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EDITORIAL COMMENT

Systolic time intervals in patients with heart failure: time to teach new dogs old tricks

Joyce N. Njoroge[1] and John R. Teerlink[1,2]*

[1]School of Medicine, University of California San Francisco, San Francisco, CA, USA; and [2]Section of Cardiology, San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA

This article refers to 'Association between systolic ejection time and outcomes in heart failure by ejection fraction' by P.A. Patel *et al.*, published in this issue on pages 1174–1182.

Systolic ejection time (SET) is a non-invasive measurement of the time interval of flow across the aortic valve that correlates with left ventricular (LV) function and can be measured using conventional echocardiography, arterial tonometry, or bioelectrical impedance.[1,2] With conventional Doppler echocardiography, measured SET is highly reproducible and less dependent on image quality, with the potential of being a clinically useful tool and an interesting topic of research. In current practice, ejection fraction (EF) carries the strongest weight in determining prognosis and guiding diagnosis and therapy. However, the measurement of LVEF has significant inter-observer and intra-observer variability and is highly dependent on image quality and modality.[3]

In this issue of the Journal, Patel and colleagues investigated the correlation between shorter SET and increased risk of death or heart failure hospitalization in patients with heart failure with reduced EF (HFrEF).[4] Additionally, they compared the sensitivity of using systolic time intervals compared to using more novel imaging modalities such as global longitudinal strain.

In 1968, Weissler *et al.*[5] extended the observations of others and demonstrated the reliable association of shortening of SET to LV failure. The mechanism of the decreased SET is incompletely understood, but was posited to be secondary to myofibril dysfunction associated with compensatory increases in sympathetic signalling producing altered calcium fluxes in the cardiomyocyte. Increased adrenergic tone as well as exogenous calcitropes,[6] such as dobutamine and milrinone, increase heart rate and reduce SET. The authors found that shorter SET reflected clinical variables that are known to portend poor prognosis in heart failure including decreased stroke volume/cardiac index, LVEF, and rapid heart rate. When compared to more novel imaging techniques such as tissue Doppler imaging, speckle tracking strain imaging, and three-dimensional evaluation, systolic time intervals may provide clinically meaningful data with less measurement variability, especially in cases of difficult echocardiographic windows and severe LV dysfunction with EF $< 35\%$.[7] Nonetheless, the direct prognostic value of systolic time intervals has not been well-investigated.

In the current study by Patel and colleagues,[4] the authors demonstrated a correlation between shorter SET and increased risk of death or hospitalization for heart failure in patients with HFrEF (EF $\leq$40%) but not heart failure with a preserved EF (HFpEF; EF $\geq$50%) or mid-range EF (HFmrEF; EF 41–49%). The echocardiographic measurements included SET, pre-ejection period, R to E time, diastolic filling time, EF, LV dimensions, left atrial dimensions, and diastolic function parameters, with coverage probabilities of the three readers ≥ 0.85 suggesting good inter-rater reliability. Patients with HFrEF had a shorter median SET (280 ms) compared to HFpEF (315 ms) and controls (309 ms). For a 10 ms increase in SET there was a 17% decrease in the odds ratio of the 1-year risk of all-cause mortality or heart failure hospitalization in patients with HFrEF even when controlled for EF% and heart rate. Using a Kaplan–Meier plot of SET by quartile, it was demonstrated that patients in the lowest two quartiles of SET compared to the highest two quartiles had worse outcomes. However, no correlation was seen with change in SET and these outcomes in patients with HFpEF or HFmrEF. While this study was very well performed, the data are based on a relatively small number of patients (545 patients in total and only 171 in the HFrEF cohort) and events (46 and 44 death or heart failure hospitalizations in the HFrEF and HFpEF groups, respectively), although there was a relatively high event rate. Additionally, when looking at individual event outcomes with all-cause hospitalization, heart failure hospitalization, and death within 1 year, SET only correlated with death when adjusted for appropriate co-morbidities, labs, therapies and echo findings. The mechanism behind the relationship between LV function and SET as well as its direct prognostic value is yet to be established.

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*Corresponding author. San Francisco Veterans Affairs Medical Center, Cardiology 111C, 4150 Clement Street, San Francisco, CA 94121-1545, USA. Tel: +1 415 221-4810, x24160, Fax: +1 415 750-6950, Email: john.teerlink@ucsf.edu

Is there a meaningful role for SET in contemporary cardiovascular medicine? The article by Patel and colleagues, as well as other investigations, suggest that SET can contribute significantly to determining prognosis in addition to standard variables, especially in patients with HFrEF. Larger cohort studies of patients can attempt to confirm the clinical significance of SET as a reliable measurement in evaluating HFrEF outcomes and will also allow an estimate of SET thresholds that correlate with increased morbidity and mortality. Another recent study by Biering-Sorensen and colleagues not only supported the prognostic utility of SET in a middle-aged African-American community free of cardiovascular disease, but also demonstrated that SET was an independent predictor of the subsequent development of heart failure.[8] Thus, SET may have a role in predicting incident heart failure in asymptomatic patients and clinical outcomes in patients with HFrEF. In addition, measuring systolic time intervals in patients with HFpEF may allow physicians to better understand and monitor the different phenotypes of this heterogeneous condition given the correlation between SET and diastolic dysfunction.[9]

The authors also discuss the potential utility of measuring SET as a therapeutic target for emerging and novel medical therapies. The SHIFT trial demonstrated that ivabradine, a drug that selectively decreases heart rate, improved the composite of cardiovascular mortality or heart failure hospitalization. In a subsequent analysis of the SHIFT data, ivabradine was noted to increase SET beyond the anticipated rate-related effects, suggesting a possible direct effect on SET via an unknown mechanism.[10] Omecamtiv mecarbil is a novel agent that selectively activates cardiac myosin,[11] directly addressing the defect producing the shortened SET as promulgated by Weissler over 50 years ago. Multiple studies have demonstrated a direct relationship between omecamtiv mecarbil plasma concentrations and increases in SET.[12–15] In healthy volunteers, changes in SET were directly related to improvements in stroke volume, fractional shortening and EF.[13] Subsequent studies have demonstrated consistent increases of SET toward normal and decreased LV dimensions in patients with acute (ATOMIC-AHF[15]) and chronic (COSMIC-HF[14]) HFrEF treated with omecamtiv mecarbil. In COSMIC-HF, patients with HFrEF receiving oral omecamtiv mecarbil for 20 weeks also had decreased heart rates, suggestive of sympathetic withdrawal. GALACTIC-HF (ClinicalTrials.gov NCT02929329) is an ongoing cardiovascular outcomes trial in over 8000 patients with HFrEF designed to test the hypothesis that the aforementioned improvements in cardiac performance seen with omecamtiv mecarbil translate into benefits on cardiovascular death and heart failure events, as well as patient-reported outcomes. While this trial will provide additional insights, it will not definitively distinguish between SET as a direct therapeutic target or as a pharmacodynamic marker of omecamtiv mecarbil effects.

Ejection fraction has been a well-established tool in the evaluation of patients with heart failure. With the advent of new imaging modalities, including three-dimensional echocardiography, global longitudinal strain and further advances in other measures of systolic and diastolic myocardial function, subjectivity in assessments of cardiac function will continue to decrease and a more nuanced understanding of the abnormalities contributing to HFrEF and HFpEF will emerge. Nonetheless, an old trick, SET, may be an additional tool to return to the new evolving armamentarium in evaluating and treating our heart failure patients.

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