Pulse deficit in atrial fibrillation — a different perspective on rhythm or rate control strategy

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ABSTRACT

Background: Pulse deficit (PD) is a frequently unused but crucial clinical finding in atrial fibrillation (AF) diagnosis.

Aims: We aimed to investigate the relationship between PD and exercise intolerance in AF patients to remodel the treatment in case of a favorable outcome.

Methods: This prospective study was conducted with 273 permanent AF patients between September 2019 and October 2020. An exercise stress test stratified by age and sex-matched was performed to determine exercise intolerance, and the patients were divided into 2 groups based on physical capacity: low (<75 percentile as Group 1) (n = 160; 58.6%) and adequate (≥75 percentile as Group 2) (n = 113; 41.4%).

Results: The mean (standard deviation [SD]) PD of exercise intolerance patients was significantly higher than patients with adequate exercise capacity (17 [4] vs. 12 [2]; *P* <0.001). Moreover, PD was independently associated with exercise intolerance after adjusting for potential covariates (odds ratio [OR], 0.59; 95% confidence interval [CI], 0.51–0.69; *P* <0.001). In both univariate and multivariable analyses, higher heart rates had a stronger relationship with exercise intolerance (mean [SD], 107 [11] vs. 99 [10]; *P* <0.001; OR, 0.92; 95% CI, 0.89–0.96; *P* <0.001). Also, there was a positive correlation between heart rate and PD (r = 0.431; *P* <0.001).

Conclusions: Increased PD was associated with decreased exercise capacity in persistent AF patients. Rhythm control strategy should be considered to increase left ventricular filling pressures in AF patients with high PD and exercise intolerance.

Key words: atrial fibrillation, exercise test, pulse rate

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INTRODUCTION

Atrial fibrillation (AF) is a leading cause of morbidity and mortality, affecting 1%–2% of the population [1, 2]. Most patients with AF have palpitations, shortness of breath, weakness, and fatigue, which reduce exercise capacity and impair the quality of life [3]. Symptoms are primarily caused by a loss of atrioventricular synchronization due to rapid and irregular heart rate (HR) [4]. Also, the development of cardiomyopathy due to uncontrolled HR causes exercise intolerance symptoms [5]. Treatments to prevent these symptoms and complications are long-term and costly [6].

Pulse deficit (PD) is a pulse sign that can be effortlessly and non-invasively detected in physical examination in patients with AF. It is the difference between the apical HR and distal HR measurements. In addition to AF, PD can be examined in premature ventricular contractions, pacemaker patients, severe hypotension, and hypovolemia [7]. While 60–80 mm Hg pressure is required to open the aortic valve, 8–14 mm Hg pressure is sufficient for the mitral valve to close [8]. The aortic valve cannot be opened due to insufficient left ventricular filling pressure, but PD occurs as a result of mitral valve closure [8]. As a re-

WHAT'S NEW?

Rate or rhythm control in permanent atrial fibrillation (AF) management is still a matter of debate today. Current AF guidelines emphasized that advanced evaluation of the pathophysiological process involving clinical characteristics, blood biomarkers, and substrate determination may improve personalized therapy. However, there remains a need for a robust assessment of these processes. The authors revealed that a higher pulse deficit, a noninvasive and simple sign of inadequate left ventricular filling pressure, is associated with lower exercise capacity in AF patients. A significant regression or disappearance of the pulse deficit is physiologically expected with rhythm control. Therefore, a rhythm control strategy will be more beneficial than the rate control in symptomatic AF patients with a more extensive apex-pulse deficit to improve exercise intolerance. The present study reports that pulse deficit counts may be included in the preceding clinical characteristics after their relevance is corroborated by more extensive studies.

sult of inadequate left ventricular filling pressure (LVFP) in patients with AF, symptoms such as a decrease in exercise capacity, weakness, fatigue, and an increase in PD in the physical examination will be expected.

Consequently, this suggests that rhythm control will be more effective in relieving symptoms than rate control in patients with AF with high PD. However, there is no data in the literature on this subject. Therefore, this study examines the relationship between PD and exercise capacity in patients with AF and reshapes the treatment accordingly if there is a significant relationship.

