The association between biventricular pacing and cardiac resynchronization therapy-defibrillator efficacy when compared with implantable cardioverter defibrillator on outcomes and reverse remodelling

Anne-Christine Ruwald1,2*, Valentina Kutyifa1, Martin H. Ruwald1,2, Scott Solomon3, James P. Daubert4, Christian Jons2, Andrew Brenyo5, Scott McNitt1, Duc Do6, Kenji Tanabe6, Amin Al-Ahmad6, Paul Wang6, Arthur J. Moss1, and Wojciech Zareba1

1Heart Research Follow-up Program, University of Rochester Medical Center, 265 Crittenden Blvd. CU 420653, Rochester, NY 14642, USA; 2Department of Cardiology, Gentofte University Hospital, Hellerup, Denmark; 3Cardiovascular Division, Brigham and Women’s Hospital, Boston, MA, USA; 4Cardiology Division, Duke University Medical Center, Durham, NC, USA; 5Greenville University Health System, Greenville, SC, USA; and 6Division of Cardiovascular Medicine, Stanford University, Stanford, CA, USA

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Aims
Previous studies on biventricular (BIV) pacing and cardiac resynchronization therapy-defibrillator (CRT-D) efficacy have used arbitrarily chosen BIV pacing percentages, and no study has employed implantable cardioverter defibrillator (ICD) patients as a control group.

Methods and results
Using Kaplan–Meier plots, we estimated the threshold of BIV pacing percentage needed for CRT-D to be superior to ICD on the end-point of heart failure (HF) or death in 1219 left bundle branch block (LBBB) patients in the MADIT-CRT trial. Patients were censored at the time of crossover. In multivariable Cox analyses, no difference was seen in the risk of HF/death between ICD and CRT-D patients with BIV pacing ≤ 90% [HR = 0.78 (0.47–1.30), P = 0.344], and with increasing BIV pacing the risk of HF/death was decreased [CRT-D BIV 91–96% vs. ICD: HR = 0.63 (0.42–0.94), P = 0.024 and CRT-D BIV ≥ 97% vs. ICD: HR = 0.32 (0.23–0.44), P < 0.001]. The risk of death alone was reduced by 52% in CRT-D patients with BIV ≥ 97% (HR = 0.48, P < 0.016), when compared with ICD patients. Within the CRT-D group, for every 1 percentage point increase in BIV pacing, the risk of HF/death and death alone significantly decreased by 6 and 10%, respectively. Increasing BIV pacing percentage was associated with significant reductions in left ventricular volume.

Conclusion
In patients with LBBB, who were in sinus rhythm at enrolment, BIV pacing exceeding 90% was associated with a benefit of CRT-D in HF/death when compared with ICD patients. Furthermore, BIV pacing ≥ 97% was associated with an even further reduction in HF/death, a significant 52% reduction in death alone, and increased reverse remodelling. Clinical trials.gov identifier: NCT00180271.

Keywords
Cardiac resynchronization therapy • Left bundle branch block • Implantable cardioverter defibrillator • Biventricular pacing • Efficacy • Heart failure and death

Background
Implantation of a cardiac resynchronization therapy with a defibrillator (CRT-D) device improves survival and cardiac function in patients with left ventricular (LV) systolic dysfunction, prolonged QRS-duration, and mild-to-severe heart failure (HF).1–4 In recent years, there has been much emphasis on choosing the right patients for CRT-D implantation, as studies have found that certain patients

* Corresponding author. Tel: +1 5857565228, Fax: +1 5852735283, Email: annechristinehuth@hotmail.com

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do not benefit from a CRT-D. At the pinnacle of this are QRS characteristics, where studies have shown that the benefit of CRT-D is reserved for patients with a left bundle branch block (LBBB). 

