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Original Article CARDIOLOGY

Systolic aortic regurgitation predicts all-cause mortality and hospitalization in outpatients with heart failure and preserved ejection fraction

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ABSTRACT

OBJECTIVE: Systolic aortic regurgitation (SAR) is considered to be a specific sign of heart failure (HF). However, the prevalence and importance of SAR in patients with HF and preserved ejection fraction (HFpEF) is unknown. Therefore, we sought to examine the prevalence of SAR in HFpEF outpatients, and its association with all-cause mortality and/or cardiovascular hospitalizations during 1-year follow-up.

METHODS: We enrolled 301 consecutive outpatients with HFpEF (mean age of 67.3±9.6 years, 53.5% women) and prospectively followed up for 1 year. Demographic, clinical, echocardiographic, and laboratory data were obtained at study entry. The composite endpoint of the study was all-cause mortality or HF-related hospitalizations at one year.

RESULTS: SAR was noted in 30 (9.9%) of the patients, and 38 patients (12.6%) reached the primary endpoint. The primary composite endpoint at 1 year was greater for patients with SAR (26.3%) compared to those without SAR (7.6%, p<0.001). After adjusting for important covariates, SAR remained independently associated with primary outcome (OR 2.315; 95% CI 1.188–5.477; p=0.008).

CONCLUSION: This is the first study to demonstrate that the presence of SAR is associated with adverse events in HFpEF patients.

Keywords: Echocardiography; heart failure and preserved ejection fraction; outcome; prognosis; systolic aortic regurgitation.

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Heart failure with preserved ejection fraction (HFpEF) is the most frequent form of heart failure (HF) in ambulatory patients, and therefore, early identification of high-risk patients for hospitalization and/or death is crucial [1, 2]. Improvements in risk stratification by identification of new risk scores, biomarkers and imaging techniques have been extensively investigated in the past decade [3–5]. Several echocardiograhic parameters such as left ventricular hypertrophy, pulmonary hypertension, and various indices of diastolic stiffness have also been associated with worse prognosis in HFpEF [6–8].

Aortic regurgitation usually occurs in diastole but systolic aortic regurgitation (SAR) is caused by the inability of ventricular contraction to overcome the aortic pressure in systole [9]. SAR is usually associated with premature ventricular contractions or atrial fibrillation [10]. In a small study, SAR was detected in 2.3% of patients admitted to hospital and was more frequent in patients with HF [11]. Though there is growing evidence that SAR is not an exceptional phenomenon, the prevalence and prognostic significance of SAR in patients with HF remains unknown. Therefore, the aim of this study

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is to examine the prevalence and significance of SAR in predicting all-cause mortality or HF-related hospitalizations in HFpEF patients.

MATERIALS AND METHODS

Patients

After Ethics Committee approval (MUSKU, 16.08.2016, 14/2) this prospective study was conducted in our hospital between March 2017 and May 2018. The study group included all consecutive adult outpatients diagnosed with HFPEF. Patients were defined as HFpEF according to current guidelines [12]. Patients were excluded if they need hospitalization during the index admission. Patients with severe valvular heart diseases, severe chronic pulmonary disease; hypertrophic cardioyopathy; and pregnant patients were excluded from the study.

Measurements, Data Collection and Endpoints

For each patient, data for comorbid conditions, patients' demographic characteristics, medications, and echocardiographic parameters were recorded at admission to the outpatient cardiology clinic. Data were collected by telephone interviews and outpatient clinical visits.

All of the consecutive outpatients with HFpEF underwent comprehensive transthoracic echocardiography [13]. Systolic aortic regurgitation is explained as the inability of the ventricular beat to overcome the aortic pressure associated with some degree of valvular incompetence. Therefore, the SAR was defined as the presence of blood flow from the aorta to the left ventricular outflow tract during systole (Fig. 1). The presence/absence of SAR was recorded. Routine laboratory variables and NT-proBNP levels were measured at admission to the outpatient.

All patients were prospectively followed up for 12 months or until death. The written informed consent was obtained from all patients. The primary composite endpoint was all-cause death and hospitalization for HF at 12 months.