METHODS

Study population and design

A total of 368 patients diagnosed with permanent AF were included in this prospective study between September 2019 and October 2020. The exclusion criteria were as follows: moderate and severe chronic obstructive pulmonary disease (forced expiratory volume in one second <80%), congestive heart failure (left ventricular ejection fraction [LVEF] <50%), left radial artery obstruction (>50%), anemia (hemoglobin <10 g/dl), unable to exercise stress test (orthopedic problems, fragility), elderly (>75 years), obesity (body mass index >29 kg/m^2), severe valvular heart disease. The study was conducted with 273 patients (Figure 1). For PD examinations, one physician counted the left radial pulse with the bare hand simultaneously with another, who counted the apical heartbeat with apical auscultation for one minute in the supine position. Succeeding, the physicians changed places, and the measurements were repeated. The present study was approved by the Local Ethics Committee, and written informed consent was obtained from all participants.

Exercise stress test

Exercise capacity was evaluated with an exercise stress test performed on a treadmill. The standard Bruce protocol was used. This protocol consists of 10 phases of 3 minutes that enable steady-state development before the workload is increased [9]. Exercise capacities were evaluated by staging formed as a result of metabolic equivalence (MET) values during the exercise test. MET is defined as the workload that occurs during exercise. It refers to the units of oxygen (O_2) consumed by a person at rest. One metabolic unit refers to 3.5 ml of O_2 consumed per minute per kilogram of body weight. MET is calculated using the formula "respiratory O_2 uptake/3.5" [9]. Then, estimated MET values were calculated according to age and gender. Veterans Affairs cohort formula for males (estimated METs = 18.7 – [0.15 × age]) and St. James Take Heart Project formula for females (14.7 – [0.13 × age]) were applied [10, 11]. Subsequently, percentages of estimated METs were calculated ([achieved METs/estimated METs] × 100). According to percentages of estimated METs, the patients were classified into low (Group 1, <75 percentile) and adequate (Group 2, ≥75 percentile) physical capacity groups. The test was terminated if significant chest pain, ST depression, or malignant arrhythmia were observed in the patients.

Echocardiographic evaluation

According to the recommendations of the American Society of Echocardiography, all echocardiographic examinations were performed using a high-quality ultrasound machine (Philips HD 11 XE, Bothell, WA, USA). The left ventricle and atrial diameters were measured using parasternal standard views. Early diastolic mitral inflow velocity (E) was measured using the pulsed wave Doppler method by placing the sample volume at the mitral valve leaflet tips level. Early diastolic mitral annular velocity (e') was measured using pulsed tissue Doppler imaging from the lateral corner of the mitral annulus in the apical 4-chamber view. Five consecutive measurements of E and e' were averaged. E/e' ratio was calculated. LVEF (by Simpson's method) was assessed from the apical 4-chamber view.

Statistical analysis

Data were presented as mean (standard deviation [SD]) for continuous variables with normal distribution, median (interquartile range [IQR]) for non-normal distribution, and percentage (%) for categorical variables. The Shapiro-Wilk test assessed the normal distribution of variables. Comparisons of the variables across the groups were performed using a Student t-test or Mann-Whitney U test or a one-way

