Incremental Prognostic Value of Ventricular-Arterial Coupling over Ejection Fraction in Patients with Maintenance Hemodialysis

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Background: Left ventricular ejection fraction (LVEF) is a predictor of adverse outcomes in hemodialysis patients. LVEF is, however, an integral parameter determined by contractility, loading condition, and coupling. We sought to determine whether these components would better predict adverse outcomes and have incremental prognostic value over a validated clinical score and EF.

Methods: Two hundred thirty-four hemodialysis patients were prospectively followed up for primary composite endpoint: all-cause death, nonfatal myocardial infarction, and hospitalization due to worsening heart failure (HF). Load-independent contractility (end-systolic elastance [Ees] and preload recruitable stroke work [PRSW]) and arterial afterload (arterial elastance [Ea]) were noninvasively estimated. Ventricular-arterial coupling was assessed using the Ea/Ees ratio. LV global longitudinal strain (GLS) and mitral E-wave over annular velocity E′ ratio (E/E′) were also measured.

Results: During a median follow-up of 776 days, 30 patients developed the primary endpoint. Ees, PRSW, GLS, S′, Ea/Ees, E/E′, and EF were independently associated with the outcome after adjusting for the clinical score and prior HF hospitalization, whereas end-diastolic volume index or arterial afterload parameters were not. The nested Cox models indicated that Ea/Ees had independent and incremental predictive value over the model based on the score and either EF or E/E′. Furthermore, Ea/Ees continued to have predictive value after adjusting for GLS. The classification and regression analysis stratified event rates ranging from 4.2% to 68.8%.

Conclusions: LV contractility and Ea/Ees were independently associated with adverse outcome in hemodialysis patients. Ea/Ees had an incremental prognostic value over the clinical score and EF. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: Contractility, Prognosis, Hemodialysis, Load-independent, Ventricular-arterial coupling

Over the last decades, the number of patients receiving hemodialysis has continued to increase in United States, European countries, and Japan.[1-3] Cardiovascular disease is the leading cause of morbidity and mortality, accounting for >50% of all deaths.[4] Thus, accurate cardiovascular risk stratification is crucial. Several validated clinical risk scores have been proposed to predict cardiovascular outcomes[5,6]; their predictive powers, however, are modest. Left ventricular (LV) ejection fraction (EF) is widely used as a measure of systolic function and is an independent predictor of adverse outcomes in hemodialysis patients.[7-11] The prognostic ability of EF, however, can be limited because it is susceptible to loading conditions,[12] which change dramatically during interdialytic intervals in hemodialysis patients.[13]

Recently, noninvasive approaches using echocardiography have been developed to estimate the following load-independent physiologic determinants.[14] End-systolic elastance (Ees) is a measure of LV intrinsic contractility, which is minimally affected by preload and afterload.[12] Preload recruitable stroke work (PRSW) is another load-independent parameter of LV contractile function.[15] Effective arterial elastance (Ea) reflects the net impact of arterial afterload on the heart, which is related to systemic vascular resistance (SVR) and inversely related to total arterial compliance. The ratio of Ea to Ees (Ea/Ees) represents the interaction of the heart and large arteries, which is called as ventricular-arterial coupling.[10] The coupling is important because it demonstrates

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Abbreviations

AROii = Second Analyzing Data, Recognizing Excellence and Optimizing Outcomes

BP = Blood pressure

CART = Classification and regression tree

Ea = Effective arterial elastance

EDV = End-diastolic volume

EDVI = End-diastolic volume index

Ees = End-systolic elastance

EF = Ejection fraction

ESV = End-systolic volume

ESVI = End-systolic volume index

GLS = Global longitudinal strain

HF = Heart failure

HR = Hazard ratio

ICC = Intraclass correlation coefficient

LA = Left atrial

LV = Left ventricular

LVEF = Left ventricular ejection fraction

PRSW = Preload recruitable stroke work

SV = Stroke volume

SVR = Systemic vascular resistance

SVRI = Systemic vascular resistance index

mechanical efficiency in transferring the blood from the heart to the arterial system.

Accordingly, the purpose of this study was (1) to elucidate the association between these load-independent physiologic determinants of cardiac function and adverse clinical outcomes; (2) to assess whether they had incremental predictive value over EF in hemodialysis patients; and (3) to propose a statistically driven risk stratification algorithm.

