

EDITORIAL COMMENT

# Prolonged QRS in Heart Failure With Preserved Ejection Fraction

## Risk Marker and Therapeutic Target?\*

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Clinical trials of therapeutic agents for heart failure with preserved ejection fraction (HFpEF) have yielded little beyond disappointment for physicians caring for these ubiquitous patients who comprise over one-half of the annual 1,000,000 heart failure (HF) discharges in the United States (1). The most recent and largest HFpEF trial, TOPCAT (Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist), although nominally negative, may reveal insights into the risk of different patient subgroups. HFpEF has changed names, has struggled with identity crises, and likely reflects several different processes (2). Recently, the application of computerized analysis and grouping of phenotypic variables has suggested 3 subsets of patients with HFpEF (3). Phenotypically characterizing the heterogeneous constituents of the HFpEF syndrome into clinically meaningful groups may allow researchers and clinicians to move toward a future of precision medicine.

QRS duration derives from a simple, inexpensive, century-old, universally available test. Furthermore, QRS duration predicts adverse cardiac outcomes in community-based populations and in patients with

heart failure with reduced ejection fraction (HFREF) (4,5). Whether QRS duration has prognostic importance in HFpEF is unclear. So, in this issue of *JACC: Heart Failure*, Joseph et al. (6) assessed 3,426 patients in TOPCAT with HFpEF to determine if QRS duration  $\geq 120$  ms predicts adverse events. Although QRS duration and morphology were not adjudicated by a core laboratory, a small number (2%) of actual electrocardiograms were manually confirmed by a blinded cardiologist with reasonable concordance

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( $r = 0.82$ ). Figure 1A from their paper (6) reveals a few patients with QRS duration  $\sim 50$  ms, which is unexpectedly short because only 2% of normal individuals exhibit a QRS below 69 ms (7). Nevertheless, QRS duration is generally accurate, and this is a minor point. However, QRS morphology, especially left bundle branch block (LBBB), is less “black and white”; indeed, LBBB is increasingly categorized as “strict” or not (8). A prolonged QRS ( $\geq 120$  ms) was observed in 17.9% of TOPCAT patients. According to investigator-entered data, more than one-half of the prolonged QRS tracings reflected nonspecific intraventricular conduction delay; that is, right bundle branch block (5%) and LBBB (3.9%) were uncommon in TOPCAT. Previously, another broad HF study identified bundle branch block one-half as frequently in the HFpEF cohort as in the HFREF cohort ( $\sim 14\%$  vs  $\sim 30\%$ ) (9). Interestingly, a wide QRS was more than twice as prevalent in the TOPCAT patients enrolled in the Americas (25.3%) as those from Russia/Georgia (10.2%). This marked geographic variation had surfaced earlier, as the primary endpoint occurred only one-third as often in the Russia/Georgia subset (2). Several characteristics predicted QRS  $\geq 120$  ms, including older age; male sex; white race; and lower

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values for hemoglobin, glomerular filtration rate, and ejection fraction (EF). The composite primary endpoint of cardiovascular (CV) death, aborted cardiac arrest, or HF hospitalization was associated with QRS  $\geq 120$  ms in the overall cohort (adjusted hazard ratio: 1.29). Only the HF hospitalization component of the composite was significantly associated with prolonged QRS after adjustment. Although the important association with HF hospitalizations is without question, the mortality linkage disappoints. Specifically, in the Americas, CV mortality was insignificant in univariate analysis, and the adjusted hazard ratio for CV mortality was right at unity; moreover, although prolonged QRS has predicted sudden death in some studies (10), only 1 aborted cardiac arrest was tallied in patients with QRS  $\geq 120$  ms. (Admittedly, aborted cardiac arrest was very rare in the entire study.)