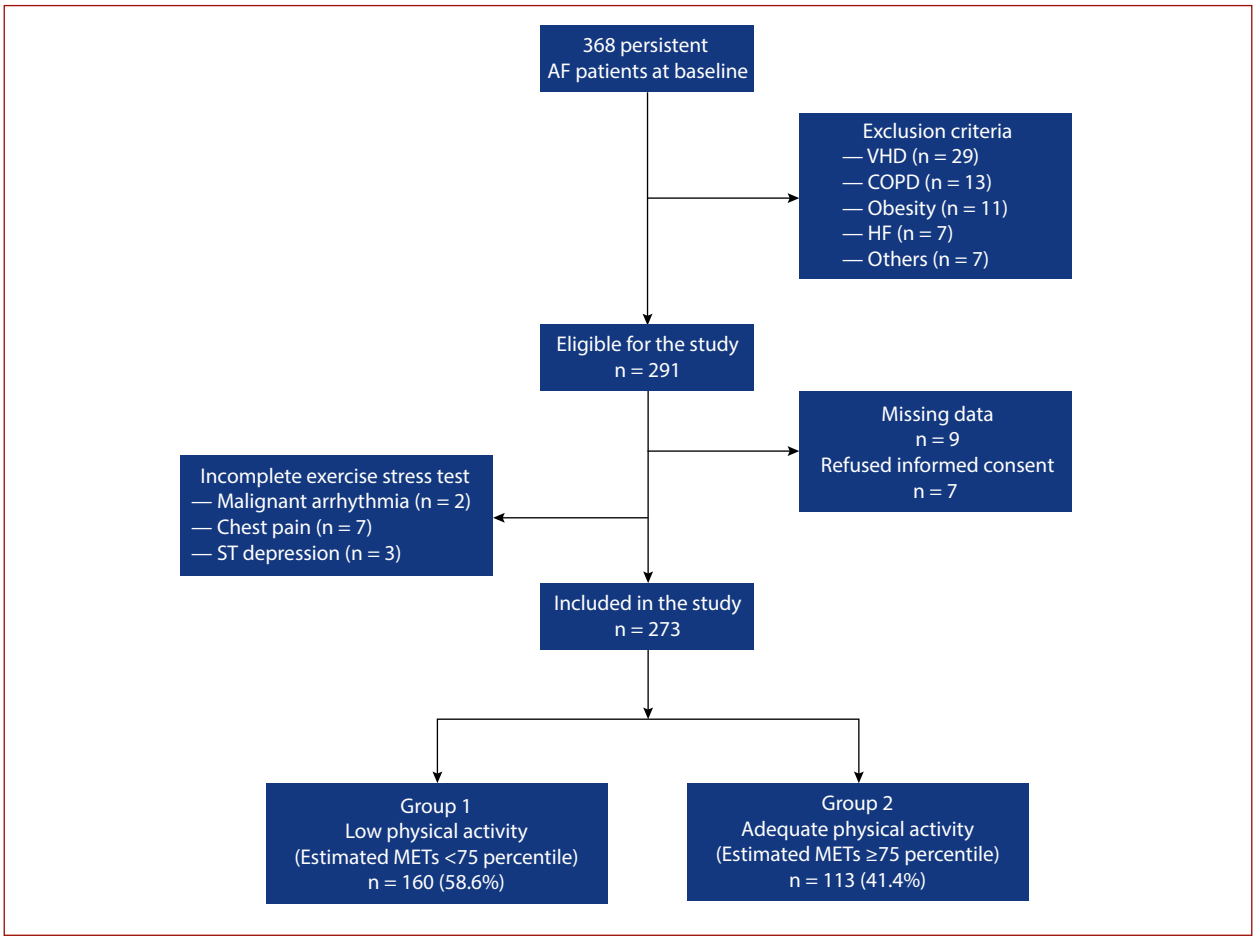

Figure 1. Patient enrollment. A total of 273 permanent AF patients were included in the study. The patients were divided into two groups according to exercise capacity matched by age and sex: Group 1; low physical capacity group (percentage of estimated METs <75 percentile) and Group 2; high physical capacity group (≥75 percentile)

Abbreviations: AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; HF, heart failure; METs, metabolic equivalents; VHD, valvular heart disease

ANOVA combined with a Tukey-Kramer post hoc analysis for continuous variables, and Chi-square ($\chi 2$) test for categorical variables. Also, logistic regression analyses were performed to define independent predictors of exercise intolerance. Finally, Pearson correlation was applied to determine the correlations. All statistical analyses were studied using the SPSS version 22.0 software package (IBM SPSS, Chicago, IL, USA) and MedCalc version 15.8 statistical software (MedCalc Software, Ostend, Belgium). Statistical significance was defined as $P < 0.05$.

RESULTS

Baseline characteristics of the patients are presented in Table 1. The mean (SD) age of the participants was 60.3 (5.0) years, and the majority were women (n = 165; 60.4%). Based on their exercise capacity, the patients were divided into the Group 1 (n = 160; 58.6%) and Group 2 (n = 113; 41.4%). The mean (SD) age of Group 2 was 59.8 (4.6) years, and the mean (SD) age of Group 1 was 61.0 (5.4) years ($P = 0.03$). The proportion of male participants was significantly higher in Group 1 ($P < 0.001$). Hypertension and coronary artery disease rate were higher in Group 1 than Group 2 ($P = 0.03$). There were no differences between the groups for drug usage rates. β-blocker equivalent dosages had no difference between the groups ($P = 0.69$).