Statistical Analysis

In the evaluation of the differences between the categorical variables Fisher's exact test was used in row and column tables and Pearson Chi-Square Test was used for 2x2 tables. To compare continuous variables groups, independent t-tests, and Mann-Whitney U tests were used. Univariate and multivariable logistic regression analyses were performed to determine independent predictors of outcomes.For statistical analysis, the Jamovi (Jamovi Project 2018, version 0.9.1.7, retrieved from https://www.jamovi.org) (open source) program was used

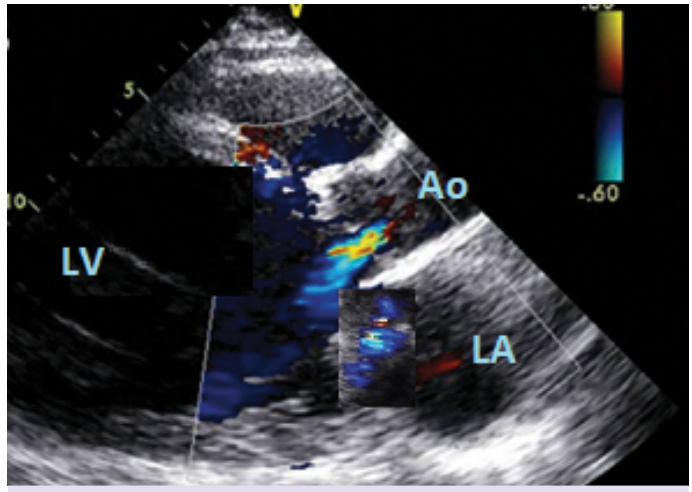

Figure 1. Color Doppler echocardiography showing simultaneous aortic and mitral regurgitation flows during the systole.
LV: Left ventricle; LA: Left atrium; Ao: Aorta.

RESULTS

A total of 301 consecutive ambulatory HFpEF patients, aged 18 years or older (mean age of 67.3±9.6 years, 53.5% women) were included.

Comparison of Patients with and Without SAR

SAR was noted in 30 (9.9%) patients. The patients with SAR were older, were more likely be symptomatic (higher NYHA functional class, more frequent crepitant rales, and orthopnea), were more likely to have chronic lung diseases, and atrial fibrillation compared to without SAR (Table 1). Patients with SAR had higher NT-proBNP levels and were more likely to have mitral regurgitation (moderate or greater) on admission.

Comparison of Patients who Reached and who Had not Reached Primary Outcome

Thirty-eight patients (12.6%) reached the composite endpoints at one year. Comparison of the patients who reached and who had not reached primary outcome are presented in Table 2. However, patients who died or who were hospitalized for HF during the study period were older, had more frequently atrial fibrillation, and chronic obstructive pulmonary disease compared to patients

Table 1. Characteristics of patients according to the presence of systolic aortic regurgitation

	Without SAR (n=271)	With SAR (n=30)	p
Gender (female)	145 (53.5)	16 (53.3)	0.354
Age, years	65 (57–78)	69 (65–81)	<0.001
Body mass index, kg/m^2	28 (26–36)	28 (25–32)	0.086
Smoking	55 (20.3)	8 (19.1)	0.213
NYHA III/IV symptoms	61 (22.5)	16 (53.3)	<0.001
Orthopnea	60 (22.1)	15 (50.0)	0.001
Pulmonary crepitations	52 (19.1)	9 (30.0)	0.004
Comorbidities			
Hypertension	196 (72.3)	22 (73.3)	0.355
Diabetes mellitus	68 (25.1)	8 (26.7)	0.425
Chronic kidney disease	22 (8.1)	2 (6.7)	0.462
Coronary artery disease	61 (22.5)	7 (23.3)	0.152
Cerebrovascular disease	16 (5.9)	2 (6.7)	0.314
Chronic obstructive pulmonary disease	33 (12.2)	7 (23.3)	0.041
Atrial fibrillation	72 (26.6)	16 (53.3)	<0.001
Laboratory data			
NT-proBNP, pg/ml	301.8 (151–795)	535 (184–1356)	<0.001
Fasting blood glucose, mg/dl	98 (90–155)	99 (92–154)	0.138
Serum creatinine, mg/dl	0.80 (0.7–1.0)	0.81 (0.7–1.0)	0.525
Hemoglobin, g/dl	12.7 (12.1–14.3)	12.9 (11.9–14.5)	0.674
Echocardiography			
LVEF, %	59 (53–62)	58 (51–65)	0.680
IVS dimension, mm	12 (10–13)	11 (10–12)	0.451
≥ Moderate mitral regurgitation	65 (23.4)	10 (33.3)	0.044
Pulmonary systolic pressure (mmHg)	27 (15–34)	30 (16–39)	0.065