It is generally believed that the beneficial effect of CRT-D when compared with implantable cardioverter defibrillator (ICD) is derived from biventricular (BIV) pacing of the ventricles, thus eliminating dysynchrony and improving cardiac function. The percentage of BIV pacing capture in the ventricles may be negatively influenced by a number of factors, including atrial tachyarrhythmias, premature ventricular complexes, and programming of the atrio-ventricular delay, giving way to the patient’s intrinsic conduction and thus reducing the percentage of BIV pacing. Previous studies have investigated the optimal level of BIV pacing percentage. Using arbitrarily chosen BIV pacing levels ranging from 85 to 98%, these studies found higher BIV pacing percentage to be associated with more pronounced CRT benefit, and that optimal CRT benefit was seen with a BIV pacing percentage as close to 100% as possible. 

Importantly, none of these studies incorporated ICD patients as a reference group. Therefore, the CRT-D efficacy threshold for beneficial BIV pacing percentage, when compared with ICD, remains unknown. Using the LBBB patients of the MADIT-CRT population, we sought to investigate the percentage of BIV pacing needed for a CRT-D device to be superior to an ICD device on the end-point of HF or death. We further aimed to evaluate the effect of BIV pacing on LV reverse remodelling and to determine which factors are associated with a high percentage of BIV pacing.

Methods

MADIT-CRT

From 22 December 2004 through 22 June 2009, the Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy (MADIT-CRT) trial randomized 1820 patients with mild HF, ischaemic (NYHA class I–II) or non-ischaemic cardiomyopathy (NYHA class II), depressed left ventricular ejection fraction (LVEF) (< 30%), and prolonged QRS complex (> 130 ms) in a 3:2 fashion for implantation with either a CRT-D or an ICD device. Patients were excluded if they were not in sinus rhythm at enrolment, if they had experienced atrial fibrillation within 1 month prior to enrolment, or if they had experienced a myocardial infarction, a percutaneous intervention or a coronary artery bypass graft surgery within 3 months prior to enrolment.11

Previous studies have shown that the beneficial effect of CRT-D is limited to patients with LBBB QRS morphology. 

Accordingly, the current study excluded patients who presented with non-LBBB (n = 539). Cardiac resynchronization therapy-defibrillator patients were excluded if data on BIV pacing were missing (n = 48), or if they were not in the DDD, DDR, DDI, or DDDR pacing mode (n = 14). The current study population consequently consisted of 1219 LBBB patients, who were implanted with either an ICD (n = 520) or a CRT-D (n = 699) device.

Biventricular pacing threshold

The average percentage of BIV pacing throughout the follow-up period was determined as the average percentage of LV pacing throughout the follow-up period, obtained from the last available interrogation before death or end of study.

The BIV pacing threshold for CRT-D efficacy was defined as the BIV pacing percentage with a risk of HF/death as similar as possible to the risk of HF/death in ICD patients. This was estimated by visual assessment of Kaplan–Meier plots, using CRT-D patients with different levels of BIV pacing from 88 to 100%, and testing each one percentage point increase in BIV pacing compared with a control group of ICD patients (results not shown). Thereby, we identified the BIV pacing level where the risk of HF/death in CRT-D patients was similar to the risk in ICD patients. This BIV pacing level was subsequently tested in multivariable Cox regression analyses adjusting for relevant factor associated with the endpoint of HF/death.

End-points

An independent HF and mortality committee adjudicated all HF and death events throughout the follow-up period. As previously described, the primary end-point of the MADIT-CRT study was a combined endpoint of hospitalization for HF events or death.

Accordingly, the end-point of HF/death was used to determine the BIV pacing efficacy threshold of CRT-D. The influence of BIV pacing percentage was subsequently tested on the secondary end-point of death alone, defined as all-cause mortality.

Echocardiographic measurements

A two-dimensional echocardiographic examination was performed before device implantation and during the 1-year follow-up visit to evaluate changes in LV and atrial volumes. Measurements were done according to the standard protocol by the American Society of Echocardiography. 

