EDITORIAL

Left ventricular mechanical dyssynchrony by phase analysis as a prognostic indicator in heart failure

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Heart failure (HF) is a major public health problem. Recent estimates indicate that more than 5 million patients have clinically manifest HF in the United States and more than 650,000 new cases are diagnosed annually.[1] Overall prognosis in this population remains poor. A recent study using a national registry in Sweden of more than 1 million hospital admissions between 1988 and 2004 compared the impact of HF vs the most common forms of cancer (lung, colorectal, prostate, and bladder cancer for men and lung, colorectal, bladder, breast, and ovarian cancer for women).[2] Annual incidence of first-ever hospitalization for HF and cancer per 100,000 were 484 and 373 for men and 470 and 350 for women older than 20 years. HF was associated with unadjusted case-fatality rate of 59% within 5 years compared to 58% for patients with cancer. The total cost of HF in the United States for 2013 is estimated at $32 billion which is projected to increase to $70 billion by 2030.[3] These mortality and economic figures highlight the public health care burden of HF.

Over the last few decades, device-based therapies have revolutionized the treatment of HF. Implantable cardioverter defibrillators (ICDs) are used for the primary and secondary prevention of sudden cardiac death in patients at high risk.[4] In addition, cardiac resynchronization therapy (CRT) or biventricular pacing has been shown to reverse ventricular remodeling, ameliorate mitral regurgitation, improve left ventricular ejection fraction (LVEF), and decrease HF hospitalization and all-cause mortality.[4] Initial studies were performed in patients with New York Heart Association (NYHA) class III or ambulatory class IV HF symptoms, LVEF $\leq$ 35%, and QRS duration $\geq$ 120 ms. The bulk of the data was in patients with class III symptoms, left bundle branch block (LBBB) pattern, and QRS $>$ 150 ms.[5] Recent evidence extended the benefit of CRT to patients with milder HF. A meta-analysis of five randomized clinical trials that included 4,317 patients with NYHA class I or II HF, LVEF $\leq$ 40%, and QRS $\geq$ 120 ms demonstrated a 19% reduction in overall mortality (95% CI 1-35%) and a 32% reduction in HF events or hospitalization (95% CI 21-41%) in patients receiving CRT + ICD vs ICD alone.[6] In this analysis, 29 patients needed to be treated to prevent 1 death, and 15 needed to be treated to prevent 1 HF hospitalization. In asymptomatic patients (NYHA class I), the reduction in HF hospitalization remained statistically significant while the reduction in mortality was not. This analysis was limited by a small number of events analyzed for asymptomatic patients. The recently updated guidelines state that CRT can be useful in patients with NYHA class II HF (class I indication for patients with LVEF $\leq$ 35%, sinus rhythm, LBBB, QRS $\geq$ 150 ms and class IIa indication for similar patients with QRS 120-149 ms or with atrial fibrillation and class IIb for patients with non-LBBB and QRS $\geq$ 150 ms) and may be considered in patients with NYHA class I HF (class IIb indication for patients with LVEF $\leq$ 30%, ischemic etiology, sinus rhythm, LBBB, QRS $\geq$ 150 ms). CRT is not indicated for patients with NYHA class I or II HF, non-LBBB, and QRS $<$ 150 ms (class III).[1,4]

It is widely recognized that as much as a third of patients that receive CRT based on current indications do not derive clinical benefit.[7] Furthermore, a subset of patients that do not have prolonged QRS may benefit from CRT due to the presence of mechanical but not electrical dyssynchrony. This created a need for identifying LV mechanical dyssynchrony using imaging. Traditionally, this has been performed with echocardiography which provides several parameters that assess mechanical dyssynchrony ranging from septal wall to

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posterior wall delay and tissue Doppler imaging to speckle tracking and three-dimensional echocardiography.[8] These echocardiographic parameters showed modest sensitivity and specificity for predicting response to CRT in a multicenter study with large intraobserver and interobserver variations with poor agreement between these different parameters.[9,10] A recent multicenter trial randomized 809 patients with NYHA class III or IV HF, LVEF $\leq$ 35%, QRS $<$ 130 ms, and evidence of LV mechanical dyssynchrony by echocardiography that underwent CRT implantation to CRT capability turned on or off.[11] CRT did not reduce the rate of death or hospitalization for HF and there was a signal for increased mortality in the group that had CRT turned on (HR 1.8, 95% CI 1.1-2.9). This highlights the risk of CRT implantation in patients that will not benefit from resynchronization beyond the wasted resources. Indeed, in a recent article in the *Journal* Friehling et al[12] demonstrated that right ventricular pacing may worsen LV synchrony in patients with LBBB.