METHODS

Study Population

We prospectively recruited 251 participants through advertisement among patients receiving hemodialysis for at least 3 months at two Japanese hospitals (Hidaka Hospital and Gunma University Hospital). Patients were hemodynamically stable, and hemodialysis was performed 3 times weekly (3–5 hours/day). Patients with > mild left heart valvular heart diseases ($n = 10$) and limited image quality ($n=7$) were excluded, leaving 234 patients for the final analysis. Among the 234 participants, 150 subjects (64%) also participated in another prospective observational study focusing on novel blood biomarkers in dialysis patients.[16] The unique insights from this present study compared with the previous one are summarized in the Discussion section of this article. The study protocol was approved by the institutional medical ethics committee of the two hospitals, and written informed consent was obtained from all patients.

Data Collection

We collected data about patients' demographic characteristics and clinical variables related to the delivery of hemodialysis from the hospital charts. Bloods were sampled before starting dialysis sessions. A recently validated 2-year mortality risk score in the hemodialysis cohort (the second Analyzing Data, Recognizing Excellence and Optimizing Outcomes cohort score or AROii score) was used as a clinical risk parameter.[6] This score was calculated from 13 clinical and laboratory parameters (age, smoking status, body mass index, cardiovascular disease history, cancer history, chronic kidney disease etiology, vascular assess, blood flow rates, and levels of hemoglobin, ferritin, C-reactive protein, serum albumin, and creatinine).

Cardiovascular Function Analysis

Echocardiographic examinations were performed using commercially available ultrasound systems. Because loading conditions can change during an interdialytic interval, all participants were studied just before a hemodialysis session after the 1-day interdialytic interval.[13] The LV end-diastolic (EDV) and end-systolic (ESV) volumes and EF were determined from the biplane method of disks.[17] Stroke volume (SV) was also determined from the biplane method of discs because 14% of subjects had prominent sigmoid septum, which would affect LV outflow Doppler profile. Left atrial (LA) volume was calculated using the biapical area-length method.[18] LV volume and mass and LA volume were subsequently indexed by body surface area. The early filling (E-wave), the peak late diastolic (A-wave) velocities, and deceleration time were assessed from transmitral flow. The peak systolic (S′), early diastolic (E′), and late diastolic (A′) mitral annular velocities were measured at septal annulus using spectral Doppler. All measures represent the mean of measurements from three beats for subjects in atrial fibrillation.

The following hemodynamic parameters were estimated noninvasively. End-systolic blood pressure (BP; 0.9 × systolic BP) was calculated as described elsewhere.[10] Total afterload was defined by the Ea (0.9 × systolic BP/SV). SVR index (SVRI), the nonpulsatile component of afterload, was determined by calculating mean BP/cardiac index × 79.9. Arterial compliance was estimated by the ratio of SV to pulse pressure. LV elastance was assessed using the modified single-beat method Ees (determined from BP, SV, and preejection and total systolic periods determined on LV outflow Doppler, EF, and an estimated normalized ventricular elastance at arterial end-diastole).[14] Single-beat PRSW was determined from stroke work/[EDV − k × EDV + (1 − k) × LV wall volume, where stroke work = mean BP × SV, LV wall volume = LV mass/1.05, and k was assumed to be 0.7.[15] V_0, the intercept of the end-systolic pressure volume relationship at an end-systolic pressure of 0 mmHg, was also estimated from Ees, end-systolic BP, and ESV. Ventricular-arterial coupling was assessed using the coupling ratio (Ea/Ees).[10]

In a subgroup of 207 patients (88% of the whole population) who had DICOM-format echo movies, myocardial deformation was also assessed as global longitudinal strain (GLS) using vendor-independent two-dimensional speckle tracking software (TomTec Imaging Systems, Unterschleissheim, Germany) as described elsewhere.[19,20] The LV endocardial borders were traced manually in the apical four- and two-chamber views. GLS was obtained by averaging peak longitudinal strains from the four- and two-chamber views. According to the new definition from the standardization task force,[21] we reported the absolute values of GLS in this manuscript and tables in order to avoid unnecessary confusion. An experienced echocardiologist, who was unaware of patients' data, analyzed all echocardiographic measurements.

The reproducibility of Ees, Ea, Ea/Ees, and GLS was assessed in 15 randomly selected patients. An intra- and interobserver agreement was evaluated after the same observer and another experienced reader repeated the analysis using intraclass correlation coefficients (ICCs) and coefficient of variation.

Endpoint and Follow-Up

Our primary endpoint was a composite of all-cause death, nonfatal myocardial infarction, and hospitalization due to worsening heart failure (HF). The secondary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, and hospitalization for HF. These endpoints were manually collected from the medical records and adjudicated by experienced cardiologists.

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