidimensional imaging, and pulse wave (PW) Doppler and Tissue Doppler analysis.

Echocardiography

TTE was performed with the patient on her left side, after 10 minutes of resting, with the exam table elevated by 30°. The exam was carried out using a 3.5 MHz probe, with an ECG trigger. We used an echo-Doppler system equipped with a multifrequency transducer, Philips, Epiq 7, Ultrasound System for Cardiology, Healthcare, viale Sarca 235, Milan (Italy). We assessed: intraventricular septum thickness in the diastole and in systole cycles, left ventricular diastolic and systolic diameter, left ventricular posterior wall thickness during diastole and systole cycles, ejection fraction, and fractional shortening. Peak velocities of early (E wave) and late (A wave) trans-mitral flow and deceleration time were determined, and E' wave and A' wave were determined by Tissue Doppler Imaging at the mitral annulus level. E/A ratio, E'/A' ratio, and E/E' ratio were calculated. LV mass was determined according to the formula by Devereux *et al*.[8] and indexed according to body surface area to obtain LV mass index, the normal values of these echocardiogram parameters were according to the American Society of Echocardiography. Left ventricular diastolic dysfunction (LVDD) was diagnosed according to current guidelines by PW Doppler of mitral inflow and Tissue Doppler Imaging of the mitral annulus.[9] All LVDD subjects had abnormal diastole cycles, with all different degrees of severity. All echo data were derived at end-expiration at an average of 5 cycles. Cardiomyopathy diagnosis was formulated according to well-established criteria.[10] We estimated left atrial (LA) volume according to the prolate ellipsoid formula from the anterior-posterior diameter of LA (D1), the superior-inferior diameter of LA (D2), and the mediolateral diameter of LA (D3). The echocardiographic findings of our population are described in Table 2.

Table 1. Clinical characteristics.

	HPMW with PAF n. 125	HPMW on Sinus rhythm (control group) n. 125	Chi-squared	Odds ratio relative risk	P
Age	53±3 years	51±6 years	-	-	<0.45
Obesity	31 (24.8%)	15 (12%)	10	2.85	<0.0016
Diabetes	30 (24%)	28 (22.4%)	0.09	1.09	<0.76

HPMW, hypertensive postmenopausal women; PAF, permanent atrial fibrillation.

Statistical analysis

The general characteristics of the study population were described by the mean±standard deviation. We used the Student's t-test for continuous variables, only age, and the Chi-square test for categorical variables. A P<0.05 for both tests was considered significant.

Results

In a population of 8945 consecutive women, 4497 were hypertensive (50.2%) and 125 PAF (0.3%). We observed a highly significant difference between these two groups for obesity: 31 (24.8%) in the AF-group and 15 (12%) in the CG, Chi-squared 10, OR 2.85, C.I. 95%, P<0.0016, and for increased LA volume: 37 (29.6%) in the AF-group and 13 (10.4%) in the CG, Chi-squared 14.4, OR 3.62, C.I. 95%, P<0.0001. There was no difference in type 2 diabetes, without insulin requirements, prevalence: 30 (24%) in the AF-group and 28 (22.4%) in the CG, Chi-squared 0.09, OR 1.09, C.I. 95%, P<0.76, or LVDD: 24 (19.2%) in the AF-group and 20 (16%) in the CG, Chi-squared 0.44, OR 1.25, C.I. 95%, P<0.5. In contrast to what we expected, LV hypertrophy had a lower incidence of 59 (47.2%) in the AF-group than in the CG – 84 (67.2%), Chi-squared 10.21, OR 0.44, C.I. 95%, P<0.0014. All the results are summarized in Table 2.

Discussion

Our data confirm the loss of the estrogen-progestin hormone's beneficial effect against cardiovascular diseases in menopause. Estrogen-progestin hormone deficiency produces an increase in blood pressure in postmenopausal women, compared to pre-menopausal women of the same age. This phenomenon can be explained by the estrogenic deficiency that normally vasodilates the vascular wall, by activation of the renin-angiotensin-aldosterone system, the increase in sympathetic activity, and by hyperinsulinemia.[11] In our population, only 125 women had PAF, the 0.3% of the entire sample. This finding provides important data in the scientific literature because the prevalence of PAF in HPMW is extremely controversial. Numerous studies on large population cohorts have claimed that the AF rate varies greatly between races and ethnic groups, despite the uniformity of the conditions predisposing to the development of AF.[12] The study conducted by Rodriguez on a large population of post-menopausal women proved that traditional risk factors confer on all racial groups a comparable individual risk of developing AF, emphasizing the role of predisposing factors in the onset of the arrhythmia.[13] For this reason, the identification of AF predisposing factors is crucial to realizing useful preventive strategies. The main strength of our study is the statistically significant difference between the group of HPMW and the CG for obesity and for increased LA volume. These differences are not influenced by age, because the age of women enrolled was substantially homogeneous in the two groups. Obesity is widely recognized as a critical risk factor for AF. It was shown that an increase in adiposity produces systemic inflammation,[14] localized in the pericardial fat, autonomic alterations,[15] and an increase in cardiac chamber size.[16] The identification of obesity as a potentially modifiable risk factor allows us to realize an effective preventive strategy that could reduce the risk of developing AF, but also decrease endothelial dysfunction, dyslipidemia, insulin resistance, and, therefore, cardiovascular risk.[17] A study of a large, multi-ethnic cohort of postmenopausal women concluded that low levels of BMI and regular physical activity play a protective effect on the development of AF.[18] Although vigorous exercise may be associated with an increased risk of developing AF,[19] Azarbal revealed that regular physical activity in postmenopausal women is associated with a modest, but significant, reduction in the incidence of AF after multivariate adjustment, including BMI. If obesity is a predisposing factor to AF, increased LA volume is the precursor and the cardiac manifestation of a higher BMI.[20] Wang *et al*. observed that the increase in the risk of AF in obese patients is due to the differences in size in the left atrium, between obese patients and normal-weighted individuals.[21] However, LA enlargement is not exclusively due to high BMI, but also increased plasma volume,[22] LVDD,[23] and the abnormal activation of the neuro-hormonal system

