Increased Right Ventricular Pressure as a Predictor of Acute Decompensated Heart Failure in End-Stage Renal Disease Patients on Maintenance Hemodialysis

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ABSTRACT

Background and Objectives: Many patients with end-stage renal disease (ESRD) on hemodialysis (HD) have reduced vascular compliance and are likely to develop heart failure (HF). This study aimed to determine the factors associated with acute decompensation events among ESRD patients undergoing HD.

Methods: We retrospectively investigated ESRD patients on HD using a medical record review. We divided the patients into those admitted to hospital due to acute decompensated heart failure (ADHF) and those who were not. We compared the medical histories, electrocardiograms, and echocardiographic and laboratory data between the two groups.

Results: Of the 188 ESRD patients on HD, 87 were excluded, and 101 were enrolled (mean age: 63.7 years; 52.1% male). Thirty patients (29.7%) were admitted due to ADHF. These patients exhibited similar left ventricular ejection fraction (LVEF), left ventricular (LV) mass index, and E/E' values compared to the non-ADHF group. However, the ADHF group exhibited significantly higher tricuspid regurgitation (TR) jet velocity (2.9±0.6 vs. 2.5±0.4 m/s; p=0.004) and right ventricular systolic pressure (RVSP) (43.5±17.2 vs. 34.2±9.9 mmHg; p=0.009) than the non-ADHF group, respectively. A multivariate logistic regression analysis demonstrated that the TR jet velocity (odds ratio, 8.356; 95% confidence interval, 1.806–38.658; p=0.007) was an independent predictor of ADHF after adjusting for age and sex, while the LVEF and E/E' were not.

Conclusions: Our data showed that an increased TR jet velocity was an independent predictor of ADHF events in ESRD patients on HD, but the LVEF and E/E' were not.

Keywords: End-stage renal disease; Hemodialysis; Heart decompensation; Pulmonary hypertension
INTRODUCTION

Cardiovascular (CV) disease is a common complication and the most frequent cause of death in patients with end-stage renal disease (ESRD) who are on hemodialysis (HD). In particular, heart failure (HF) is a strong, independent, adverse prognostic indicator in ESRD patients. According to some registries of patients undergoing renal replacement, the prevalence of HF was found to be about 30–40%. Dialysis patients with HF exhibit a lower two-year survival rate after the initiation of dialysis (65%) compared to those without HF (83%). Patients with ESRD are hemodynamically distinct from healthy people, and many factors can cause or aggravate HF in this population. This trend is likely due to the presence of left ventricular hypertrophy (LVH) and other risk factors, such as chronic volume overload, anemia, inflammation, oxidative stress, and mineral bone disorders. Approximately 75% of incident dialysis patients have LVH, and 75–85% have hypertension (HTN). These features reduce vascular compliance and can lead to insufficient compensation along with volume overload, which may cause greater vulnerability to sudden worsening of HF.

HF is a clinical syndrome characterized by typical symptoms and signs caused by structural and/or functional cardiac abnormalities. Since HF is a progressive, complex clinical disease, it is difficult to evaluate its prognosis using only a few objective indicators, such as the HF biomarker N-terminal pro B natriuretic peptide (NT-pro BNP). Episodes of acute decompensated heart failure (ADHF) can worsen the prognosis of HF. Each acute event that results in myocardial and renal damage contributes to progressive left ventricular (LV) dysfunction of renal dysfunction. Many ESRD patients with a preserved left ventricular ejection fraction (LVEF) >50% experience frequent ADHF events. Therefore, hospitalization for ADHF events has particular significance in both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) patients and can be used as a predictor of mortality in patients with HF. According to the current HF guidelines, prevention of hospital admission is recommended as the major goal of treatment for HF.

If the cause of HF is clear, such as ischemic heart disease (IHD) or valvular heart disease (VHD), ADHF can be predicted based on the severity of the abnormality, and the prognosis of HF can be improved by treating that specific cardiac abnormality. However, many ESRD patients without definitive cardiac disease also experience ADHF events. As a result, it is important to identify the hemodynamic features of these events. Therefore, we aimed to determine the hemodynamic factors associated with ADHF events among ESRD patients without significant IHD or VHD who were also undergoing HD.

