ORIGINAL ARTICLE

Effect of Interventricular Electrical Delay on Atrioventricular Optimization for Cardiac Resynchronization Therapy

See Editorial by Rickard and Varma

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BACKGROUND: Routine atrioventricular optimization (AVO) has not been shown to improve outcomes with cardiac resynchronization therapy (CRT). However, more recently subgroup analyses of multicenter CRT trials have identified electrocardiographic or lead positions associated with benefit from AVO. Therefore, the purpose of this analysis was to evaluate whether interventricular electrical delay modifies the impact of AVO on reverse remodeling with CRT.

METHODS: This substudy of the SMART-AV trial (SMARTDELAY Determined AV Optimization) included 275 subjects who were randomized to either an electrogram-based AVO (SmartDelay) or nominal atrioventricular delay (120 ms). Interventricular delay was defined as the time between the peaks of the right ventricular (RV) and left ventricular (LV) electrograms (RV-LV duration). CRT response was defined prospectively as a >15% reduction in LV end-systolic volume from implant to 6 months.

RESULTS: The cohort was 68% men, with a mean age of 65±11 years and LV ejection fraction of 28±8%. Longer RV-LV durations were significantly associated with CRT response (*P*<0.01) for the entire cohort. Moreover, the benefit of AVO increased as RV-LV duration prolonged. At the longest quartile, there was a 4.26× greater odds of a remodeling response compared with nominal atrioventricular delays (*P*=0.010).

CONCLUSIONS: Baseline interventricular delay predicted CRT response. At long RV-LV durations, AVO can increase the likelihood of reverse remodeling with CRT. AVO and LV lead location optimized to maximize interventricular delay may work synergistically to increase CRT response.

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WHAT IS KNOWN?

- Routine atrioventricular (AV) optimization for cardiac resynchronization therapy (CRT) is no longer recommended because the results of multicenter randomized trials have been disappointing.
- Anatomic position of the left ventricular (LV) lead for CRT has limited utility to predict response. However, pacing at sites of late mechanical or electrical delay are associated with improved outcomes. Both prolonged LV delay (QLV interval, onset of QRS to LV) and interventricular delay (right ventricular [RV]-LV duration) are associated with better CRT response rates.

WHAT THE STUDY ADDS?

- AV optimization, using an algorithm that promotes fusions with intrinsic conduction and maximizes acute hemodynamic response (SmartDelay), is associated with improved CRT response compared with nominal AV delay programming when pacing at sites with long RV-LV durations. There is no benefit of (AV) optimization at pacing sites with short RV-LV durations.
- The CRT nonresponder rate can be decreased significantly by choosing pacing sites or pacing electrodes of multipolar leads with long RV-LV duration (>70 ms) and using AV optimization.

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with symptomatic heart failure (HF), left ventricular (LV) systolic dysfunction, and QRS prolongation. CRT results in LV reverse remodeling, as well as improvement in clinical outcomes, including reductions in HF hospitalizations and mortality.[1–5] Despite the consistently observed benefits of CRT in randomized clinical trials, many patients remain classified as nonresponders.[1,6] Multiple factors have been identified impacting the response rate, including patient characteristics (eg, sex and pathogenesis of HF) and electrocardiographic properties, such as QRS duration and morphology. In addition to these nonmodifiable clinical characteristics, procedural factors can also affect response rates. For example, pacing at LV sites with late electrical or mechanical activation has been associated with better outcomes.[7–18] In contrast, early enthusiasm has waned for the role of optimizing atrioventricular (AV) timing may play in improving responder rates because of disappointing results from multicenter randomized trials.[19–22]

Recent studies have indicated that atrioventricular optimization (AVO) may be useful in certain subgroups of patients with CRT. For instance, LV-only pacing with AVO may be beneficial among patients with left bundle branch block (LBBB) and normal AV conduction times.[23] LV delay at the LV pacing site also identifies a subgroup that is associated with improved outcomes with AVO during biventricular pacing.[24] Prolonged interventricular delay, as measured by the difference in activation time between the right ventricular (RV) and LV leads, is associated with better CRT response.[17–19] The present study was designed to assess whether AVO further improves the benefit of pacing at long RV-LV durations.