The echocardiography findings of the groups are given in Table 2. There was no significant difference between the mean (SD) LVEF in the 2 groups (57.7 [4.7] vs. 58.2 [4.6]%; $P = 0.46$, respectively). The mean (SD) right ventricle (RV) in Group 1 diameters were slightly wider than Group 2 (35.1 [2.4] and 34.4 [2.3] mm, respectively, P = 0.03). The mean (SD) E/e' ratio in Group 1 was higher than in Group 2 (9.08 [1.51] vs. 8.71 [1.41]; $P = 0.03$, respectively).

The apical heartbeats, distal beats measured from the left radial artery, PD levels, and METs are presented in Table 2. The mean (SD) percentages of the estimated METs of Group 1 and Group 2 were 74.9 (16.8) and 132.0 (22.1) ($P < 0.001$). The mean (SD) PD counts (17 [4] vs. 12 [2] bpm; $P < 0.001$, respectively) (Figure 2A), apical HRs (107 [11] vs. 99 [10] bpm; $P < 0.001$, respectively) (Figure 2B), and distal HRs (91 [10] vs. 86 [9] bpm; $P = 0.001$, respectively) were significantly higher in Group 1 compared to Group 2. When

Table 1. Clinical characteristics of the study population

	Total n = 273	Group 1 n (%) = 160 (58.6)	Group 2 n (%) = 113 (41.4)	*P*-value
Age, years	60.3 (5.0)	61.0 (5.4)	59.8 (4.6)	0.03
Male, n (%)	108 (39)	81 (50)	27 (24)	<0.001
BMI, kg/m^2	26.2 (1.9)	26.2 (2.1)	26.1 (1.6)	0.91
History of, n (%)				
CAD	53 (19)	38 (23)	15 (13)	0.03
Stroke/TIA	35 (12)	20 (14)	15 (10)	0.48
Hypertension	226 (82)	139 (86)	87 (77)	0.03
Diabetes mellitus	59 (21)	37 (23)	22 (19)	0.47
Active smoking	71 (26)	37 (23)	34 (30)	0.19
Laboratory data				
Hemoglobin, g/dl	13.6 (1.6)	13.6 (1.6)	13.5 (1.5)	0.63
WBC, 10^3/µl	7.6 (2.1)	7.8 (2.4)	7.4 (1.6)	0.12
Creatinine, mg/dl	0.8 (0.2)	0.8 (0.2)	0.7 (0.1)	0.12
Glucose, mg/dl	99 (61–356)	101 (61–313)	97 (61–356)	0.10
Medications, n (%)				
ACEi/ARB	165 (60)	103 (64)	62 (55)	0.11
BB	188 (68)	113 (70)	75 (66)	0.45
Digoxin	128 (46)	68 (48)	60 (44)	0.51
CCB	66 (24)	41 (25)	25 (22)	0.50
BB doses, mg/day	50 (25–200)	50 (25–200)	50 (25–200)	0.69

Group 1: low physical capacity (<75 percentile), Group 2: adequate physical capacity (≥75 percentile). BB doses were presented as metoprolol equivalent doses as follows: metoprolol 50 mg = bisoprolol 5 mg = carvedilol 12.5 mg = nebivolol 5 mg [32] placing them in a unique position to prescribe the antihypertensive agent best suited to the individual patient. In individuals with diabetes mellitus, blood pressure (BP). Values are presented as the mean (SD), median (IQR), or n (%)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blockers; BMI, body mass index; CAD, coronary artery disease; CCB, non-dihydropyridine calcium channel blocker; TIA, transient ischemic attack; WBC, white blood cell; other — see Figure 1

Table 2. Echocardiographic, exercise treadmill parameters and pulse examination findings

	Total n = 273	Group 1 n (%) = 160 (58.6)	Group 2 n (%) = 113 (41.4)	*P*-value
Echocardiography				
LVEF, %	57.9 (4.7)	57.7 (4.7)	58.2 (4.6)	0.46
LVSD, mm	33.2 (1.7)	33.3 (1.7)	33.1 (1.8)	0.24
LVDD, mm	48.0 (2.2)	48.1 (2.2)	47.8 (2.2)	0.31
RV, mm	34.8 (2.4)	35.1 (2.4)	34.4 (2.3)	0.03
LA, mm	33.2 (2.5)	33.3 (2.5)	33.0 (2.4)	0.32
E/e'	8.82 (1.49)	9.08 (1.51)	8.71 (1.41)	0.03
Pulse examination				
Apical HR, bpm	104 (11)	107 (11)	99 (10)	<0.001
Distal HR, bpm	89 (10)	91 (10)	86 (9)	0.001
PD, bpm	14 (4)	17 (4)	12 (2)	<0.001
Peak exercise capacity (METs)	7.63 (2.44)	6.21 (1.71)	9.64 (1.83)	<0.001
Estimated METs, %	98.5 (34.1)	74.9 (16.8)	132.0 (22.1)	<0.001

