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Kloosterman, Mariëlle; Maass, Alexander H

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Sex differences in optimal atrioventricular delay in patients receiving cardiac resynchronization therapy

Mariëlle Kloosterman¹ · Alexander H. Maass¹

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Sirs:

Individual optimization of the atrioventricular (AV) delay has been part of standard protocol in several landmark cardiac resynchronization therapy (CRT) trials. While optimized delays can result in acute improvements in left ventricular diastolic and systolic function [1, 2], the role of routine AV delay optimization remains unclear since large clinical trials failed to show long-term improvement in clinical and echocardiographic outcome [3, 4]. Furthermore, AV optimization is time-consuming, costly; optimization methods are subjected to a high degree of variability, and sometimes complexity; and a “gold standard” is missing. A survey by Gras et al. [5] demonstrated that nearly 58% of cardiologist do not optimize CRT devices after implantation. However, suboptimal programmed delays may result in a 10–15% decline in cardiac output over time [6], and optimal AV delay settings will differ from the manufacturer’s set interval in at least a subset of patients. This might be particularly true in women. In a subgroup analysis of the SMART-AV delay trial, women who received AV optimization responded more favorably than women with fixed delays [3]. We sought to compare sex differences in optimal sensed and paced atrioventricular (AV) delay programming in a real-world CRT population.

This was a single-center, retrospective, observational study performed at the University Medical Centre Groningen in the Netherlands. 328 consecutive patients with echocardiographic optimization data who received a CRT device from March 2010 until November 2016 were identified. Eligibility criteria for CRT implantation were based on the standard European Society of Cardiology (ESC) guidelines

at the time of implantation [7]. After a median of 34 days (interquartile range 28–43 days), all patients received echocardiographic AV optimization as part of standard care using the iterative method, performed during atrial sensing and atrial pacing in supine position by one experienced cardiologist (AHM). In short, a long AV interval was programmed which was gradually shortened in 20-ms steps until truncation of the A wave was observed on mitral inflow Doppler. Then, the AV interval was prolonged in 10-ms steps until maximal E and A wave separation was obtained and mitral valve closure coincided with, or occurred shortly after, atrial contraction. During and after AV optimization, we analyzed the QRS pattern (duration and morphology) to ensure biventricular capture.

The Dutch Central Committee on Human-related Research (CCMO) allows the use of anonymous data without prior approval of an institutional review board, provided data are acquired during routine patient care. All data were handled anonymously. Data analysis was performed with SPSS 23.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean with standard deviation (SD). Categorical variables are summarized as frequencies and percentages. Differences between sensed and paced AV delay between the sexes were determined using the Student’s *t* test. A multiple regression analysis was performed to study the contribution of gender on sensed and paced optimal AV delays, while adjusting for heart failure etiology, age at implantation, baseline PR duration, and baseline QRS duration. A *P* value of ≤ 0.05 was considered significant.

Average age of the population was 69 ± 12 years, 64% was men, left ventricular ejection fraction was $25 \pm 8\%$, and 52% had a non-ischemic heart failure etiology. Heart rate during sensed and paced echocardiographic AV optimization was 70 ± 12 bpm and 74 ± 12 bpm, respectively ($P < 0.001$). Women had smaller left atrial volume indexed for body surface area (35 ± 12 vs 40 ± 13 ml/m², $P = 0.03$), more often non-ischemic heart failure etiology (78 vs 39%, $P < 0.001$),

✉ Alexander H. Maass
a.h.maass@umcg.nl

¹ Department of Cardiology, University of Groningen,
University Medical Center Groningen, P.O. Box 30.001,
9700 RB Groningen, The Netherlands

and shorter intrinsic PR intervals (173 ± 34 vs 194 ± 42 ms, $P < 0.001$).