METHODS

The present analysis is a substudy of the SMART-AV trial (SMARTDELAY Determined AV Optimization). SMART-AV was a multicenter randomized trial of AVO techniques among patients with advanced HF undergoing CRT implantation.[20] This trial was approved by an institutional review committee at each institution, and all subjects gave informed consent. Details of the RV-LV analysis of SMART-AV have been published previously.[25] There were 275 patients included in the RV-LV substudy, which included subjects randomized to a nominal AV delay or AVO using the SmartDelay (SD) algorithm. The sensed and paced AV delay was 120 ms in the nominal group, whereas the SD algorithm was used to program sensed and paced AV delays separately in the AVO group. Simultaneous RV and LV pacing (ie, LV offset, 0 ms) was used in both groups. The RV and LV leads were positioned at the discretion of the implanting physician with no guidance to maximize RV-LV duration. At the final lead positions, surface lead II, RV and LV electrograms were recorded simultaneously on paper strips at a sweep speed of 100 mm/s. RV-LV interval was measured by a blinded core laboratory with no knowledge of lead position or clinical outcomes. The RV-LV interval was measured in sinus rhythm and in the absence of pacing as the interval from the first major peaks of the RV and LV electrograms during a cardiac cycle with the resolution of 5 ms (Figure 1). The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because this was a study using a proprietary algorithm.

The primary end point of the SMART-AV trial was LV end-systolic volume (LVESV). The CRT response rate for the present analysis was defined prospectively as a >15% reduction in LVESV.[18,20,24,25] The echocardiographic end points were analyzed blindly by a core laboratory. Off-line software (Pro-Solv, version 3.0, or GE Echo Pac, version 6.0) was used for measurements. Two-dimensional–derived LV volumes were determined in the apical 4- and 2-chamber views by the biplane method of discs. In 84% of images, the apical 2-chamber view image quality was deemed excellent or good with respect to visualization of the anterior wall. All echocardiographic measures were performed at baseline and after 6 months of CRT.

Baseline clinical parameter data were compared across quartiles of RV-LV duration. Continuous variables were summarized as means and standard deviations, unless otherwise noted, and compared across RV-LV quartiles with a Cuzick test for trend. Binary variables were compared across quartiles with a Cochran-Armitage test for trend. Categorical variables with >2 response levels were compared across quartiles with a Cochran-Mantel-Haenszel test.
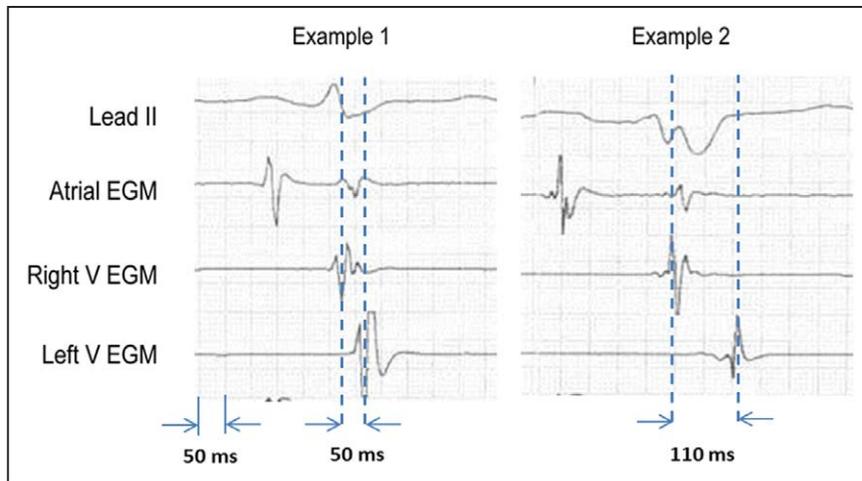
Figure 1. Two examples of right ventricular (RV)-left ventricular (LV) duration measurements in study patients.
The calipers are aligned with the peaks of the RV and LV electrogram (EGM).

The effects of RV-LV on changes in relative and absolute LVESV were evaluated using general linear models (for continuous RV-LV) and 1-way ANOVA F tests for trend (for quartile of RV-LV). Responses to CRT were compared by RV-LV durations grouped in quartiles. Potential interactions between RV-LV timing and AVO were assessed via general linear modeling (for continuous RV-LV) and logistic regression (for RV-LV quartile).

