JACC: HEART FAILURE
VOL. 4, NO. 11, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2016.09.004

EDITORIAL COMMENT

Left Bundle Branch Block

Is it "Unsafe at Any Speed"?*

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The recent history of cardiac resynchronization therapy (CRT) mirrors our increasing understanding of the correctable harm induced by left bundle branch block (LBBB). In 2009, Adelstein and Saba (1) reported single-center outcomes that demonstrated CRT to be efficacious primarily in those with LBBB. Shortly thereafter, 2 large multicenter randomized trials, MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) and RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial), demonstrated CRT to be a powerful intervention for the reduction of the combined endpoint of heart failure (HF) hospitalization or death, with beneficial effects essentially limited to patients with LBBB (2,3). In particular in MADIT-CRT, compared with patients with other forms of wide QRS complex, those with LBBB had the highest mortality and HF event rate in the control (implantable cardioverter-defibrillator-only) arm, whereas they were transformed dramatically by CRT, exhibiting the lowest primary endpoint event rate (4). By 2012, the growing consensus linking CRT benefit with LBBB contributed to the updated American Heart Association and American College of Cardiology guidelines, in which a class I indication for CRT was limited to symptomatic patients with left ventricular ejection fractions (LVEFs) ≤35% and LBBB (5). Thus, in patients with low LVEFs, the conduction abnormality was in effect officially highlighted as a correctable pathological process.

Clinical trials for CRT have focused on patients most at risk for HF events, typically setting a maximum LVEF inclusion threshold of 30% to 40%. However, it is important to recognize that LVEF is an imperfect risk stratification tool, a lesson gleaned from studies addressing sudden cardiac death (SCD). A recent review of SCD observed that "the lack of uniform methodology in the assessment in LVEF, only modest reproducibility of LVEF measurements, and poor sensitivity and specificity of LVEF in risk stratification…hampers its ability to be independently used as an ideal risk-stratification tool on which to base decision of [implantable cardioverter-defibrillator] prophylactic therapy" (6). These comments lend understanding to data from the Oregon Sudden Unexpected Death Registry, in which despite severely reduced LVEF (≤35%) being a strong predictor of SCD, only 30% of reported cases of SCD exhibited LVEFs ≤35%, compared with 22% of patients with LVEFs of 36% to 54% and 48% of patients with LVEEFs ≥55% (7). The Oregon study confirmed prior data from Maastricht (8).

Early CRT trials logically paired LVEF ≤35% with history of significant HF symptoms. Both COMPANION (Comparison of Medial Therapy, Pacing and Defibrillation in Heart Failure Trial) and CARE-HF (Cardiac Resynchronization-Heart Failure Trial) required an LVEF ≤35% with at least New York Heart Association functional class III symptoms and wide QRS complex as requirements for study entry, and both showed CRT efficacy (9,10). Building on these trials, MADIT-CRT and RAFT focused on patients in New York Heart Association functional class II who

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

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were minimally symptomatic, showing that CRT could not only treat HF symptoms but also prevent HF progression.

As the degree of symptom severity has decreased for the identification of patients who benefit from CRT, and as there is now acceptance that CRT can be used for the prevention of HF, there is increasing evidence that current LVEF thresholds for CRT may be too low. Although MADIT-CRT required an enrolling site LVEF ≤30% for randomization, when the echocardiographic core laboratory analyzed these studies, it was found that more than one-third of patients enrolled in MADIT-CRT were deemed to have LVEFs >30%, actually ranging up to 45.3% (11). Kutyifa et al. examined outcomes in patients with LVEFs >30% and learned that CRT exhibited a 44% reduction in the combined endpoint of HF hospitalization or death (11). This is similar to data from PROSPECT (Predictors of Response to CRT), a multicenter study that required LVEF ≤35% for entry but whose core laboratory found that more than 20% of patients had LVEFs >35% (12). The patients with less depressed LVEFs (>35%) exhibited similar clinical and echocardiographic improvement as those with traditional entry values (≤35%). Additionally, REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) studied 610 patients who received CRT devices with LVEF ≤40% in patients with New York Heart Association functional class I or II symptoms and QRS duration ≥120 ms (13). Despite this higher LVEF threshold (i.e., not 35%), REVERSE still found CRT to improve ventricular function and decrease rates of HF hospitalization. Given that CRT is effective primarily in patients with LBBB, these trials all offer indirect evidence that patients with LBBB and LVEFs >35% possess an increased risk for adverse events.