Optimal sensed and paced AV delays were shorter for women (respectively, 65 ± 17 vs 80 ± 28 ms, and 136 ± 23 vs 154 ± 34 ms, both $P < 0.001$). This held true irrespective of baseline PR duration, QRS duration, or heart failure etiology (Fig. 1a, b). In multiple regression analysis, gender was a significant independent predictor variable for a shorter optimal sensed ($\beta - 12$ ms, 95% confidence interval -18 ms to -6 ms, $P < 0.001$) and optimal paced AV delay ($\beta - 12$ ms, 95% confidence interval -19 ms to -5 ms, $P = 0.001$). Notably, only 1 woman (0.8%) had an optimal sensed AV delay of > 100 ms (Fig. 1c), while the standard sensed manufacture settings range from 100 ms [Medtronic] to 150 ms [St. Jude Medical].

We show that women have shorter optimal sensed and paced AV intervals, and shorter optimal AV intervals than manufacturer pre-settings, suggesting that default settings are not optimal for practically all women. In theory, maximizing efficiency of CRT requires not only synchrony within

and between the ventricles, but also optimal AV delay as both passive and active ventricular filling contribute to stroke volume and cardiac output. Experimental physiological and pathophysiological studies support the rationale to optimize AV delays [1, 2].

In clinical practice, many techniques are available for optimizing AV delays, including echocardiography, device-based algorithms, and several other (non)invasive techniques [8, 9]. However, given the complexity and technical skill required for most methods, the reproducibility and consistency of measurements vary substantially [10]. AV delays are a highly individual characteristic of each patient and dependent on many factors including but not limited to underlying heart condition, atrial and ventricular lead position, atrial size, and intra-atrial conduction. Additionally, echo Doppler Mitral inflow patterns during optimization are influenced by heart rate, rhythm, and volume loading conditions. Furthermore, AV delays are not static values and may vary in time and different circumstances (e.g. supine vs upright, exercise vs rest). This illustrates the complexity of enhancement of

Fig. 1 Sex differences in optimal sensed and paced AV delays. Optimal sensed (a) and paced (b) AV delays, determined using the iterative echocardiographic method, are shown for the total population and subgroups of intrinsic PR duration, QRS duration, and heart failure etiology. Women had uniformly shorter optimal sensed AV and

paced AV delays. c Columns show the distribution of optimal sensed AV delays for men and women (%). Only one woman had an optimal sensed AV > 100 ms. * $P \leq 0.005$. ICM, ischemic cardiomyopathy; NICM, non-ischemic cardiomyopathy; NS, non-significant

AV hemodynamics and may in part explain why AV optimization has not consistently translated into long-term improvements in clinical outcomes or CRT response rates [3, 4]. Consequently, manufacturer AV delay settings are not routinely adjusted post-implantation.

We can speculate that optimized AV delays, with the shortest possible AV delay that ensures a high degree of biventricular pacing and does not compromise transmitral Doppler A wave, may provide the opportunity to maximize response. The benefit of AV optimization may not lie in conversion of non-responders to responders, but in increasing the magnitude of CRT response [11], this might be particularly true in women. We report a shorter baseline PR interval in women. Optimizing AV delay could potentially reduce the number of women with suboptimal resynchronization because of shorter PR intervals promoting intrinsic ventricular activation. This might possibly explain part of the gender effect on CRT response [12]. Women had smaller LAVI and more often non-ischemic cardiomyopathy. The larger atria in men and possibly decreased conduction velocities due to scarring in the setting of ischemic cardiomyopathy might partially explain their longer AV delay. To assess if individual patients achieve maximal response, a score, such as the CAVIAR response score, may be used to compare predicted amount of remodeling with actual clinical response [13].

We show that manufacturer AV delay settings are not optimal for practically all women. Ideally, optimization should be individualized. However, given the multitude of AV optimization methods without a clearly defined gold standard, interpretation of AV optimization data is difficult and the best method and appropriate timing for optimizing and assessing AV delays remains to be defined [14, 15]. Nevertheless, a working understanding of AV optimization is important for all physicians who manage these patients. In that context, it is desirable to, at the very least, consider differences in optimal AV delays between the sexes. If we want to achieve “satisfactory” instead of “optimal” AV intervals, an empiric sensed AV interval of 60–70 ms seems to be a satisfactory solution for the majority of women. Prospective research is warranted to confirm these findings.

Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interest.

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