Values are presented as the mean (SD)

Abbreviations: E, early left ventricular filling velocity; e', tissue velocity during early left ventricular filling; HR, heart rate; LA, left atrium; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic diameter; PD, pulse deficit; RV, right ventricle; other — see Figure 1 and Table 1

the patients' estimated METs were classified into quartiles, the mean (SD) PDs were significantly different in all quartiles (18 [4], 15 [3], 13 [3], and 11 [2] bpm, respectively) (Figure 2C). The mean (SD) apical HRs were significantly higher in the third and fourth quartile (102 [11] and 97 [8] bpm, respectively). However, there was no significant difference between the first and second quartiles (108 [10] and 108 [12] bpm, respectively) (Figure 2D).

Logistic regression analyses demonstrated the associations between clinical variables and exercise intolerance (Table 3). After a multivariable adjustment, age, sex, apical HR, and PD were independently associated with limited exercise tolerance. Covariates included significant variables in the univariate analysis, LVEF, beta-blocker doses, and the proportion of digoxin and non-dihydropyridine calcium channel blocker usage. In the bivariate correlation analysis, the E/e' ratio, apical HR, and left atrial (LA) volume significantly correlated with PD (r = 0.219; *P* <0.001; r = 0.431; *P* <0.001; r = 0.224; *P* <0.001, respectively) (Table 4).

DISCUSSION

This study demonstrates the clinical importance of PD examination in AF patients. While billions of dollars are spent every year on AF, it has been shown that PD examination,

