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Fluid status and outcome in patients with heart failure and preserved ejection fraction☆,☆☆

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ABSTRACT

Background: Most heart failure with preserved ejection fraction (HFpEF) patients, at some point, present to an emergency department with typical symptoms of volume overload. Clinically, most respond well to standard diuretic therapy, sometimes at the cost of renal function. The study sought to define the prognostic significance of fluid status versus renal function in patients with HFpEF.
Methods: One hundred sixty-two consecutive patients with HFpEF were enrolled in our prospective registry. Twelve patients with clinically overt decompensation were excluded. Fluid status at baseline was determined by bioelectrical impedance spectroscopy. The primary outcome measure was a combined end point consisting of hospitalization for heart failure and/or death for cardiac reason.
Results: Mean age was 74.4 ± 8.4 years. Ninety-one (61%) patients were hypo- or normovolemic (relative fluid overload [Rel. FO] −0.7 ± 5.7%) while 59 (39%) patients presented with fluid overload (Rel. FO 11.5 ± 2.7%). During a median follow-up of 24.3 months (interquartile range: 19.8–33.2), 34% of patients reached the combined end point. Multivariate Cox hazard analysis identified fluid overload (hazard ratio: 3.09; 95% confidence interval: 1.68–5.68; $p < 0.001$) as an independent predictor of adverse outcome. Patients with fluid overload and normal renal function showed a worse event-free survival compared to the subgroup with normohydration and impaired renal function (log-rank: $p = 0.042$).
Conclusion: HFpEF patients with measurable fluid overload face a dismal prognosis as compared to euvolemic patients. Our data, while preliminary, suggest that patients with fluid overload may face a better outcome under continued fluid removal irrespective of changes in eGFR.

1. Background

Abnormal fluid distribution and volume overload are hallmarks of acute and chronic heart failure (HF) [1]. At some point in their disease, most HF patients present acutely to an emergency department with typical symptoms of progressive volume overload [2]. During the following hospitalization, most patients clinically respond well to standard diuretic therapy, usually at the cost of renal function. Based on the assumption that overt fluid overload is the result of progressive fluid accumulation [3], current international practice guidelines recommend a correction of volume status using diuretics to reduce the total fluid volume [4,5].

However, hospitalizations due to fluid overload remain frequent in HF patients, with a plethora of explanations seem to be applicable. First, while the dynamics and clinical significance of the heterogeneity in volume overload and fluid distribution are yet to be evaluated [6,7], clinicians may simply fail to adequately assess fluid status in the outpatient setting, due to a lack of objective methods of measurement [7]. Second, physicians are faced with the quandary to choose between guideline-recommended use of loop diuretics and strategies aiming at a long-term preservation of renal function by discontinuing diuretic treatment. Surrogate markers, such as the presence or absence of elevated jugular venous pressure, dyspnea, peripheral edema, third heart sound, or hepatojugular reflux, are commonly considered the mainstays of volume status evaluation [6]. However, these markers lack sensitivity and reliability, especially because affected patients often suffer from concomitant conditions that may mask or modulate fluid status, such

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as obesity, chronic obstructive pulmonary disease, chronic kidney disease (CKD), or diabetes mellitus (DM) [8]. While elevated serum levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) show a direct relationship with adverse outcome and higher New York Heart Association functional classes [2] in HF patients, its exact role in the estimation of volume overload is controversial. Despite a strong correlation between serum NT-proBNP and total body water [9], elevated NT-proBNP may also have other causes, such as atrial fibrillation (AF), pulmonary embolism, renal failure, advanced age, anemia, or bacterial sepsis [4,5].

Even invasively measured hemodynamic parameters, such as the pulmonary arterial wedge pressure (PAWP) failed to show a tight correlation with gold standard measurements [10], such as tracer techniques, e.g. iodinated^{131I} human serum albumin [2].