Further evidence for the potential harm of LBBB in patients with LVEFs >35% comes from pacing research. Given the similar left ventricular activation pattern on electrocardiography, right ventricular (RV) pacing is a "close relative" to LBBB. In DAVID (Dual-Chamber Pacing or Ventricular Backup Pacing in Patients with an Implantable Defibrillator), which required an LVEF ≤40% for study entry, frequent RV pacing was found to increase the rate of the combined endpoint of HF hospitalization or death (14). This led to the more recent BLOCK-HF (Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction), which compared CRT with RV pacing in patients with LVEFs <50% and a need for ventricular pacing because of advanced atrioventricular block (15). BLOCK-HF found that CRT decreased the composite endpoint (all-cause mortality, urgent intravenous diuretic therapy, or a 15% or more increase in left ventricular end-systolic volume index) by 26% compared with RV pacing (15).

Overall, there is considerable evidence that: 1) LVEF is an imperfect measure of cardiovascular risk for either SCD or HF events; 2) CRT benefits patients with minimal symptoms; 3) CRT appears effective in patients with LVEFs higher than current guidelines (35%); and 4) surrogates for LBBB, such as RV pacing, are detrimental in patients with LVEFs up to 50%. Taken together, it becomes entirely reasonable to suspect that LBBB may be pathogenic in patients exhibiting low LVEFs (≤35%) (4), or those identified as "mid-LVEF" (35% to 50%).

SEE PAGE 897

In this issue of *JACC: Heart Failure*, Witt et al. (16) present a novel examination of the impact of LBBB in this mid-LVEF population. The investigators retrospectively analyzed clinical data from a well-respected high-volume echocardiography laboratory. Witt et al. present strong evidence that LBBB confers harm in mid-LVEF patients, observing that "within 5 years a majority of the patients with LBBB had either died, had an ICD placed, or had a clinical event that would typically prompt device placement." Most notably, the investigators report a significant 17% increase in mortality compared with patients matched for LVEF and other factors but without LBBB. (Patients with right bundle branch block or hemiblock electrocardiographic patterns were excluded.) The investigators appropriately close by suggesting that the mid-EF population with LBBB warrants prospective evaluation with a CRT intervention study.

Although the study by Witt et al. (16) is an excellent first step, it is limited by its retrospective nature. To build their study population, the investigators allowed patients to undergo electrocardiography within 1 year of baseline echocardiography. These patients might have had changes in their conduction abnormalities within that time frame. Although experienced electrophysiologists reviewed all electrocardiograms, the investigators did not specify whether they applied the rigorous Strauss criteria for "strict LBBB" (17). Medications were not identified in this study, and it is unknown whether there were differences between the 2 groups. Of the 1,436 patients with LBBB, only 485 underwent follow-up echocardiography within 2 years, and 267 within 2 to 5 years, compared with 572 patients and 334 patients, respectively, in the control population with narrow QRS complexes. Thus, fewer patients with LBBB had follow-up with echocardiography, raising

JACC: HEART FAILURE VOL. 4, NO. 11, 2016
NOVEMBER 2016:904–6

the possibility of ascertainment bias. Furthermore, an imaging core laboratory was not used. Moreover, the follow-up for outcomes such as ventricular tachycardia or device implantation was limited to records available to the Mayo Clinic and may have been incomplete. It is instructive that such a large population of patients were identified with LBBB and mid-LVEF, given the recent enrollment failure in a trial for mid-LVEF CRT (18). Last, there is no inclusion of baseline HF symptoms in the clinical characteristics, which would offer an important dimension to the risk stratification of patients beyond assessment of LV function.

Substantial evidence and data from CRT trials confirm that LBBB worsens prognosis in patients with low LVEFs (4). The current study by Witt et al. (16), combined with indirect evidence from previous trials, makes a strong case that LBBB acts adversely in the so-called mid-LVEF range (i.e., 35% to 50%). Indeed, perhaps LBBB is deleterious at any level of LVEF—or, to take the analogy with automobile safety, "at any speed" (19). This implies that current guidelines for CRT may fail to reach patients at increased risk for potentially preventable cardiac morbidity and mortality. The shortcomings of Witt et al.'s nevertheless important study—lack of medications, lack of randomization, lack of a standardized echocardiographic core laboratory, incomplete study population follow-up, and lack of information on HF symptoms—would be best addressed by a prospective trial. Given the implications of the Witt et al. (18) findings, this would be useful data to obtain, although prior attempts have not succeeded (18). There is need to better delineate which patients with LBBB and mid-LVEF are at most risk for increased cardiac morbidity and mortality and which patients might most benefit from early treatment with CRT.

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KEY WORDS cardiac resynchronization therapy, heart failure, left bundle branch block, sudden cardiac death