In the current study, paired echocardiographic measurements were available for 965 of 1219 (79%) patients, 443 of 520 (85%) ICD patients, and 522 of the 699 (75%) CRT-D patients. For the echocardiographic analysis, we excluded patients who crossed over to another device or had their device explanted before the 12 months echocardiogram (n = 23), leaving us with 942 of 1219 (77%) patients for the current analysis, 433 of 520 (83%) ICD patients, and 509 of 699 (73%) CRT-D patients.

Statistics

Baseline characteristics were compared between the groups using χ² and Fisher’s exact test for dichotomous variables and the Kruskal–Wallis test for continuous variables. The cumulative probabilities of the end-points were displayed by the method of Kaplan–Meier using the log-rank test to analyse differences in the risk between groups. Event rates per 100 patient-years were calculated by dividing the total sum of events, by the sum of follow-up years, and multiplied by 100. Within the CRT-D population, negative binomial regression was used to test for trend between increasing BIV pacing and event rates of HF/death. The Cochran–Armitage trend test was used to test for trend between increasing BIV pacing and the crude mortality rate. A multivariable Cox proportional hazards regression model for the end-point of HF/death was created in the CRT-only population using best subset regression to determine the variables related to the end-point. When setting the limit for entry in to the model at P < 0.05, the following variables were included: prior myocardial infarction, hospitalizations before enrolment, and baseline glomerular filtration rate (GFR) (mL/min/1.73 m²), LVEF (%), and QRS width (ms).
This model was subsequently applied to test the BIV pacing efficacy threshold for CRT-D when compared with ICD, as found in Kaplan–Meier plots. The same multivariable Cox proportional hazard model was used to estimate the risk of death alone. If patients crossed over during the follow-up and their device was explanted or changed to another device, the patients were censored from the analyses at the time of cross-over.

Hazard ratios (HR) with their 95% confidence intervals (CI) and two-sided P-values are reported.

Reverse remodelling was evaluated as mean reductions with standard deviations, and as dichotomized variables of left ventricular end-systolic volume (LVESV) reduction from baseline to 1 year. Comparisons between groups were conducted by Student’s t-tests for continuous variables, and by χ² or Fisher’s exact tests for dichotomized variables. In the echocardiographic analyses, patients were excluded if they had a device change or explant within the first year.

Within the 699 CRT-D patients, logistic regression was utilized to identify factors associated with high BIV pacing, defined as BIV ≥ 97%, reporting odds ratios with 95% CI and two-sided P-values. Best subset regression was used to identify factors predicting high BIV pacing, setting the limit for entry into the model at P < 0.05. A C-statistic for the model is reported.

A two-tailed P-value < 0.05 was considered statistically significant. Analyses were performed using SAS statistical software 9.3 version (SAS Institute, Cary, NC, USA).

Results

Biventricular pacing threshold

The distribution of BIV pacing percentage in the 699 CRT-D LBBB patients was skewed, with most patients receiving a high percentage of BIV pacing (Figure 1).

The threshold of BIV pacing where CRT-D was not superior to ICD on the end-point of HF/death was estimated by visual assessment of Kaplan–Meier plots using CRT-D patients with different levels of BIV pacing with ICD patients as a control group. The BIV pacing percentage threshold where the risk of HF/death was as similar to ICD as possible was determined to be BIV pacing ≤ 90% (Figure 2A).

As shown in Figure 2A, the Kaplan–Meier plot demonstrates decreasing risk of HF/death with increasing percentage of BIV pacing, with BIV pacing ≤ 90% being non-superior to an ICD device, and the groups CRT-D BIV 91–96% and CRT-D BIV ≥ 97%, being superior to an ICD device. This resulted in the creation of four groups: CRT-D BIV ≤ 90% (n = 80, 11.4%), CRT-D BIV 91–96% (n = 134, 19.2%), CRT-D BIV ≥ 97% (n = 485, 69.4%), and ICD patients (n = 520). As it was our goal to determine the threshold of BIV pacing, where CRT-D was not associated with a benefit on HF/death, we created groups based on the outcome, and thus, no pre-specification of BIV pacing groups was employed.

