Utility of Left Atrial Expansion Index and Stroke Volume in Management of Chronic Systolic Heart Failure

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Background: Titration of evidence-based medications, important for treating heart failure (HF), is often underdosed by symptom-guided treatment. The aim of this study was to investigate, using echocardiographic parameters, stroke volume and left ventricular (LV) filling pressure to guide up-titration of medications, increasing prognostic benefits.

Methods: A total of 765 patients with chronic HF and severely reduced LV ejection fractions (<35%), referred from 2008 to 2016, were prospectively studied. Echocardiographic guidance was performed in 149 patients. LV filling pressure was assessed by left atrial expansion index, and stroke volume was estimated from diameter and time-velocity integral in the LV outflow tract. Up-titration of evidence-based medications and adjustment for side effects or worsening clinical conditions according to those parameters were performed. Propensity score matching was used to match pairs of patients with (n = 110) or without (n = 110) echocardiographic guidance. End points were 4-year frequencies of HF hospitalization and all-cause mortality.

Results: During a mean follow-up time of 4.1 years, rates of adverse events were 58 (52.7%) with no echocardiographic guidance and 36 (32.7%) with echocardiographic guidance (P < .0001). Echocardiography provided effective guidance to reduce prescribing frequency and dose of diuretics and to promote evidence-based medication prescription. It reduced HF rehospitalization and all-cause mortality. By multivariate analysis, prognostic improvement was associated with up-titration of medications with echocardiographic guidance.

Conclusions: There was a statistically significant difference in long-term prognosis between propensity score–matched pairs of patients with chronic severe HF with and without echocardiographic guidance. These findings need further validation in large prospective clinical trials. (J Am Soc Echocardiogr 2018;■:■-■.)

Keywords: Left atrial expansion index, Stroke volume, Severe systolic heart failure, Echocardiographic guidance, All-cause mortality

Heart failure (HF), either acute or chronic, is a clinical syndrome caused by a structural and/or functional cardiac abnormality, resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[1] This means that two major components associated with HF symptoms are inadequate cardiac output and high filling pressure. Several evidence-based treatments exist that reduce symptoms and mortality for HF, including β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists, neprilysin inhibitors/ARBs, and channel blockers.[1] Up-titration of evidence-based medications to maximal tolerable doses has been recommended. However, treatment rates and doses are still lower than recommended guidelines.[2] Efforts should be made to improve approaches to closing the treatment gap at both systems of care and individual levels. If more information were available in HF treatment, physicians might have more confidence to up-titrate evidence-based medications and down-titrate loop diuretics in clinical practice. Stroke volume and left ventricular (LV) filling pressure (LVFP) are the major components to guide management in patients with severe systolic dysfunction. Echocardiography-based

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This work was funded by the Ministry of Science and Technology (102-2628-B-650-002-MY3) and Kaohsiung Veterans General Hospital (VGHKS11-CT3-02), Taiwan.

Conflicts of Interest: None.

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0894-7317/$36.00

https://doi.org/10.1016/j.echo.2018.01.001

Abbreviations

ACEI = Angiotensin-converting enzyme

ARB = Angiotensin receptor blocker

BNP = Brain natriuretic peptide

HF = Heart failure

LA = Left atrial

LV = Left ventricular

LVEF = Left ventricular ejection fraction

LVFP = Left ventricular filling pressure

LVOT = Left ventricular outflow tract

NYHA = New York Heart Association

PS = Propensity score

SHFM = Seattle heart failure model

TDI = Tissue Doppler imaging

Vol_{max} = Maximal left atrial volume

Vol_{min} = Minimal left atrial volume

hemodynamic measurements can be used to serially measure the response to medical interventions, such as fluid and drug therapy, in critically ill patients who are at risk for HF or tissue hypoperfusion.[3,4] However, in the setting of advanced decompensated systolic HF, serial tissue Doppler imaging (TDI) measurements may be inaccurate in monitoring filling pressure.[5] Recent studies have revealed that LVFP can be predicted by left atrial (LA) expansion index, which has been proved effective in predicting several disease entities,[6-9] including advanced systolic HF. We postulated that echocardiography, when used serially in an integrative assessment of LA expansion index and stroke volume during follow-up visits, can be useful in managing ambulatory patients with advanced systolic HF. Accordingly, the present study, with echocardiographic assessments of those data, was undertaken to test the hypothesis that these better guidance methods would promote the prescription of maximal tolerable evidence-based medications, which would provide increased prognostic benefit.

