Editorial Comment

Echocardiographic Insights into the Hemodynamics of Systolic Heart Failure: Can This Guide Titration of Medical Therapy?

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In this issue of *JASE,* Hsiao *et al.*[1] demonstrate in a small, nonrandomized comparison study that the use of echocardiographic assessment of stroke volume (SV) and left ventricular filling pressure (LVFP; estimated using left atrial expansion index [LAEi]) to guide titration of medications in patients with chronic heart failure with reduced ejection fraction (HFrEF) decreases heart failure (HF) rehospitalization and all-cause mortality. This is driven by more aggressive up-titration of guideline-directed medical therapy (GDMT) for HF in the echocardiography-guided arm. It is notable that E/e′ ratio, another estimate of LVFP,[2] was unchanged over time in both groups.

For the HF cardiologist, one of the most challenging clinical scenarios occurs when a patient presents reporting dyspnea, poor exercise tolerance, and marginal blood pressure but does not appear overtly volume overloaded. A reflexive strategy may be to decrease vasodilators while increasing diuretics to alleviate presumptive volume overload and prevent further hypotension. This study suggests that such a strategy may not be optimal and that these patients may in fact benefit from more targeted therapy depending on their SV and LVFP.

Clinicians lack a method to accurately estimate hemodynamics in a real-time, noninvasive fashion. In this study, echocardiographic estimates of SV and LAEi (as a surrogate for LVFP) provide a snapshot into the current hemodynamic state of the patient. LAEi was calculated as the difference between left atrial maximum (at end-systole) and minimum (at end-diastole) volumes, divided by left atrial minimum volume, and expressed as a percentage. As illustrated in Table 1, the "best" approach may not always be the same for decisions made on the basis of clinical judgment alone compared with echocardiographic guidance.

In clinical follow-up for patients with compensated HF, we are often biased toward maintaining inertia in patients who are stable and doing well to avoid potentially destabilizing an otherwise balanced situation. This study suggests that more active titration of HF GDMT can achieve meaningful downstream outcomes. Echocardiographic assessment of SV and LVFP can assist with recognizing when a patient is in this steady state that may permit further up-titration of GDMT.

Despite the benefits, the strategy used in the study may be time intensive and requires specific expertise in echocardiographic acquisition and interpretation. The method for LAEi appears to be reproducible, with low interobserver variability. In current clinical practice, most centers routinely estimate forward SV and left atrial volumes, arguing for the potential for feasible integration and uptake in the community in addition to academic centers. A barrier would be obtaining these measurements at each clinic visit rather than only at the time of a dedicated echocardiographic examination.

Over the past decade there has been a growing focus on reduction of HF readmission. Nevertheless, readmission rates across the United States remain high, with an almost one-in-five chance of readmission at 30 days,[3] despite penalties from the Centers for Medicare and Medicaid Services for high readmission rates in patients with HF. Thus, the time trade-off for obtaining echocardiography-based estimates of SV and LVFP at each outpatient clinic visit would be fewer hospitalizations and improved survival, arguing that this may potentially be cost-effective for hospitals and payers through the reduction in readmissions, provided these promising results are validated in a larger randomized clinical trial.

FREQUENCY OF MONITORING PATIENTS

In the present study, there are differences in the frequency of follow-up for the symptom-guided and echocardiography-guided cohorts. The echocardiography-guided cohort was seen more frequently in clinic, with nine to 14 visits each year (every 1–2 weeks for 2 months, then every month for 2–3 months, and once every 3 months for the remainder of year), while the symptom-guided patients were seen biannually.

Despite this difference in frequency, prior studies have not convincingly demonstrated that more frequent monitoring translates into better clinical outcomes. One example is telemonitoring studies, with three large randomized trials evaluating the use of intensive telemonitoring versus usual care in patients with HF who did not show any benefit with increased monitoring. Strategies in these studies included remote monitoring with daily calls for symptoms and weights in Tele-HF,[4] daily assessment of electrocardiogram, blood pressure, and body weight in TIM-HF,[5] and regularly scheduled telephone coaching with home telemonitoring of daily weight, blood pressure, heart rate and symptoms in BEAT-HF.[6]

Explanations for negative results in the telemonitoring studies, in contrast to improvements with echocardiography-guided visits, are likely driven by differences in accessible information on patients. The data available in the telemonitoring studies are ultimately similar to information routinely available in cardiology clinics, which include a combination of blood pressure, weight trends, heart rate, and clinical symptoms. There is no additional information or insight into the

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Table 1 HF management can vary between symptom-guided and SV/LVFP-guided management

SV and LVFP	Clinical signs and/or symptoms	Symptom-guided management	SV- and LVFP-guided management
Low SV, low LVFP (inadequate preload)	Fatigue, hypotension	Decrease diuretics; decrease afterload reduction	Decrease diuretics, consider giving fluids; maintain afterload reduction
High SV, high LVFP (fluid overloaded)	Dyspnea	Increase diuretics	Increase diuretics; increase afterload reduction
Low SV, high LVFP (decompensated and fluid overloaded)	Dyspnea, fatigue, hypotension	Increase diuretics; decrease afterload reduction	Increase afterload reduction; consider increasing diuretics
Normal SV, normal LVFP (compensated)	Clinically "feels well"	Continue current therapy	Increase afterload reduction

patient's current hemodynamic profile. It has been demonstrated that weight is not always a good surrogate for LVFP.[7] Thus, the utility of frequent weight measurement may provide some guidance on the basis of overall trends but may not always be an accurate reflection of a patient's current hemodynamic state.