METHODS

Study design and study population
This was a retrospective, observational, single-center cohort study. We reviewed the medical records of 188 ESRD patients on HD between January 2018 and December 2020 at Kosin University Gospel Hospital. Patients who had no available echocardiogram results were excluded. Demographic and comorbidity data were obtained from the hospital medical records. Patients with significant coronary artery disease (defined as coronary artery stenosis >50% on coronary angiography or coronary angio-computed tomography or a history of previous coronary artery bypass graft or percutaneous coronary intervention), significant VHD (e.g., moderate to severe aortic stenosis/regurgitation, mitral stenosis/regurgitation,
and tricuspid regurgitation), a history of surgery for aortic disease, malignancy, death due to non-cardiac origin, and lack of follow-up were excluded. We divided the remaining patients into a group that contained those who were admitted due to at least one episode of ADHF and a second group of those who were not. We defined an “ADHF event” as a hospital admission or a visit to the emergency department due to “pulmonary edema or pulmonary congestion” according to the patients’ medical records. We compared the medical histories, electrocardiograms, and echocardiographic and laboratory data between the two groups. HTN was defined as a systolic blood pressure (BP) >140 mmHg or a diastolic BP >90 mmHg as recorded by repeated BP measurements or a previous diagnosis of HTN. Diabetes mellitus (DM) was defined as a fasting plasma glucose level >126 mg/dL or hemoglobin A1C (HbA1c) >6.5 during two consecutive assessments or current treatment for DM.

This study was approved by the Ethics Committee of Kosin University Gospel Hospital in Busan, South Korea (No. 2021-02-013). The requirement for written informed consent was waived because of the retrospective nature of the study.

Echocardiography measurement
Standard 2-dimensional echocardiography was performed on all participants in the left lateral decubitus position using a 3.5-MHz transducer (Vivid E9; GE Healthcare, Boston, MA, USA and Philips iE33; Philips Medical Systems, Bothell, WA, USA). Measurements of the diameter of the LV cavity, the LV end-diastolic/end-systolic volume, and the LV mass index were acquired according to the criteria outlined by the American Society of Echocardiography (ASE). The LVEF was measured using Simpson's method. Pulsed-wave Doppler imaging of the trans-mitral LV inflow was carried out in the apical four-chamber view, with the sample volume placed at the level of the mitral valve tips. Doppler variables were analyzed during three consecutive beats. The following measurements of global LV diastolic function were recorded: the peak early (E) and late (A) diastolic mitral flow velocity, the E/A ratio, and the early (E') diastolic mitral annular velocity. The maximal tricuspid regurgitation (TR) velocity (TR jet velocity [TR V\text{max}]; in m/s) was obtained from continuous-wave Doppler of the TR signal. Right ventricular systolic pressure (RVSP; in mmHg) was calculated from the maximal TR V\text{max} using the simplified Bernoulli formula as follows: 4×(TR V\text{max})\text{2}+right atrial (RA) pressure (the RA pressure was determined according to the diameter and collapse of the inferior vena cava, as recommended by ASE guidelines).

Statistical analysis
Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 2.5 for Windows (SPSS, Inc., Chicago, IL, USA) and SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). Data normality was tested using the Kolmogorov-Smirnov test. Values are expressed as the mean (± standard deviation) for numerical variables or as the number of participants and the percentage for categorical variables. Continuous variables were compared using the Student's t-test. The analysis of categorical data was performed using the χ² test. Multivariate logistic regression models for predicting an ADHF were constructed to identify independently associated variables. The cut-off value of the TR jet velocity for predicting an ADHF with corresponding sensitivity and specificity was estimated using a receiving operator characteristic (ROC) curve analysis. A p value < 0.05 was considered to indicate statistical significance.
RESULTS

Of the 188 ESRD patients on HD, 87 were excluded (IHD: n = 37, VHD: n = 10, malignancy: n = 20, patients without echocardiograms: n = 14). Finally, 101 patients were enrolled (mean age: 63.7 years; 52.1% male), and 30 of those patients (29.7%) were admitted to a medical facility due to ADHF (Figure 1). In their baseline characteristics (Table 1), the groups exhibited similarities in age and sex, and there were no differences in the prevalence of HTN or DM. The ADHF group showed a trend for a higher interdialytic weight gain (IDWG), but there was no statistical significance (−2.8±1.2 kg vs. −2.3±1.0 kg, respectively; p=0.080). Medication records revealed no significant difference in the use of RAS blockers and beta-blockers between the groups (Table 2). Upon echocardiography (Table 3), there was no significant difference in the LVEF (59.9±9.4% vs. 63.3±7.3%; p=0.057), LV end-diastolic dimension (48.4±7.8 mm vs. 48.4±6.0 mm; p=0.993), LV mass index (135.7±45.0 g/m² vs. 129.0±38.8 g/m²; p=0.564), or E/E’ (15.8±6.3 vs. 14.9±5.8; p=0.498) between the groups. However, the ADHF group exhibited a significantly higher TR jet velocity (2.9±0.6 m/s vs. 2.5±0.4 m/s; p=0.004) and a higher RVSP (43.5±17.2 mmHg vs. 34.2±9.9 mmHg; p=0.009). There was no significant difference in the time delay from HD to echocardiography (0.7±0.7 days for ADHF vs. 0.6±0.7 days for non-