METHODS

Study Population

The prospective, observational study registered consecutive patients aged 20 years or older who had LV ejection fractions (LVEFs) < 35% and had been discharged from Kaohsiung Veterans General Hospital for decompensated HF no more than 6 months before registration and received regular follow-up care at a special HF clinic between January 2008 and July 2016. Exclusion criteria included any history of the following: (1) mitral stenosis or prosthetic mitral valve, (2) atrial septal abnormality (e.g., atrial septal defect or aneurysm), (3) more than mild severity of aortic regurgitation or stenosis, (4) inadequate echocardiographic image quality, and (5) any history of malignancies (with potential of confounding effect to all-cause mortality). The treatment strategies (symptom or echocardiography guided) depended on referred doctors and operating volume of echocardiography-guided strategy. In total, 616 patients received management based on symptomatic guidance by primary care cardiologists (S.-K.L., H.-R.H., C.-C. Lai, C.-J. Wu, T.-C. Yeh, W.-H. Wang, and K.-R.C.), and 149 patients received management based on echocardiographic guidance by primary care cardiologists (S.-H.H. and C.-C.C.).

The echocardiographic guidance group received treatment assisted by echocardiographic parameters every visit. Physicians adjusted and up-titrated evidence-based medications according to echocardiographic findings, particularly LVFP, stroke volume, and cardiac index. Histories of hyperlipidemia, hypertension, and smoking were recorded by the examining physicians. At the index examination, subjects were considered hypertensive if they had high blood pressure or were currently receiving drug treatment for hypertension. Diabetes mellitus was defined according to American Diabetes Association criteria.[10] At enrollment, creatinine clearance was estimated using the Cockcroft-Gault equation, and renal dysfunction was defined as creatinine clearance < 60 mL/min/1.73 m^2.[11] The end points of the study were HF hospitalization and all-cause mortality. The study protocol was approved by the institutional review board of Kaohsiung Veterans General Hospital. Patients gave written informed consent.

Echocardiographic Measurements

Conventional Echocardiographic and Tissue Doppler Measurements. LVEF was calculated using the Simpson biplane technique. Pulmonary artery systolic pressure was estimated using Doppler echocardiography by calculating the right ventricular–to–right atrial pressure gradient during systole. Right atrial pressure, estimated on the basis of echocardiographic characteristics of the inferior vena cava,[12] was then added to the calculated gradient. LV mass was calculated using the formula described by Devereux and Reichek.[13] LV mass was indexed to body surface area. Using pulsed-wave Doppler to line up the LV outflow tract (LVOT) in the apical five-chamber view and measuring the diameter of LVOT in parasternal long-axis view, stroke volume could be estimated by multiplying the area of the LVOT by time-velocity integral. The stroke volume multiplied by heart rate revealed cardiac output and the cardiac output divided by body surface area revealed cardiac index. Pulsed-wave TDI was performed in apical views and a pulsed-wave Doppler sample volume was placed at the level of the mitral annulus over the septal and lateral borders. The pulsed-wave TDI tracing, recorded over five cardiac cycles at a sweep speed of 100 mm/sec, was used for offline calculations. The average early diastolic velocity (e′) of the septal and lateral mitral annuli was used in the E/e′ ratio for assessing diastolic filling.[14] The severity of mitral regurgitation, which was evaluated semiquantitatively from the area of regurgitant jet by color Doppler, was classified as absent or trivial (0), mild (1+), moderate (2+), or severe (3+).

LA Volume Parameter Measurements. All volume measurements were calculated using the biplane area-length method in apical four- and two-chamber views.[15] LA volumes were measured at two points, immediately before mitral valve opening (maximal LA volume [Vol_{max}]) and at mitral valve closure (minimal LA volume [Vol_{min}]). LA expansion index was calculated as [(Vol_{max} − Vol_{min}) × 100%]/Vol_{min}. In all patients, LA volumes were indexed to body surface area.[6] On the basis of the logarithmic relationships between LA expansion index and LVFP in systolic HF, instantaneous LVFP could be estimated using the following equations: for sinus rhythm, LVFP (mm Hg) = 62.0 − 9.5 × ln (LA expansion index); and for atrial