Changes in relative LVESV between the 2 AVO groups were compared within each quartile of RV-LV using a 2-sample t test. The effects of AVO on CRT response within various RV-LV and clinical characteristic subgroups were evaluated using multivariable logistic regression modeling, adjusted for the clinical characteristics of baseline ejection fraction (EF), LVESV, pathogenesis of HF, LBBB, sex, New York Heart Association classification (NYHA class), QRS duration, and age.

Two group comparisons were made using 2-sample t tests for continuous variables and χ^2 tests for categorical variables. An $\alpha = 0.05$ threshold was used to demonstrate statistical significance, with no adjustments made for multiple comparisons. SAS, version 9.4, was used for statistical analysis.

RESULTS

Patient Population

This substudy included 275 patients and was representative of those included in the main SMART-AV study.[20,25] The mean age was 65±11 years, and 68% were men. The LVEF was 28±8%, the baseline LVESV was 130±61 mL, and 94% of subjects had NYHA class III functional status at enrollment. An LBBB morphology was present in 77% of subjects with a QRS duration of 149±25 ms and PR interval of 197±46 ms. The clinical characteristics were well matched between the SD and nominal programming groups (P>0.05).

The sensed and paced programmed AV delays were 120 ms for all subjects in the nominal group by protocol, and 123±34 and 171±35 ms, respectively, in the SD group. The percentage of atrial pacing was 21.7±25.1% versus 22.8±26.7% (P=0.74), and the percentage biventricular pacing was 95.8±7.8% versus 95.7±6.6% for the 2 groups, respectively.

RV-LV Analyses

The RV-LV duration quartiles were at 40, 65, and 100 ms for the full cohort. As expected, the RV-LV duration was longer for patients with LBBB compared with non-LBBB (77±38 versus 40±37 ms; P<0.001). Of note, 97% of LBBB and 81% of non-LBBB subjects had a positive RV-LV duration, indicating earlier activation of the RV electrode than the LV electrode in sinus rhythm. This is consistent with LV electrical delay even in the presence of non-LBBB in a vast majority of subjects.

The magnitudes of relative and absolute changes in LVESV from baseline to 6 months are shown in Table 1 for each RV-LV quartile. Both end points were strongly associated with RV-LV duration (both P<0.001). To ensure that these findings were not an artifact of grouping into quartiles, further analysis was performed with RV-LV duration assessed as a continuous variable. Again, there was a strong relationship between interventricular delay and the change in LVESV with a 2.0% relative decrease and 2.5 mL absolute decrease in LVESV for every 10-mL prolongation of RV-LV duration (both P<0.001).

Table 1. Relationship of Right Ventricular-Left Ventricular Duration Quartile With LVESV Changes

End Point	Evaluation	Q1 (≤40 ms)	Q2 (45–65 ms)	Q3 (70–100 ms)	Q4 (≥105 ms)	*P* Value
LVESV	Relative, %	−2.8±29.6%	−9.0±30.5%	−17.3±30.6%	−24.9±28.1%	<0.001
	Absolute, mL	−6±35	−14±37	−28±43	−33±40	<0.001

LVESV indicates left ventricular end-systolic volume.

There were important clinical differences between subjects in the various RV-LV duration quartiles as shown in Table 2. Specifically, at longer interventricular delays, subjects were more likely to be women, have nonischemic cardiomyopathy, LBBB, longer QRS duration, and lateral or posterior LV lead position—all markers of an improved response with CRT. To explore this relationship further, multivariable analysis was performed on response rates (>15% reduction of LVESV). Baseline EF, LVESV, pathogenesis of HF, LBBB, sex, NYHA class, QRS duration, and age were included as main effects in these analyses. RV-LV duration remained a strong independent predictor of the reverse remodeling response for the entire cohort, with an 11% increased odds of response per 10-ms increase in RV-LV duration (P=0.005).

AVO Analyses

To evaluate the impact of AVO on this effect, the 2 groups (nominal and AVO) were analyzed separately. Figure 2 provides relative changes in LVESV from implant to 6 months by RV-LV quartile for each group. The magnitude of LVESV reduction for the AVO group was greater than the control group as RV-LV duration prolonged, approaching clinical significance in the longest quartile

(P=0.051), although a significant interaction between AVO and RV-LV quartile was not observed (P=0.66). However, a significant interaction between AVO group and continuous RV-LV duration was observed (Table 3). For every 10-ms increase in RV-LV duration, patients in the AVO group had a 22% increase in the odds of response compared with a 7% increase in the odds of response for the control group (interaction P value, 0.046).