The authors appropriately concluded that QRS duration is a phenotypic marker of adverse outcomes in patients with HFpEF. A robust “dose-response” effect beginning at a QRS of about 100 ms supports their assertion. Armed with this association, can we intervene to target the putative risk factor? In other words, shorten the QRS! No (known) drugs accomplish this unless we take the long view and prevent hypertrophy (from hypertension), infarction, and/or fibrosis. Spironolactone, the active agent in TOPCAT, may indeed reduce fibrosis; however, the wide QRS subgroup did not exhibit a trend for greater benefit from study drug. A more prolonged treatment period certainly might be required. In the non-pharmacological realm, cardiac resynchronization therapy (CRT) has obviously been employed to treat the combination of prolonged QRS and HF. Applying CRT to TOPCAT-like patients is problematic, however. First, CRT is currently only indicated for HFrEF, specifically EF  $\leq 35\%$ , with concomitant significant QRS prolongation. A Class I indication requires a QRS  $\geq 150$  ms with LBBB morphology. CRT is appropriate in certain patients manifesting non-LBBB with QRS  $\geq 150$  ms or an LBBB pattern with QRS  $\geq 120$  ms. Still, a glimmer of opportunity exists. Although most CRT trials (in HFrEF) had an inclusion criterion of EF  $\leq 35\%$ , core laboratory analysis (when performed) often rated the EF higher. In the PROSPECT (Predictors of Response to CRT) trial, 24% of the 361 echocardiograms had an adjudicated EF above the entry criterion of 35%, and these patients responded similarly to CRT as those with lower EF (11). However, for EFs approaching normal values, data is truly scant. Moreover, the evidence for significant CRT benefit has increasingly converged on definite LBBB (8) and/or LBBB with QRS  $\geq 150$  ms, a rarity in the

TOPCAT HFpEF population (3.9%). (Presumably, the LBBB rate was slightly higher in the America stratum.) Electrically delayed lateral left ventricular (LV) activation in LBBB, or electrical dyssynchrony, engenders mechanical dyssynchrony (delay in lateral wall contraction), both of which are ameliorated with CRT. Although mechanical dyssynchrony has been reported in patients with HFpEF, the magnitude may or may not be different than hypertension patients without HFpEF, and is distinctly less than observed in wide QRS-HFrEF CRT candidates (12,13). Mechanical dyssynchrony has been reported in HFrEF without prolonged QRS, and small studies reported benefit with CRT. However, the EchoCRT (Echocardiography Guided Cardiac Resynchronization Therapy) study enrolled 809 patients with EF  $\leq 35\%$ , QRS  $\leq 130$  ms, and echocardiographic evidence of LV dyssynchrony. The EchoCRT study found no reduction in HF hospitalization or all-cause mortality; in fact, mortality was significantly higher in the CRT arm (14). There are a few small, mechanistic studies concerning CRT in HFpEF. Penicka et al. (15) described a patient with HFpEF, QRSD 127 ms (“LBBB-like”), and New York Heart Association functional class III HF, with only mild diastolic dysfunction undergoing CRT; LV end-diastolic pressure declined from 19 to 8 mm Hg, both positive and negative dP/dt improved, and exercise time increased. Wang et al. (16) used temporary biventricular pacing in 24 patients with LVEF  $> 50\%$ , and LV mechanical dyssynchrony with reduction in dyssynchrony and improved negative dP/dt. These small temporary or permanent examples are intriguing, but the strongly negative results of Echo-CRT must be kept in mind. A different type of dyssynchrony, namely interatrial, was reported by Eicher et al. (17), who described 29 patients with HFpEF with prior HF admissions and elevated B-type natriuretic peptide who had electrocardiographically advanced interatrial block, severe interatrial mechanical delay (more than 60 ms in 17 patients), elevated pulmonary artery pressures, mitral A-wave truncation, and pulmonary capillary wedge pressure of  $49.4 \pm 11.6$  mm Hg not stemming from mitral regurgitation. In 3 patients, pacing the left atrium via the coronary sinus improved the left atrial electrical and mechanical delays and reduced the V waves (17). The prevalence and potential therapeutic implications of interatrial dyssynchrony need amplification.

By probing the low-tech electrocardiogram, the TOPCAT investigators have added prolonged QRS to our risk catalogue in HFpEF. Conversely, the aforementioned high-tech hierarchical cluster analysis had identified a highest-risk subgroup that

intriguingly exhibited significantly prolonged QRS (3). Having arrived at a focus on QRS duration by either the low or high (tech) road, we still have our work cut out for us to use this knowledge to advance therapy in HFpEF.

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