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

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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 echocardiographic 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
is to examine the prevalence and significance of SAR in predicting all-cause mortality or HF-related hospitalizations in HFP EF 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 HFP EF. Patients were defined as HFP EF 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 cardiomyopathy; 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 HFP EF 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.

RESULTS
A total of 301 consecutive ambulatory HFP EF 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...
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: 2.109; 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 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
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).

**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 outcomes.
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).

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