A similar finding was observed using CRT response rate—the primary end point of this study. As RV-LV duration prolongs, there was a progressive separation between the 2 groups with the significance reached for the longest quartile (Table 4). The overall response rate in this cohort was 52%. Patients with long RV-LV times (≥70 ms) had significantly greater response rates than those with short RV-LV (<70 ms; 62% versus short 40%, respectively; P<0.001).

To explore this relationship further, multivariable analysis was performed on response rates. These results are shown in Figure 3, where it can be observed that the magnitude of response increased monotonically as interventricular delay prolonged. No benefit of AVO was noted at the shortest quartile of RV-LV intervals (≤40 ms). However, at the longest 1 (≥105 ms), 2 (≥70 ms) or 3 (≥45 ms) quartiles, there was a significantly higher response rate with AVO. AVO improved the odds of an

Table 2. Comparison of Baseline Clinical Parameters in RV-LV Quartiles

Characteristics	Baseline RV-LV, ms				P Value
	Q1 (≤40 ms)	Q2 (45–65 ms)	Q3 (70–100 ms)	Q4 (≥105 ms)	
No. of patients	69	65	73	68	NA
AVO	36	36	32	39	NA
Nominal AV delay	33	29	41	29	NA
Age, y; mean±SD	64±10	67±13	64±11	68±10	0.14
Sex (men)	79.7%	72.3%	56.2%	63.2%	0.009
Ischemic heart disease (yes)	71.0%	66.2%	57.5%	48.5%	0.004
NYHA functional class II	7.5%	0.0%	2.7%	1.5%	0.92
NYHA functional class III	86.6%	96.9%	94.5%	97.1%	0.92
NYHA functional class IV	6.0%	3.1%	2.7%	1.5%	0.92
PR, ms; mean±SD	201±53	202±43	190±40	194±48	0.27
QRS, ms; mean±SD	140±21	137±24	149±20	169±23	<0.001
LBBB (Yes)	53.6%	69.2%	89.0%	94.1%	<0.001
LVESV, mL; mean±SD	118±49	132±62	140±69	129±61	0.18
LVEDV, mL; mean±SD	163±53	178±68	182±76	175±68	0.32
LVEF, %; mean±SD	29.3±8.4%	28.2±8.7%	25.4±8.4%	28.1±7.9%	0.092
Lead position: RAO (apical)	9.7%	9.4%	9.9%	11.8%	0.68
Lead position: LAO (posterior/posterolateral/anterolateral)	91.9%	95.3%	98.6%	98.5%	0.030
BiV pacing, %; mean±SD	95.7±5.3	94.9±10.0	95.9±6.5	96.5±6.7	0.39
Programmed paced AV delay, ms; mean±SD	163±44	152±40	136±26	140±26	0.004
Programmed sensed AV delay, ms; mean±SD	134±28	125±26	115±18	113±20	<0.001

AV indicates atrioventricular; AVO, atrioventricular optimization; BiV, biventricular; LAO, left anterior oblique; LBBB, left bundle branch block; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association classification; RAO, right anterior oblique; and RV, right ventricular.
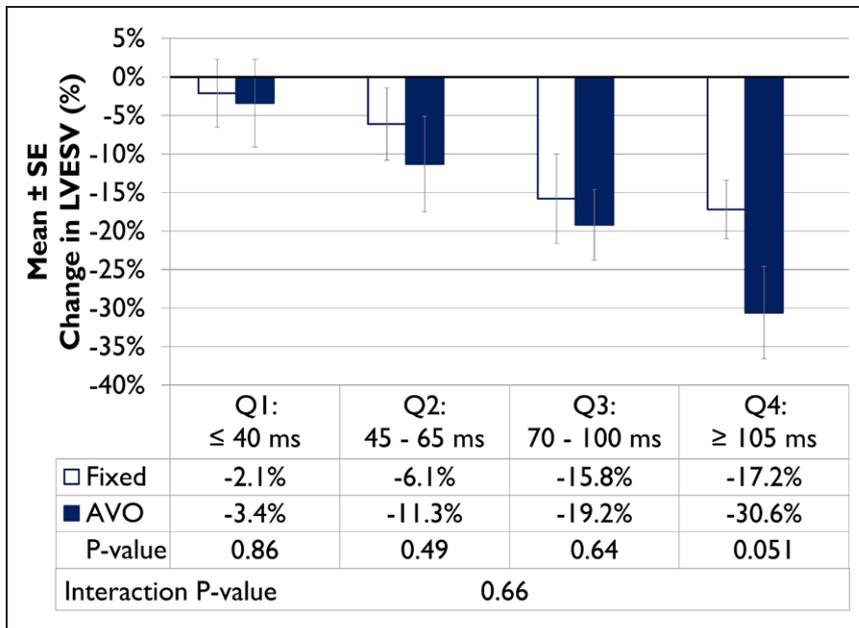
Figure 2. The relationship of atrioventricular optimization (AVO) subgroups and right ventricular-left ventricular duration on the percentage change in left ventricular end-systolic volume (LVESV).