Table 1 shows the baseline characteristics of ICD patients and the three groups of CRT-D BIV pacing. With increasing BIV pacing percentage the QRS width, GFR, and frequency of ACE/ARB usage increased, whereas the baseline age decreased.

Cardiac resynchronization therapy with a defibrillator efficacy and biventricular pacing

During a mean follow-up of 3.1 ± 1.3 years, 267 out of 1219 (22%) LBBB patients reached the primary end-point of HF/death, with 165 out of 520 (31.7%) ICD-LBBB patients and 102 out of 699

Figure 1  Distribution of biventricular pacing in cardiac resynchronization therapy-defibrillator patients with left bundle branch block QRS morphology. Bar graph showing the skewed distribution of biventricular pacing percentage in the study.
CRT-D-LBBB patients \( (P < 0.001) \). For the end-point of death alone, 72 out of 1219 (6%) LBBB patients died, with 36 out of 520 (6.9%) ICD-LBBB patients and 36 out of 699 (5.2%) CRT-D-LBBB patients \( (P = 0.220) \).

With increasing BIV pacing percentage, we observed a steady decrease in the event rates per 100 patient-years for the end-point HF/death (Figure 3), with a significant test for trend within the CRT-D population \( (P \leq 0.001) \).

Correspondingly, in multivariable Cox regression analysis, we observed a 6 and 10% statistically significant relative risk reduction in HF/death and death alone, respectively, for each one percentage point increase in BIV pacing (Table 2).

**Cardiac resynchronization therapy with a defibrillator efficacy**

**Heart failure/death**

Among the CRT-D patients, BIV pacing \( \leq 90\% \) was associated with similar risk of HF/death when compared with ICD (Figure 2A). This was confirmed in multivariable Cox hazard regression analyses,
adjusting for baseline LVEF, QRS width, and GFR along with prior myocardial infarction and hospitalizations prior to enrolment (Table 2). When compared with ICD patients, BIV pacing 91–96% and BIV pacing ≥97% were associated with significantly reduced risk of HF/death when compared with CRT-D BIV pacing 91–96% (Table 2).

All-cause mortality
As shown in Figure 2B, the threshold for BIV pacing where CRT-D was superior to ICD was different for the end-point of all-cause mortality.
This was confirmed in multivariable analysis, with no significant difference between ICD patients and CRT-D BIV ≤ 90%, CRT-D BIV 91–96%, with both HR > 1 (Table 2). Cardiac resynchronization therapy with a defibrillator BIV ≥ 97% was associated with a significant 52% reduced risk of death alone, when compared with ICD patients, and a 63% risk reduction when compared with CRT-D patients with BIV pacing < 97% (Table 2).

**Biventricular pacing and reverse remodelling**

Left ventricular reverse remodelling was overall high in this LBBB population of CRT-D patients, with a mean LVESV reduction of 35.2 ± 14.5%. As shown in Figure 4, a high echocardiographic CRT-D response was strongly associated with the level of BIV pacing. However, interestingly, there was no significant difference between the BIV ≤ 90% and BIV 91–96% (LVESV reduction:

| Table 2 | The influence of biventricular pacing on cardiac resynchronization therapy efficacy compared with ICD on outcomes |