Table 1. Baseline characteristics

| Variable                  | Pt without admission for ADHF (n=71) | Pt with admission for ADHF (n=30) | p value |
|---------------------------|-------------------------------------|----------------------------------|---------|
| Age (years)               | 64.1±13.7                           | 65.5±12.5                        | 0.629   |
| Male                      | 37 (52.1)                           | 16 (53.3)                        | 0.911   |
| HTN                       | 45 (63.4)                           | 22 (73.3)                        | 0.367   |
| DM                        | 35 (49.3)                           | 14 (46.7)                        | 0.831   |
| Dyslipidemia              | 28 (39.4)                           | 17 (56.7)                        | 0.129   |
| Stroke                    | 7 (9.9)                             | 5 (16.7)                         | 0.333   |
| Thyroid disease           | 2 (2.8)                             | 2 (6.7)                          | 0.580   |
| Atrial fibrillation       | 4 (5.6)                             | 5 (16.7)                         | 0.121   |
| Body weight, pre HD (kg)  | 57.5±16.8                           | 49.2±28.2                        | 0.139   |
| Body weight, post HD (kg) | 54.2±17.4                           | 46.9±26.9                        | 0.178   |
| IDWG (kg)                 | −2.3±1.0                            | −2.8±1.2                         | 0.080   |

All values are presented as mean±standard deviation. ADHF = acute decompensated heart failure; HTN = hypertension; DM = diabetes mellitus; HD = hemodialysis; IDWG = interdialytic weight gain.
ADHF; p=0.790). Based on their laboratory tests (Table 4), the ADHF group demonstrated a higher NT-pro BNP level (21,275.7±14,404.8 pg/dL vs. 11,895.7±13,441.4 pg/dL; p=0.003) than the non-ADHF group. In regard to iron status, there were no significant differences in the serum iron, ferritin, and total iron-binding capacity between groups. A multivariate logistic regression analysis (Table 5) showed that the TR jet velocity (odds ratio [OR], 8.356; 95% confidence interval [CI], 1.806–38.658; p=0.007) was an independent predictor of ADHF after adjusting for age and sex and that the LVEF (p=0.065) and E/E′ (p=0.144) were not. Per the ROC curve analysis (Figure 2), a TR jet velocity >2.8 m/s was associated with ADHF with 47.7% sensitivity and 76.4% specificity (area under the curve [AUC], 0.656).

**DISCUSSION**

There are many factors that can affect acute decompensation in ESRD patients, and most are difficult to quantify, such as volume overload, microvascular dysfunction, right ventricular (RV) dysfunction and remodeling, left atrial (LA) dysfunction, peripheral abnormalities, and ventricular interdependence. However, it is clear that the higher the volume overload, the greater the hemodynamic burden on dialysis patients. Interestingly, in similar
volume overload states in ESRD, some patients tolerate the condition well without acute decompensation, while others develop pulmonary edema. Therefore, it is important to accurately assess hemodynamics in ESRD patients, although there are currently no definitive objective parameters to predict the amount of volume overload ESRD patients can tolerate. The “dry weight,” which is the most commonly used method in HD to assess solute removal, is dependent on knowledge of the body compartment capacities and the amounts of water and sodium in each compartment.

Unfortunately, this method is imprecise and cannot easily identify changes in nutritional status and lean body mass. As a consequence, acute and chronic over- or under-hydration are common among dialysis patients. Although attempts at using the lung ultrasound or intra vena cava diameter have been made, in clinical practice, these methods have large margins of operator error and can be measured in various ways according to patient hemodynamic conditions, which makes them difficult to standardize and compare.