LVESV response ≈2-fold compared with the nominal AV delay in patients with RV-LV ≥45 ms (second to fourth quartiles). At the longest RV-LV durations (fourth quartile, ≥105 ms), there was a 4.26× greater odds of an LVESV response with AVO compared with nominal AV delay programming (P=0.010).

Additional analyses were performed to assess the impact of AVO in prespecified subgroups. These results are summarized in Figure 4. Among patients with RV-LV duration below the median (<70 ms), there was no indication for a benefit of AVO overall or in any subgroup (Figure 4A). In contrast, the Forest plots (Figure 4B) show a beneficial effect of AVO programming among patients with longer RV-LV (≥70 ms) durations for the whole cohort and for several subgroups. Of note, none of the interaction P values were statistically significant for any of the other subgroups. The estimated effect of AVO in subgroups with lower responses to CRT (eg, men and non-LBBB morphology) were similar to that in women and those with LBBB morphology who are more likely to benefit from CRT.

DISCUSSION

The present study is an analysis of the interaction between interventricular electrical delay and AVO with an electrogram-based algorithm. The primary finding is that reverse remodeling with CRT, as assessed by changes in LVESV, is strongly dependent on the RV-LV interval with increased response as this interval prolongs for both the nominal and AVO subgroups. Moreover, the impact of AVO is also influenced by interventricular delay with greater changes in remodeling parameters at longer RV-LV intervals compared with nominal AV delay programming.

The SD algorithm is designed to maximize the acute hemodynamic response (LV dP/dt$_{max}$) with CRT.[26] The algorithm recommends AV delays based on the sensed and paced intrinsic AV interval, as well as QRS duration and morphology. Previous studies of biventricular or LV-only pacing suggest that optimal fusion of intrinsic conduction down the right bundle branch with LV pacing maximizes the hemodynamic response.[27–31] Thus, as the interventricular conduction delay increases, the greater the electrical resynchronization that can occur with an optimally timed stimulus. This would explain the relationship between RV-LV duration and the incremental benefit of this electrogram-based AVO method.

As noted above, even in non-LBBB subjects, most patients have earlier activation of the RV than LV at the implanted electrode sites, which suggests the presence of LV electrical delay. This also helps explain the similar benefit of AVO compared with patients with LBBB when the RV-LV duration is prolonged.

Several factors impact the magnitude of reverse remodeling and the clinical response to CRT in addition to QRS morphology. In general, better response rates are noted in women, nonischemic cardiomyopathy, and patients with longer unpaced QRS duration.[20,32–35] These factors were all associated with improved volu-

Table 3. Interaction of AVO With RV-LV on Cardiac Resynchronization Therapy Response: Continuous RV-LV

Group	Odds Ratio*	95% CI	P Value	Interaction P Value
AVO	1.22	1.11–1.34	<0.001	0.046
Fixed	1.07	0.98–1.17	0.13	0.046

AVO indicates atrioventricular optimization; CI, confidence interval; LV, left ventricular; and RV, right ventricular.

*Per 10-ms increase in RV-LV duration.