Gated SPECT myocardial perfusion imaging allows for the assessment of LV mechanical dyssynchrony using phase analysis.[13,14] This technique measures the onset of mechanical contraction across the LV which can be shown as a ''phase polar map'' similar to the perfusion polar maps or as a phase histogram. The standard deviation (phase standard deviation, PSD) and the width (encompassing 95% of the samples) of the phase histogram (phase bandwidth, PBW) have been validated as indices of LV synchrony. The advantages of this technique have been reviewed at length and they include automaticity, reproducibility, and availability with current myocardial perfusion imaging without the requirement for additional imaging.[13,14] Values for phase analysis indices in control subjects and in patients with abnormal LV systolic function, LBBB, right bundles branch block, and paced rhythm have been published.[15] Interestingly, LV mechanical dyssynchrony by phase analysis is at best moderately correlated with electrical dyssynchrony ($r = 0.5$ for PSD and QRS, $r = 0.4$ for PBW and QRS).[16] Preliminary studies performed on a small number of patients showed that phase analysis indices may be helpful in predicting CRT response.[17] Furthermore, LV mechanical dyssynchrony by phase analysis was associated with poor prognosis in patients with ischemic cardiomyopathy and LVEF $\leq$ 35%,[18] in patients with LVEF $\leq$ 40% who have an ICD,[19] and in those with end-stage renal disease.[20]

In this issue of the *Journal*, Goldberg et al[21] retrospectively studied the prognostic value of LV mechanical dyssynchrony by phase analysis in patients with non-ischemic cardiomyopathy (normal perfusion on stress and rest images with no prior history of CAD or coronary revascularization) with LVEF 35-50% and QRS $<$ 150 ms who underwent myocardial perfusion imaging for clinical indications. LV mechanical dyssynchrony indices were determined by phase analysis of the stress images using the Corridor 4DM software which expresses PSD and PBW in % rather than degrees. The study population included 324 patients (age 62 ± 13 years, 62% male, 36% diabetes, LVEF 44 ± 5%, 87% with QRS $\leq$ 120 ms) who were followed-up for 4.7 ± 2.3 years during which 86 patients (26%) died. There was no significant correlation between QRS and PSD or PBW stressing the dissociation of electric and mechanical dyssynchrony in patients with mild-moderate LV systolic dysfunction. A previous study also reported very poor correlation between the two in a similar population of patients with LVEF 35-50%.[22] When the population was divided into tertiles of PSD (<3.6%, 3.6-5.2%, >5.2%) there was a non-statistically significant trend toward higher annualized mortality with increasing PSD (4.7%, 5.6%, and 7.0%, $P = .2$). In a multivariate Cox proportional hazard model that adjusted for baseline demographics, comorbidities, medication use, QRS, and LVEF, the highest tertile of PSD was associated with a twofold increased risk of death compared to the lowest tertile (HR 1.97, 95% CI 1.06-3.66, $P = .033$). Similar findings were reported for PSD included in the model as continuous variable and for PBW. Importantly, PSD continued to be an independent predictor of death when analyzed in patients with QRS $\leq$ 120 ms.

In order to fully understand the implications of these findings, we have to appreciate the limitations of this study. First, the study population is relatively small with only 86 deaths over a mean study period of almost 5 years. Since the outcome of patients with HF is generally poor as discussed above, the interest is in prognostication over a shorter time frame. The Kaplan-Meier survival curves (Figure 4 in[21]) appear to separate at 1 year of follow-up but this is unlikely to be statistically significant given the small number of events. Second, the findings are of borderline statistical significance and are only significant in the multivariate model. Third, the distribution of PSD in this population is very narrow. The upper tertile of PSD (>5.2%) in this population lies within the normal distribution.[15] In contrast, Atchley et al[22] reported that as many as 29% of patients with LVEF 35%-50% and QRS $<$ 120 ms had a PSD $\geq$ 43° or 12%. Unlike the current study, the majority of patients studied by Atchley et al[22] had known CAD and perfusion abnormalities on imaging ($\sim$90%). It is not clear whether this is the reason for the discrepancy in prevalence of LV mechanical dyssynchrony between the two studies, but the applicability of the prognostic findings to clinical care is problematic if the prevalence of dyssynchrony in this population is

low. Fourth, as the authors point out, the presence and severity of HF symptoms (i.e., NYHA class) which is a validated prognostic indicator is not accounted for. Finally, the cause of death is not available. In another study published in this issue of the *Journal*, we show that in patients with HF and LVEF $\leq 35\%$ LV mechanical dyssynchrony is independently associated with potential sudden cardiac death events (sudden cardiac death, fatal myocardial infarction, spontaneous sustained [>30 seconds] ventricular tachyarrhythmia, resuscitated cardiac arrest, or appropriate ICD discharge).[23] In this population of 917 HF patients from the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study, patients who experienced potential sudden cardiac death events had significantly wider PSD than matched control patients ($62.3° \pm 2.4°$ vs $55.5° \pm 2.3°$, $P = .03$) and were more likely to have a PSD $\geq 60^{\circ}$ (53% vs 35%, $P = .03$). Similar to the study by Goldberg et al,[21] the number of events was relatively low (92 subjects experienced potential sudden cardiac death events) and the findings were of borderline statistical significance.

The importance of the study by Goldberg et al[21] is the finding that LV mechanical dyssynchrony may carry prognostic data independent of electric dyssynchrony and LVEF in a HF population with only mild-moderate LV systolic dysfunction that does not qualify for CRT or ICD under the current guidelines. If these findings are verified in a larger population from a multicenter study, preferably with prospective pre-specified design that includes adjudicated endpoints, they will add to our current risk stratification tools a novel prognostic indicator in this overall high-risk population and open the door for interventional studies that select patients with higher likelihood to benefit from device therapy.

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