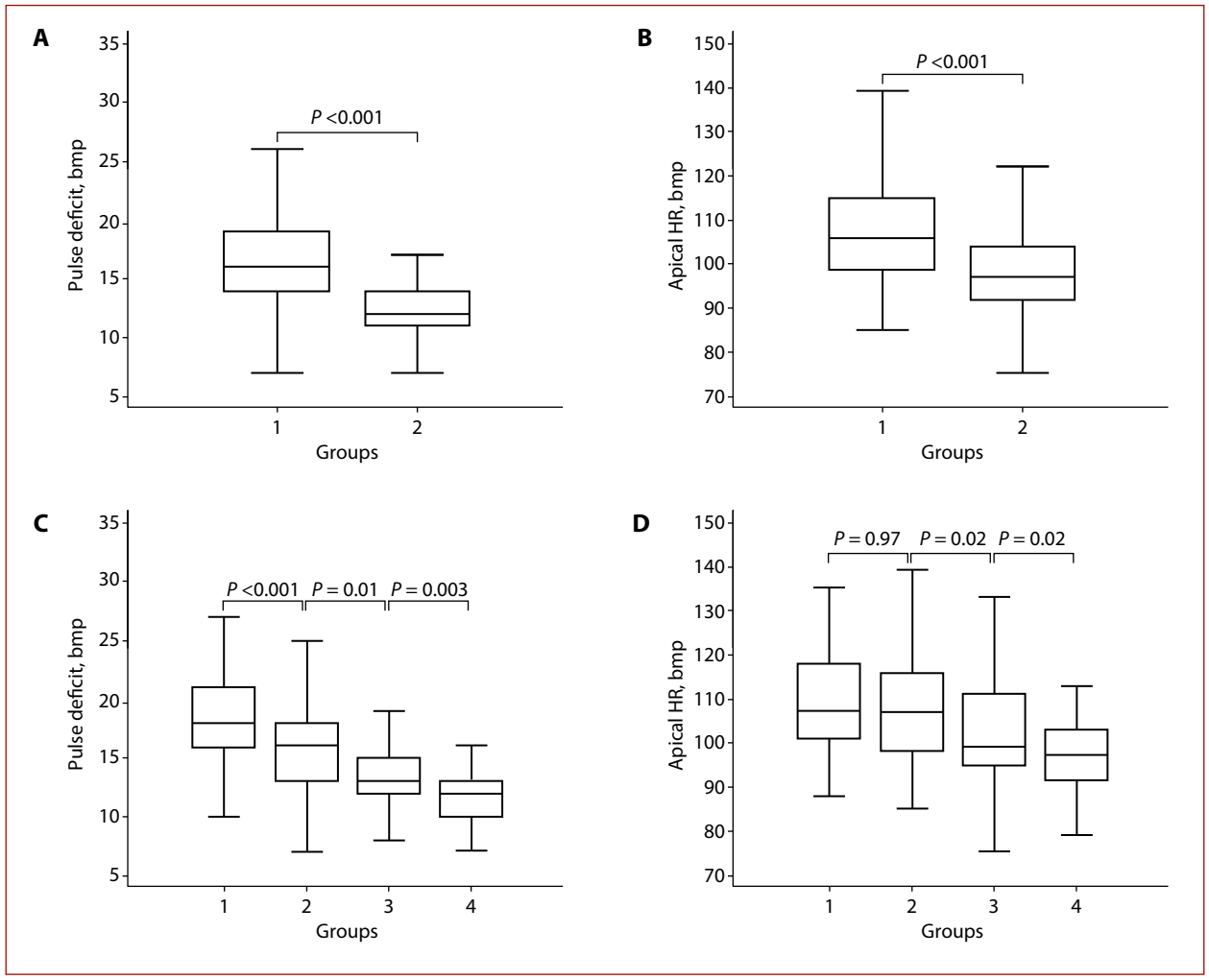

Figure 2. Box plots graphs show the distribution of the PD and apical HR between the groups. The differences between PD counts (**A**) and apical HR (**B**) in Group 1 and 2. **C.** and **D.** Depict patients' PD and apical HR distributions divided according to quartiles of estimated METs, respectively. First quartile: percentage of estimated METs <25th percentile (n = 67), second: 25–50th (n = 68), third: 50–75th (n = 70), fourth: ≥75th (n = 68)

Abbreviations: see Figure 1 and Table 2

Table 3. Univariate and multivariable analysis for exercise intolerance

Variables	Univariate analyses		Multivariable adjusted	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.06 (1.01–1.12)	0.03	1.27 (1.15–1.39)	<0.001
Gender	0.30 (0.18–0.52)	<0.001	0.05 (0.01–0.14)	<0.001
Hypertension	1.97 (1.04–3.73)	0.03	2.96 (0.99–8.84)	0.06
CAD	2.03 (1.05–3.91)	0.03	1.24 (0.47–3.28)	0.65
PD	0.68 (0.61–0.75)	<0.001	0.59 (0.51–0.69)	<0.001
Apical HR	0.92 (0.90–0.95)	<0.001	0.92 (0.89–0.96)	<0.001
LVEF	1.01 (0.96–1.07)	0.46	1.03 (0.95–1.12)	0.35
E/e'	0.83 (0.70–0.99)	0.03	0.86 (0.67–1.11)	0.27
RV	0.89 (0.80–0.99)	0.03	0.97 (0.83–1.14)	0.75

Abbreviations: CI, confidence interval; OR, odds ratio; other — see Table 1 and Table 2

Table 4. Correlations between PD and significant variables

Variables	R	*P*-value
Apical HR	0.431	<0.001
Distal HR	0.079	0.19
LVEF	0.057	0.34
LA	0.224	<0.001
E/e'	0.219	<0.001

Abbreviations: see Table 2

an easy, cheap, and noninvasive method, should not be overlooked. Even after adjusting significant covariates, the researchers found that PD was independently associated with exercise capacity. PD was significantly higher in the low exercise capacity group.

Previous studies reported that high PD had a strong relationship with inadequate LVFP resulting decrease in the stroke volume [8, 12]. Accordingly, PD counts will help determine whether an adequate stroke volume has been achieved quickly and easily after given treatment. Also, an increase in PD was significantly associated with submaximal exercise in healthy volunteers [13]. A declined stroke volume is blamed primarily for symptoms of exercise intolerance such as shortness of breath, weakness, and fatigue in patients with AF [14]. Therefore, the authors recommend PD examination to gain insight into the stroke volume in AF patients with exercise intolerance symptoms in the present study.