Table 4. Interaction of AVO With RV-LV on Cardiac Resynchronization Therapy Response: Quartile of RV-LV

RV-LV Quartile	LVESV Response Rate		
	AVO	Fixed	*P* Value
Q1: ≤40 ms	33.3%	36.4%	0.79
Q2: 45–65 ms	47.2%	44.8%	0.85
Q3: 70–100 ms	62.5%	56.1%	0.58
Q4: ≥105 ms	79.5%	48.3%	0.007
Interaction of RV-LV and AVO			0.17

AVO indicates atrioventricular optimization; LV, left ventricular; LVESV, left ventricular end-systolic volume; and RV, right ventricular.

metric remodeling in the SMART-AV trial. Although these factors predict response, there is still incremental predictive value of interventricular conduction delay within these subgroups. It is noteworthy that there may also be a benefit of AVO in many subgroups that are less likely to respond to CRT if the RV-LV duration was prolonged.

Previously, we showed that the QLV duration was also a predictor of CRT response[10] and identified a subgroup that responded to AVO in the SMART-AV trial.[24] QLV is a measure of LV delay and is independent of RV lead position in contrast to RV-LV duration. When both RV-LV and QLV were included in a multivariable analysis of response in this trial, the resulting model excluded QLV and retained RV-LV, indicating that RV-LV is the better predictor of the remodeling response.[25] As further evidence that there are differences between the 2 measures, only 47 of the 68 patients (69%) in the fourth quartile of RV-LV were also in the fourth quartile of QLV. Overall, a net of 11.3% of responders were reclassified correctly when using RV-LV compared with QLV. Futhermore, implanted CRT devices can automatically measure RV-LV times, and in fact, this feature is now in multiple manufacturers' devices, whereas QLV cannot be measured directly from intracardiac signals. Thus, RV-LV is likely to become the standard measure for assessing electrical delay.

Clinical Implications

Maximizing the magnitude of response continues to be a goal for CRT, despite optimized device programming. Recent studies suggest that a purely anatomic approach to lead position will be of limited value other than avoiding apical positions.[7,8] However, placing leads in areas of late mechanical or electrical delay is associated with better echocardiographic response. The incremental benefit of AVO with physiological selection of pacing sites could have significant impact on reducing nonresponder rates. Thus, it seems reasonable to place LV leads or pace from electrodes of multipolar leads with long RV-LV durations and utilize AVO, such as the algorithm evaluated in this study (ie, SmartDelay) that maximizes electrical resynchronization, during implant and follow-ups. Of note, these algorithms optimize AV delay and either use simultaneous biventricular pacing or pace the LV only because multicenter studies of LV offset (ie, V-V timing) have been disappointing.[36,37] Although the emphasis on CRT lead placement has been primarily on the LV lead, RV-LV duration is also affected by the RV lead position. Further study is warranted to assess whether a strategy of placing RV leads to maximize interventricular delay would improve outcomes. Our results indicate that AVO is unlikely to be of benefit in the absence of significant interventricular conduction delay, which may explain the neutral results from previous multicenter studies of such algorithms in which the lead implantation strategy was largely anatomic and the lead positioning was not targeted to maximize RV-LV delay.[19–21]