According to recent 2021 European Society of Cardiology (ESC) guidelines for HF, structural or functional abnormalities of HF were evaluated using specific echocardiographic
parameters as follows: LV mass index ≥95 g/m² in females, ≥115 g/m² in males, LA volume index >34 mL/m², E/e' ratio >9, and TR velocity at rest >2.8 m/s. Most of the patients in our study showed LVH, diastolic dysfunction, and increased TR jet velocity and tended to satisfy the structural or functional abnormality criteria for HFpEF. Of course, HF should not be diagnosed without also evaluating the symptoms and signs of patients; however, most ESRD patients display more factors of HF when the objective echocardiographic parameters are considered. As a result, these representative echocardiographic parameters may have only a limited application in ESRD patients because their cardiac structure and hemodynamics are different from those of the general population.

Of these echocardiographic parameters, the LV filling in particular can provide prognostic value in patients with ESRD. Because the ratio of the transmitral E velocity to the Ea (E/E') is known to be significantly associated with the mean pulmonary capillary wedge pressure, current HF guidelines include the E/E' in the diagnostic criteria for HF. Most recently, a study of an ESRD population showed that an E/E' ratio >15 is a reliable marker of increased LV filling pressure (with a sensitivity of 82% and a specificity of 88% in predicting LV end-diastolic pressure >15 mm Hg). In contrast, our results showed that increased RV pressure (TR jet velocity and RVSP) was significantly different between the two groups and was an independent predictor of ADHF, whereas the LVEF and E/E' ratio were not. Care should be taken when interpreting the clinical implications of these results because there may be variations that resulted from different underlying conditions and the patient’s hemodynamic status at the time of examination. Data on the prevalence of pulmonary hypertension in ESRD patients are insufficient. A recent study showed that 16.7% of ESRD patients with HD had pulmonary hypertension, which was defined as a systolic pulmonary artery pressure >35 mmHg, but that study was also a retrospective study and did not enroll enough patients to make a generalized conclusion. In terms of HFpEF, it is generally accepted that pulmonary vascular abnormalities lead to poor outcomes due to the accompanying excessive right
heart congestion and blunted RV systolic reserves. Therefore, it is likely that the RV and pulmonary artery, which are responsible for venous return, play an important role in this process that is different from diastolic dysfunction, and our results may support this point. However, since pulmonary hypertension is predominantly associated with increased LA pressure, a substantial number of these patients develop pulmonary vascular disease, which manifests as an elevation in pulmonary vascular resistance and also a reduction in pulmonary arterial compliance. As a result, it is not yet possible to interpret pulmonary hypertension separately from diastolic dysfunction or HFpEF.

Another important aspect of our study results was that the IDWG exhibited a higher tendency in the ADHF group than in the non-ADHF group, although there was no statistical significance. A high IDWG is associated with a greater risk of all-cause and CV death and increased morbidity, such as ventricular hypertrophy and major adverse cardiac events. Clinically, the IDWG should be <4.0–4.5% of the dry weight; unfortunately, many patients have an IDWG that exceeds this value. Excess volume accumulation over long inter-dialytic intervals in HD patients results in greater LA and RA enlargement and RV pressure elevation, which clinically corresponds to pulmonary circulation overload. Our main concern was that the ADHF group had a worse hemodynamic status at baseline, which seems to be the major limitation of our study.

Our study had several limitations. This study had a single-center, retrospective design, and the number of enrolled patients was too small to establish a generalized conclusion. Although we excluded ischemic heart disease, valvular disease, and cancers that can affect patient hemodynamics, we did not exclude other factors that may lead to hospitalization, such as inadequate dialysis, infection, anemia, and bleeding. And we did not evaluate other parameters of RV function such as tricuspid annular plane systolic excursion, RV fractional area change and RV strain. Finally, the timing of echocardiography was not distinguished as before or after dialysis, which can affect the patients' hemodynamic status. However, our finding that ESRD patients with an increased RV pressure had a greater risk for ADHF events has important clinical implications that may predict how well a patient can tolerate volume overload. Therefore, physicians should consider various early strategies (such as longer or more frequent dialysis treatments) to prevent ADHF in these patients.

In conclusion, our data showed that increased TR jet velocity was an independent predictors of ADHF events in ESRD patients on HD, but LVEF and E/E’ were not. This trend suggests that the RV pressure is more important than the diastolic function in predicting acute decompensation in ESRD patients on HD. Further prospective studies are needed to verify this association.

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