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CIRCULATIONAHA/2010/013474

This information is current as of December 8, 2010

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Letter to the Editor

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Word count of letter: 511
**Abbreviations:**

AVOpt = atrioventricular optimization

CRT = cardiac resynchronization therapy

AVd = atrioventricular delay

LVESV = left ventricular end-systolic volume
To the Editor:

In their recent paper Ellenbogen et al (1) compare atrioventricular optimization (AVOpt) in cardiac resynchronization therapy (CRT) to setting a fixed AV delay (AVd) of 120ms. The study demonstrated no significant difference between the fixed AVd and either echo or EGM optimized AVd, using improvement in left ventricular end-systolic volume (LVESV) at 6 months as the primary endpoint. The authors conclude that the routine use of AV optimized techniques is no longer warranted.

We believe that the study was underpowered to detect the additional response to AVOpt. In the sample size calculation the authors base their calculation on a standard deviation of 60mL and an expected response to CRT of 30mL reduction in LVESV (seen in large published trials including MIRACLE and CARE-HF). They then assumed an additional half of the CRT effect (15mL) would be possible with AVOpt and stated that this 15mL was the smallest ‘clinically meaningful difference’. However, Auricchio et al (2) showed that at most cardiac output improves by 20% in selected patients following AVOpt. Given that in clinical practice using iterative AVOpt only around 40% of patients actually require a significant change in AVd, this mean change of 15mL reduction in LVESV across the whole cohort randomized to optimization, over and above the response to CRT, was unrealistic.

It should be noted that in this study the overall benefit of CRT was almost half in the ‘fixed’ group compared to that seen in the landmark CRT trials, which included AVOpt.
As the actual response to CRT alone was 50% (15mL) less than predicted, the study had already deviated significantly from the original plan and by the authors own standards, this 15ml under-response was likely to be ‘clinically relevant’. Indeed, as the confidence intervals of medians of improvements in each of the three treatment groups included -15, it could, even by the authors’ standards, be concluded that the benefit from CRT was not significantly above the ‘clinical relevance threshold’.

We have recalculated power and sample size using the same t-test formula the authors used, but employing 50% of the median improvement in LVESV observed in the fixed group (15mL * 50% = 7.5mL) as minimal required difference between mean LVESV improvements in the Fixed and optimized groups. This showed that the study had only a 36% power to show a difference of 7.5mL. To show a 7.5mL difference with 80% power 1001 patients/group would be needed, 3 times more than currently randomized. (A more accurate calculation would be possible using the raw data of the SMART-AV study).

Therefore, we believe that 15mL was too strict a threshold when looking for a difference between the fixed and optimized groups, and as a statistical consequence, a too permissive threshold has been employed for the non-inferiority test. More importantly, as a result of a lower than anticipated response to CRT, the study was underpowered to detect a further 50% change in LVESV.
Although the authors should be congratulated for highlighting the important topic of CRT optimization, we feel that it would be unwise to categorically exclude all patients who have responded to CRT therapy, based on this study.

References