Data are presented as median with the first and third quartile (Q1–Q3) or number (%). SAR: Systolic aortic regurgitation; NYHA: New York Heart Association; NT-proBNP: N-terminal pro B-type natriuretic peptide; LVEF: Left ventricle ejection fraction; IVS: Interventricular septum.

without adverse events. Patients who had experienced primary outcome were also more likely to be symptomatic, were more likely to have mitral regurgitation and had higher NT-proBNP levels on admission. The primary composite endpoint at 1 year was greater for patients with SAR (26.3%) compared to those without SAR (7.6%, p<0.001).

Predictors of All-Cause Mortality

All-cause mortality during follow-up was 3.9% (11 patients). Multivariate analysis showed that age (OR: 2.678; 95% CI: 1.567–7.219; p=0.013), NT-proBNP>459 pg/mL (OR: 2.671; 95% CI: 1.435–7.451; p<0.001), and presence of SAR (OR: 2.673; 95% CI 1.295–5.709; p=0.001) predicted mortality.

Predictors of Hospitalization for Heart Failure

Thirty-two patients (10.6%) required at least one hospitalization due to a HF during follow-up. Multivariate analysis showed that age (OR: 2.109; 95% CI: 1.407–5.543; p=0.024), presence of orthopnea on admission (OR: 1.491; 95% CI: 1.019–3.214; p=0.039), and NT-proBNP >411 pg/mL (OR: 2.171; 95% CI: 1.409–4.341; p=0.043) predicted hospitalization due to a HF.

Predictors of Composite Endpoint

The incidence of death or hospitalization for HF at 1 year was 12.6%. Univariate analysis showed a significant association between age, presence of orthopnea and pulmonary crepitations, chronic obstructive pulmonary disease, atrial fibrillation, NT-proBNP, moderate or

Table 2. Comparison of patients who reached and did not reach the primary outcome

	Without events (n=263)	With events (n=38)	p
Gender (female)	141 (53.6)	20 (52.6)	0.323
Age, years	63 (57–77)	68 (66–81)	0.001
Body mass index, kg/m^2	27 (26–36)	28 (25–32)	0.136
Smoking	52 (19.8)	11 (28.9)	0.081
NYHA III/IV symptoms	63 (23.9)	14 (36.8)	0.065
Orthopnea	59 (22.4)	16 (42.1)	0.001
Pulmonary crepitations	50 (19.1)	11 (28.9)	0.004
Comorbidities			
Hypertension	190 (72.2)	28 (73.7)	0.653
Diabetes mellitus	66 (25.1)	10 (26.3)	0.487
Chronic kidney disease	22 (8.4)	2 (5.3)	0.432
Coronary artery disease	60 (22.8)	8 (21.1)	0.165
Cerebrovascular disease	16 (6.1)	2 (5.2)	0.365
Chronic obstructive pulmonary disease	30 (11.4)	10 (26.3)	0.035
Atrial fibrillation	70 (26.7)	18 (47.3)	0.001
Laboratory data			
NT-proBNP, pg/ml	321.8 (148–625)	612 (151–1445)	<0.001
Fasting blood glucose, mg/dl	99 (90–155)	98 (92–152)	0.165
Serum creatinine, mg/dl	0.82 (0.7–1.0)	0.81 (0.7–1.1)	0.378
Hemoglobin, g/dl	12.2 (12.2–14.3)	12. 7 (11.7–14.4)	0.652
Echocardiography			
LVEF, %	59 (53–62)	58 (51–65)	0.680
IVS dimension, mm	12 (10–13)	11 (10–12)	0.451
≥ Moderate mitral regurgitation	65 (23.4)	10 (33.3)	0.040
Pulmonary systolic pressure (mmHg)	27 (15–34)	30 (16–39)	0.065
Systolic aortic regurgitation	20 (7.6)	10 (26.3)	<0.001

Data are presented as median with the first and third quartile (Q1–Q3) or number (%). NYHA: New York Heart Association; NT-proBNP: N-terminal pro B-type natriuretic peptide; LVEF: Left ventricle ejection fraction; IVS: Interventricular septum.

greater mitral regurgitation, and SAR with primary outcome. On multivariate analysis, age (OR: 2.125; 95% CI: 1.251–4.789; p=0.006), atrial fibrillation (OR: 1.954; 95% CI: 1.190–4.621; p=0.005), NT-proBNP >359 pg/mL (OR: 3.381; 95% CI: 1.539–8.474; p<0.001), and SAR (OR: 2.315; 95% CI: 1.188–5.477; p=0.008) remained as significant variables associated with primary endpoints (Table 3).