Limitations

This study should be interpreted in light of certain methodological limitations. RV-LV duration was measured at the final lead position, so there was only 1 interval associated with each patient. Therefore, the impact of lead repositioning on interventricular delay cannot be determined from this study. In addition, echocardiographic end points were used rather than more long-term follow-
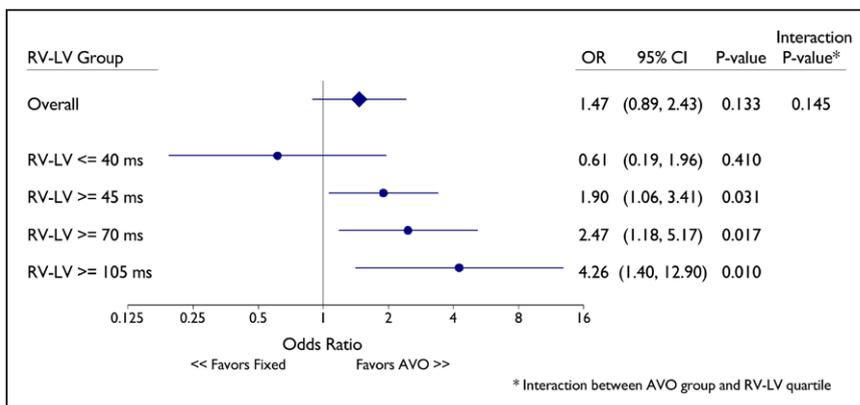
Figure 3. Multivariable logistic regression model of the impact of SD on cardiac resynchronization therapy response as defined by >15% decrease in left ventricular end-systolic volume (LVESV).
The LVESV responses of AVO (SD) vs fixed AV delay are shown at different right ventricular-left ventricular cutoffs after adjusting for baseline ejection fraction, LVESV, pathogenesis of heart failure, left bundle branch block (LBBB), sex, NYHA (New York Heart Association classification), QRS, and age. AVO indicates atrioventricular optimization; CI, confidence interval; and OR, odds ratio.
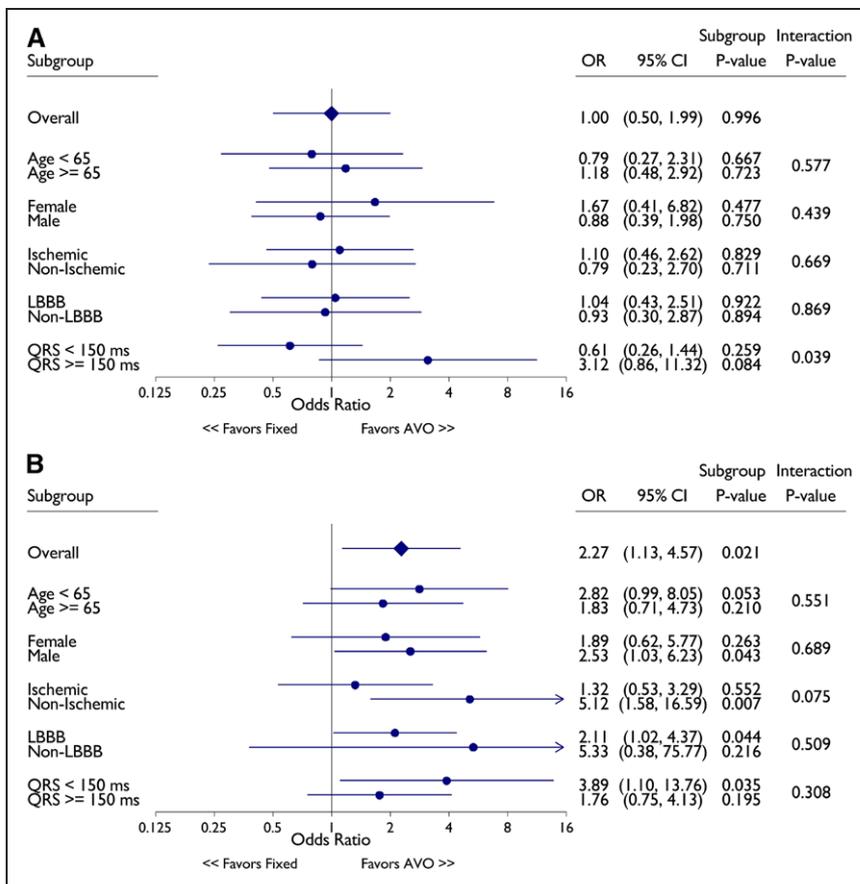
Figure 4. Univariable logistic regression results for cardiac resynchronization therapy (CRT) response at right ventricular (RV)-left ventricular (LV) duration <70 ms (A) and RV-LV ≥70 ms (B) by subgroups. CRT response as defined by >15% decrease in left ventricular end-systolic volume. AVO indicates atrioventricular optimization; CI, confidence interval; and OR, odds ratio.

ups with clinical end points, such as HF hospitalizations or mortality. However, it is well documented that reverse remodeling is a strong predictor of outcomes in CRT.[38] Finally, only 1 AVO algorithm (ie, SmartDelay) and no VV optimization was performed in this study. This algorithm was chosen because it was designed to promote electrical resynchronization and has been used in the present or similar forms in long-term studies, including COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) and MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy).[2,5] However, these results may not extrapolate to other optimization methods.

In summary, interventricular electrical dyssynchrony, as measured by RV-LV duration, was strongly associated with reverse remodeling with CRT. The incremental benefit of AVO was observed at the longest RV-LV durations. Further study is warranted to assess the value of guiding placement of leads for CRT by RV-LV durations with AVO to improve response rates with CRT.

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