The study by Hsaio *et al.*[1] suggests that the additional hemodynamic information from the echocardiographic studies is critical in driving more aggressive titration of GDMT. In the above example, for a patient with symptomatic HF, the most common reflexive adjustment to medications, whether in the clinic or via telemonitoring, would be to give a trial of increased diuretics. However, it is possible that the patient's symptoms are related to low SV, low LFVP or to low SV, high LVFP, when the optimal change might be to decrease diuretics or to increase diuretics but also to maintain afterload reduction, respectively. This information can be directly obtained from the echocardiography-directed assessments of SV and LAEi.

HEMODYNAMIC MONITORING AND BIOMARKERS

The closest strategy to echocardiography-driven hemodynamic guidance that is currently integrated into real-world clinical practice would be remote hemodynamic monitoring with implanted devices that either monitor pulmonary artery pressure (PAP) directly (CardioMEMS; Abbott Vascular, Santa Clara, CA) or measure intrathoracic impedance as a surrogate for volume status (cardiac resynchronization therapy [CRT] or implantable cardioverter-defibrillator [ICD]).

Studies with the CardioMEMS device have shown that PAP-guided HF care yields more frequent titration of medications compared with a control group using symptoms and weight alone. PAP-guided HF management led to a 39% reduction in total HF hospitalizations (over 15 months)[8,9] and all-cause 30-day readmissions.[10] Patients in the PAP-guided group had more frequent medication changes in diuretics, angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs], and nitrates or hydralazine, driven by changes in PAP, compared with the control group.[11] The medication adjustments translated into significant increases in ACE inhibitor or ARB dosing in the PAP-guided group, which were not seen in the control group.[10]

An analysis of the CHAMPION study[8] confirmed that the active PAP-monitoring group had a higher frequency of medication adjustment, with significant increases in diuretics, vasodilators, and neurohormonal antagonists; targeted intensification of diuretics and vasodilators in patients with higher PAP; and preserved renal function despite these increases in therapy.[11] It is unknown if SV or ejection fraction improved in the CHAMPION trial with the multiple medication adjustments.

In an analogous fashion, directed echocardiographic assessment of SV and LVFP in this study permitted more frequent and aggressive medication changes. The PAP data from CardioMEMS are similar to the data provided from echocardiography for the LVFP, whereby high PAP or LVFP drove up-titration of vasodilators for afterload reduction. Although the number of medication changes was not reported in this study, patients in the echocardiography-guided treatment arm achieved higher doses of GDMT.

Studies using data from intrathoracic impedance and heart rate variability from implanted ICD systems have not been as successful. Neither the DOT-HF trial,[12] which randomized patients to data from intrathoracic impedance versus standard care, nor the MORE-CARE study,[13] randomizing patients to remote monitoring with CRT-D compared with usual care, were able to demonstrate that remote monitoring with ICD or CRT-D data reduced hospital admissions. This leads to the question of how accurate the device alerts are for identifying HF decompensation and why these studies were negative, when the CardioMEMS device and serial echocardiographic assessments of SV and LVFP can affect outcomes.

In DOT-HF, a portion of the alerts were not associated with signs and symptoms of decompensated HF.[12] There are two potential gaps that may explain the discordance in findings. First, the quality and content of data provided by intrathoracic impedance in the ICD or CRT-D would likely lead to diuretic titration but not necessarily vasodilator titration. Up-titration of diuretics in one small study alleviated symptoms, improved 6-min walk distance, and improved New York Heart Association class but did not improve routine echocardiographic measures over about 3.5 weeks.[14] Second, even though the alerts may increase the frequency of patient-provider assessment, providers still lack the additional hemodynamic data provided by CardioMEMS or the echocardiographic assessment of SV and LVFP.

Recently, a study (GUIDE-IT) comparing serial N-terminal pro–brain natriuretic peptide (NT-proBNP) biomarker guided therapy compared with usual care for the end point of time to cardiovascular death or first hospitalization failed to show that the biomarker strategy was superior.[15] GUIDE-IT was notable for reductions in NT-proBNP in both arms, which was achieved with aggressive adjustments in HF GDMT even in the nonbiomarker arm. Another potential concern is that although NT-proBNP trends with variations in left ventricular wall stress, it does not necessarily differentiate between causes of wall stress and can also represent a variety of other cardiac and