Table 3. Multivariate analysis for the prediction of primary composite endpoint of all-cause death and hospitalization for heart failure at 12 months

	OR	95% CI	p
Age (per 1 y)	2.125	1.251–4.789	0.006
NT-proBNP >359 pg/mL (median)	3.381	1.539–8.474	<0.001
Orthopnea	1.058	0.341–3.377	0.912
Atrial fibrillation	1.954	1.190–4.621	0.005
≥ Moderate mitral regurgitation	0.841	0.121–2.214	0.254
Systolic aortic regurgitation	2.315	1.188–5.477	0.008

OR: Odds ratio; NT-proBNP: N-terminal pro B-type natriuretic peptide; CI: Confidence interval.

DISCUSSION

The present study showed that all-cause mortality was 3.9%, HF-related hospitalization was 10.6% and, incidence of death or hospitalization for HF was 12.6% at 1 year in ambulatory patients with HFpEF. This is the first study showing an association between SAR and adverse

events in HFpEF patients. These results reveal the need of adding the assessment of SAR in routine echocardiographic evaluation of HF patients.

The HFPEF is currently the most common form of HF, mainly because of the accelerated aging and high prevalence of comorbidities [14]. Identifying high and low-risk ambulatory patients with HFpEF can improve care by preventing delays in appropriate treatment for high-risk patients. However, currently available prediction models in patients with HF often contain variables which are not routinely collected in clinical practice [15] and data are limited in ambulatory HFpEF patients.

Previous studies revealed that aortic regurgitation is not always limited to diastole and in certain hemodynamic situations may also occur in systole [9–11]. Saura et al. performed a prospective study of all echocardiographic examinations over one month [11]. The SAR was detected in 2.3% of the all investigations and it was detected in 5.9% of patients with HF [11]. In another study, patients with dyspnea were included [16]. SAR was present in 3.3% of the patients, and the prevalence of HF was 40.3% [16]. The authors found the specificity of SAR was 99.4% for the HF diagnosis [16]. Bonaque and colleagues performed a prospective observational study and collected data from all outpatients referred to echocardiography [17]. Of the 1042 patients, the prevalence of SAR was 1% and the prevalence of HF was 12%. The 46% of the HF patients had HFpEF in this single-center study [17]. The authors found that all patients with SAR had HF, and in the subpopulation of patients with HF, SAR was found in 9%. During follow-up, 9 of the 11 patients with SAR were admitted to hospital for HF and, 4 out of 11 patients with SAR died of HF [17]. Although our study had some methodological differences with this study, we found a similar SAR prevalence of 9.9% in our study group of patients with HFpEF. Our result also revealed that presence of SAR was an independent predictor of outcomes in outpatients with HFpEF. The incidence of primary composite endpoint at 1 year was higher for patients with SAR (26.3%) compared to those without SAR (7.6%). Our preliminary study, to our knowledge, is the first to demonstrate an impact of SAR on the outcome of HFpEF. However, it is premature to recommend SAR as a predictor of adverse events in all HF patients and the incremental value of SAR for prediction of complications should be investigated in further prospective clinical trials.

Study Limitations

This is a single centre study including only ambulatory patients with HFpEF. Patients who had HF with reduced- or mid-range left ventricular ejection fraction and patients who were hospitalized for HF were excluded in this study.

Conclusions

This study provides the first evidence about the prevalence and significance of SAR in an unselected outpatient population of HFpEF. Our study revealed that, although it was not common, the presence of SAR portends a poor prognosis in patients with HFpEF.

Ethics Committee Approval: The Mugla Sitki Kocman University Clinical Research Ethics Committee granted approval for this study (date: 16/18/2016, number: 14/II).

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – IB; Design – MB; Supervision – IB; Fundings – MB; Materials – IB; Data collection and/or processing – MB; Analysis and/or interpretation – MB; Literature review – IB; Writing – IB; Critical review – MB.

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