Table 2. Echocardiographic findings.

	HPMW with PAF n. 125	HPMW on Sinus rhythm (control group) n. 125	Chi-squared	Odds ratio	C.I.	P
Increased left atrial volume	37 (29.6%)	13 (10.4%)	14.4	3.62	95%	<0.0001
LVDD	24 (19.2%)	20 (16%)	0.44	1.25	95%	<0.5
LV hypertrophy	59 (47.2%)	84 (67.2%)	10.21	0.44	95%	<0.0014

HPMW, hypertensive postmenopausal women; PAF, permanent atrial fibrillation; LVDD, left ventricular diastolic dysfunction; LV, left ventricular.

contribute to increased LA size.[24] All these conditions, however, are produced by obesity condition and contribute to the enlargement and electrical instability of the LA. The LA size, therefore, represents a useful parameter in clinical practice because it is an important risk factor for the onset and maintenance of AF and stroke.[25] It is also a decisive parameter for the success of the rhythm strategies in the presence of supraventricular arrhythmias, and has a substantial impact on clinical practice because the echocardiographic assessment of LA enlargement gives us an objective and measurable value, well related to the risk of developing AF. We observed a nonsignificant statistical difference between the group of HPMW with PAF and the CG for type 2 diabetes mellitus (DM) prevalence. There are controversial results on the impact of DM on the risk of developing AF.[26] A Spanish study evaluated the occurrence of AF in a large cohort of hypertensive patients in the absence of ischemic disease, stroke, and peripheral artery disease, from June 2006 to December 2011. The onset of AF in the diabetic population was equal to 13.3 per 1000 person-years (mean follow-up: 4.3 years), unlike in the non-diabetic population where the incidence of new-onset AF was equal to 10.4 per 1000 person-years (mean follow-up: 4.1 years). The duration of diabetes (>5 years after diagnosis), poor glycaemic control (HbA1c>7%), and oral hypoglycaemic therapy were not shown to play a statistically significant role in the development of AF in the study by Alves-Cabratosa.[27] In our diabetic women, BMI values were statistically associated with the development of AF. This result suggests that the increased risk of developing AF in diabetic patients is not related to the disease or poor glycaemic control but is due to obesity, emphasizing the need for weight reduction in diabetic patients. These results have a significant clinical impact and represent a real novelty of the study. We have identified that the major factors predisposing to the development of AF are obesity and increased LA volume, regardless of age, reducing the role of DM. This finding allows for the improvement of primary prevention strategies for the reduction of body weight and provides an effective non-invasive imaging method for the evaluation of patients in follow-up. We did not find any statistically significant difference between the group of HPMW with PAF and the CG for LVDD. LVDD represents a predisposing factor in the development of AF, however, this is a special subset of patients.[28] Tsang demonstrated that the presence and the severity of LVDD are important predictors of the onset of AF in the elderly population.[29] Given his conclusions, we may speculate that our results could be attributed to the evaluations conducted on the general population with LVDD not particularly impaired, which creates a statistically significant difference between the two groups.

However, we found a low incidence of left ventricular hypertrophy (LVH) in the HPMW group with PAF compared to the CG, but since LVH is mainly the result of organ damage due to arterial hypertension, it is reasonable to assume that a good blood pressure control could result in the partial regression of hypertrophy and a lower risk of developing AF.[30] On the basis of this evidence, we can assume that HPMW with PAF showed the echocardiographic signs of effective anti-hypertensive therapy compared to the CG.

Conclusions

Our study showed a low prevalence of PAF in HPMW. The most important predisposing factors for the development and maintenance of PAF are obesity and increased LA volume, regardless of age. This result has a considerable clinical impact because it is possible to improve preventive strategies to reduce the incidence of AF and, consequently, cardiovascular risk. The LA volume is therefore an excellent and accurate ultrasound parameter to evaluate the risk of developing AF, and it could be considered a good follow-up imaging technique. LVDD, LVH, and DM do not seem to have a predisposing role in the onset of AF. However, further studies are needed to confirm these interesting data and to follow the evolution of the risk of AF in this subset of patients.

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