Bioelectrical impedance spectroscopy (BIS) is a simple, non-invasive, and relatively inexpensive technique that allows an accurate assessment of fluid status. In the present study, we assessed fluid status and renal function of consecutively registered heart failure with preserved ejection fraction (HFpEF) patients without overt signs of decompensation and followed their clinical course. Specifically, we determined the prognostic significance of fluid status versus renal function, with the ultimate goal of perhaps judging the clinical practice of withdrawing fluid at the cost of impaired renal function.

2. Methods

2.1. Study design

Consecutive patients with a confirmed diagnosis of HFpEF were recruited in this prospective, observational, non-interventional registry performed at the Department of Cardiology of the Medical University of Vienna, Austria. The local Ethics Committee approved the study (EK #796/2010) and all patients gave their written informed consent prior to any study-related procedure.

Baseline data were collected on the day of enrollment and consisted of physical examination, 12-lead electrocardiogram, BIS, 6-min walk test (6-MWT) with Borg Dyspnea Score (BDS), and laboratory tests. Right heart catheter (RHC), coronary angiography, and transthoracic echocardiography (TTE) were performed within a maximum of 1 month. Patients with clinically overt decompensation and requirement for intravenous diuretic treatment were excluded from the protocol. Patients with significant valvular or congenital heart disease, significant coronary artery disease as diagnosed by coronary angiography or regional wall motion abnormalities of the left ventricle (LV) were also excluded.

The primary outcome measure was a combined end point consisting of hospitalization due to HF and/or cardiac death. Patients were followed in 6-month intervals by outpatient visits or telephone calls in case of immobility. The predefined primary end point was ascertained through blind adjudication by a designated team of cardiologists.

2.2. Diagnosis of HFpEF

HFpEF was diagnosed according to the current consensus statement of the European Society of Cardiology (ESC) [11] and the guidelines of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [5]. The following criteria had to be fulfilled: 1. signs or symptoms of HF, 2. left ventricular ejection fraction (LVEF) >50%, 3. Serum NT-proBNP >220 pg/ml on the day of enrollment, 4. evidence of LV diastolic dysfunction by TTE. For confirmation of diagnosis, RHC was performed in all but seven patients. HFpEF was confirmed if PAWP exceeded 12 mmHg.

2.3. Bioelectrical impedance spectroscopy

Patients underwent standardized evaluation of their fluid status using a portable whole-body BIS device, the Body Composition Monitor (BCM, Fresenius Medical Care, Bad Homburg, Germany). Patients were placed in supine position for at least 5 min before the evaluation of their fluid status. Electrodes were attached to the non-dominant hand and the ipsilateral foot. Measurements were conducted according to the manufacturer's manual. For each patient, only one bioelectrical impedance analysis was performed, as this method has an adequate reproducibility [12]. Fluid overload assessed by BCM is expressed as an absolute value in liters or as a relative value in %, calculated as the ratio between fluid overload (FO) and the content of extracellular water (ECW) and multiplied by 100 (Rel. FO = FO/ECW × 100%).

In this study, fluid overload was defined as Rel. FO ≥ 7% corresponding to the value of the 90th percentile for the reference cohort obtained from an age- and sex-matched healthy population when fluid status was measured with the same technology [13] and as it was used in a previous study in patients with CKD [14]. After baseline evaluation and inclusion in the present study, patients continued treatment at our outpatient clinic. Care-taking physicians at the outpatient clinic were independent from the study team and blinded to the results of the BIS measurement and RHC. Any decisions to adapt diuretic therapy were based on clinical assessment and according to recent guidelines on the management of HFpEF [4,5].

2.4. Transthoracic echocardiography

Patients received a TTE by board-certified physicians using high-quality scanners, such as GE Vivid 5, GE Vivid 7 (General Electric Medical System, Milwaukee, WI, USA), and Siemens Acuson Sequoia (Siemens Healthcare GmbH, Erlangen, Germany). The TTE was performed according to the guidelines of the American Society of Echocardiography [15]. Simpson's biplane method of discs was used to measure LVEF. The peak velocity of the tricuspid regurgitation jet assessed by continuous-wave Doppler together with right atrial pressure was used to measure systolic pulmonary arterial pressure (sPAP) [16].