Another remarkable outcome of the present study was that higher HR was associated with higher PD and limited exercise capacity. We found a positive relationship between PD and apical HR. This relationship was attributed to the inadequate LVFP caused by the higher HR. However, PD was high in patients with normal HR levels (<100 bpm) and low exercise capacity. The authors considered that R-R intervals' irregularity was the fundamental cause of low filling pressure in average HR conditions. Therefore, this suggests that rhythm control will produce more successful results than rate control in AF patients with more outstanding exercise intolerance complaints. Many studies previously emphasized that rate control strategy should be applied to all patients, and rhythm control treatment should be individualized [15, 16]. Given the mentioned findings, we consider that PD examination will help individualize rhythm control.

This study also showed that high apical HR was inversely proportional to exercise capacity, independently of PD levels. In limited exercise capacity, a reduced stroke volume due to inadequate left ventricular filling pressure caused by increased HR seems to be the most likely mechanism. On the other hand, increased HRs may also be to compensate for decreased cardiac output. Many studies reported that higher HR was associated with a lower quality of life in AF [17–19]. Kato et al. [20] showed that patients with AF achieved their best exercise capacity when their resting HR was between 80–100/min, and more often, rate control had no effect. Rawles et al. [21] reported that the maintenance of the HR below 90/min in AF patients may have beeficial effects on cardiac output and symptom control. Contrary to the studies mentioned above, there have been no precise data about optimal HR in patients with AF in the guidelines [2]. The guidelines recommend rhythm control in the case of AF patients, who are symptomatic despite rate control and have a poor quality of life [2]. However, as the objective data, PD counts may be more helpful in evaluating rhythm control option in AF patients.

Previous studies showed that increased E/e' ratios in AF patients were associated with diastolic dysfunction and decreased exercise capacity [22, 23]. Furthermore, Li et al. [24] reported a relationship between increased E/e' and decreased LVFP. Additionally, a relationship between inadequate LVFP and exercise intolerance in patients with AF was shown in a previous study [25]. All these studies show that the loss of atrioventricular synchronization and deterioration in myocardial relaxation are also causative in the formation of insufficient LVFP. In this study, E/e' ratio was associated with exercise intolerance in the univariate analysis; nevertheless, the E/e' was not an independent predictor of exercise intolerance in the multivariable regression analysis. In the correlation analysis, the E/e' ratios weakly but significantly contributed to PD levels.

Previous studies reported that the New York Heart Association classification, MET values in exercise stress test performed with treadmill, or symptom-limited cardiopulmonary testing with expired gas analysis were used to evaluate exercise intolerance [26, 27]. Our study measured exercise capacity by the MET values in the exercise stress test performed on the treadmill. This study also evaluated functional capacity more objectively by using METs adjusted for age and sex. In this way, parameters directly related to MET values were also taken into account.

When we classified the patients into quartiles, the PD was significantly higher in each decreasing quarter. Also, apical HR was significantly lower in the upper quartiles. However, apical HR did not differ significantly below the 50th percentile. Despite the deterioration in physical capacity, the increase in heart rate did not differ significantly in the lower quartiles, while PD increased significantly at each stage. This result considered that PD was more specific than heart rate in AF patients with insufficient functional capacity.

Abhayaratna et al. [28] showed that an increased LA size was associated with exercise intolerance. Azarbal et al. [29] reported that exercise capacity in AF patients was independent of LA sizes. In this study, LA dimensions were not associated with lower exercise capacity. However, an increased LA size had a significant relationship with higher PD. Therefore, PD counts may be involved in assessing factors favoring rhythm control in AF patients, such as the LA size.

Limitations

First, estimated METs were used to evaluate the exercise capacity of the patients. More objective results could be obtained with symptom-limited cardiopulmonary testing with expired gas analysis. Second, there are no generally accepted age and sex-adjusted MET values for evaluating exercise intolerance. Therefore, the value used was determined, taking into account previous studies [30, 31]. Also, the lack of sufficient data on PD in the literature was another limiting factor.

CONCLUSIONS

Increased PD is associated with insufficient exercise capacity in persistent AF patients. In AF patients with predominant exercise intolerance symptoms and high PD, rhythm control should primarily be considered if there are no other obstacles to make left ventricular filling sufficient. Long-term studies are needed to evaluate symptoms and exercise capacity of patients whose PD is reduced by providing rhythm control.

Article information

Conflict of interest: SS is the author of several patents and shareholder of Medicine S.A. No products were used in this case.

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