2.5. Right heart catheter and coronary angiography

RHC was performed via a jugular or femoral access. A 7F Swan-Ganz catheter (Edwards, Irvine, CA, USA) was used for the assessment of hemodynamic parameters. The average of the filling pressures recorded over eight heart cycles were documented using CathCorLX (Siemens AG, Berlin and Munich, Germany). Cardiac output (CO) was assessed by thermodilution and by the Fick method and was expressed in liters/min. Pulmonary pulse pressure (PPP) was calculated as the difference between sPAP and diastolic pulmonary arterial pressure (dPAP). Transpulmonary pressure gradient (TPG) was calculated by subtracting PAWP from mean pulmonary arterial pressure (mPAP). Diastolic pressure gradient (DPG) was calculated as the difference between dPAP and PAWP. Pulmonary vascular resistance (PVR) was calculated by dividing TPG by CO and was expressed in dynes·s·cm^{-5}. Pulmonary arterial compliance (PAC) was calculated as the ratio of stroke volume to PPP.

In the same session, patients underwent coronary angiography and those with at least one visual stenosis over 50% in one of the main vessels and/or over 70% in one of the distal vessels were excluded.

2.6. Other baseline tests

The 6-MWT was performed according to the American Thoracic Society guidelines on a corridor with a 50-m track [17]. The walking distance was measured after 6 min and patients had to grade their dyspnea on the basis of BDS between 0 and 10 [18]. Venous blood was used to measure NT-proBNP with an immunological test (Elecsys® Systems, Roche Diagnostics) and serum creatinine. The estimated glomerular filtration rate (eGFR) was derived from the Modification of Diet in Renal Disease equation. Impaired renal function was defined as an eGFR < 60 ml/min/1.73 m^2 which is equivalent to CKD stage 3 or worse [19].

2.7. Statistical analysis

Data were analyzed with SPSS Statistics (version 23, IBM, for Macintosh). *P* values from two-sided tests ≤0.05 were considered statistically significant. Data were expressed as mean ± standard deviation or frequency and percent. Student' *t* test or Wilcoxon rank-sum test was used to compare continuous variables, as appropriate. χ^2 test was used to assess group differences in categorical variables. Spearman rank correlation coefficient was utilized to measure the dependence between Rel. FO and non-normally distributed variables. For the association analysis between Rel. FO and values with Gaussian distribution, Pearson's correlation coefficient was applied. Cox proportional hazards analyses were done to determine the association of fluid overload and impaired renal function (run as categorical variables) with the predefined combined end point, adjusted for fluid overload, impaired renal function, 6-min walk distance (6-MWD), NT-proBNP, AF, and sPAP. The presence of DM and AF was entered as a categorical variable. Observation times for patients who died from a non-cardiac reason were censored. Results are expressed as hazard ratio (HR) with 95% confidence interval (CI). Crude survival curves were generated by the Kaplan—Meier method and compared with the log-rank test to verify the time-dependent discriminative power of the respective variable.

3. Results

3.1. Patient characteristics

Between December 2010 and July 2015, 162 consecutive patients with HFpEF were enrolled in our prospective, observational, non-interventional registry. Twelve patients were overtly decompensated at the baseline examination with the requirement of immediate therapy and were therefore excluded from further analyses. A detailed patient disposition of the remaining patients, according to fluid status and eGFR, is displayed in Fig. 1.

Patient baseline characteristics are displayed in Table 1. One hundred four (69%) study participants were female. Mean age was 74.4 ± 8.4 years. Ninety-one (61%) patients were hypo- or normovolemic (Rel. FO −0.7 ± 5.7%), while 59 (39%) patients presented with fluid overload

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