<table>
<thead>
<tr>
<th></th>
<th>HF/death</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Events/patients</td>
<td>Hazard</td>
<td>95% confidence</td>
<td>P-value</td>
<td>Events/patients</td>
<td>Hazard</td>
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<td>CRT-D vs. ICD</td>
<td></td>
<td>(total: 267/1219)</td>
<td>ratio</td>
<td>intervals</td>
<td></td>
<td>(total: 72/1219)</td>
<td>ratio</td>
</tr>
<tr>
<td>BIV ≤ 90%</td>
<td>19/80</td>
<td>0.78</td>
<td>0.47–1.30</td>
<td>0.344</td>
<td>9/80</td>
<td>1.89</td>
<td>0.87–4.11</td>
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<td>BIV 91–96%</td>
<td>29/134</td>
<td>0.63</td>
<td>0.42–0.94</td>
<td>0.024</td>
<td>10/134</td>
<td>1.04</td>
<td>0.51–2.12</td>
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<td>BIV ≥ 97%</td>
<td>54/485</td>
<td>0.32</td>
<td>0.23–0.44</td>
<td>&lt;0.001</td>
<td>17/485</td>
<td>0.48</td>
<td>0.26–0.87</td>
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<tr>
<td>Within the CRT-D groups</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>BIV ≥ 97% vs. BIV &lt; 97%</td>
<td>0.48</td>
<td>0.32–0.72</td>
<td>&lt;0.001</td>
<td></td>
<td>0.37</td>
<td>0.19–0.73</td>
<td>0.004</td>
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<tr>
<td>BIV by 1% increase</td>
<td>0.94</td>
<td>0.90–0.97</td>
<td>0.001</td>
<td></td>
<td>0.90</td>
<td>0.85–0.95</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*The risks of HF/death and death alone were estimated in different models using different reference groups. The top five rows were derived from a single multivariable Cox model for each end-point, using ICD patients as a reference group, whereas the risk within the CRT-groups, used BIV ≤ 97% as a reference group. All models were adjusted for prior myocardial infarction, hospitalizations before enrolment and baseline glomerular filtration rate (mL/min/1.73 m²), left ventricular ejection fraction (%), and QRS width (ms). BIV, biventricular pacing; ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy with defibrillator.

*BIV pacing as a continuous measure was determined in a model only including CRT-D patients, excluding patients with BIV pacing <80%.
Factors associated with high biventricular pacing

A logistic regression model was used to identify baseline factors associated with high BIV pacing, defined as BIV pacing ≥97%. QRS prolongation ≥150 ms, no history of ventricular arrhythmias, blood urea nitrogen (BUN) <25 mg/dL, and a pre-implantation 24-h Holter monitoring with <10 ectopies/h were all associated with an increased probability of achieving high percentage of BIV pacing. Their respective odds ratios are listed in Table 3.

Discussion

In this study, we investigated the efficacy of CRT-D compared with ICD based on different levels of BIV pacing percentage. At BIV pacing <90%, the risk of HF/death was similar in the CRT-D- and ICD-treated patients. Increasing BIV pacing percentage was associated with a decrease in the risk of HF/death and an increase in LV reverse remodelling. Consistently, every 1% increase in BIV pacing percentage was associated with a 6% risk reduction in HF/death and a 10% risk reduction in death alone.

Our results are consistent with those of Koplan et al.,7 Hayes et al.,8 and Gasparini et al.,10 who found decreasing risk of HF/death and death with increasing BIV pacing. However, these studies only included CRT patients and defined their BIV pacing groups from arbitrary values found by either pre-specification or median/quartile values of BIV pacing. In the current study, we established an efficacy threshold for BIV pacing where CRT-D implantation had a similar effect on HF/death as an ICD device. We found that LBBB patients, who are in sinus rhythm at enrolment, require a BIV pacing percentage greater than 90% in order for CRT-D to be more beneficial than an ICD device. Furthermore, we observed a decrease in the risk of HF/death with increasing BIV pacing percentage, which is consistent with findings from previous studies.7,8

Even on the end-point of death alone we observed a 52% risk reduction in CRT-D patients with BIV ≥97%, when compared with

Table 3

Factors associated with high biventricular pacing

<table>
<thead>
<tr>
<th>Odds ratio: BIV ≥97% vs. BIV &lt;97%</th>
<th>95% confidence intervals</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectopy ≤10/h prior to implantation</td>
<td>3.98</td>
<td>2.71–5.84</td>
</tr>
<tr>
<td>No history of ventricular arrhythmias</td>
<td>2.04</td>
<td>1.05–3.95</td>
</tr>
<tr>
<td>QRS ≥150 ms</td>
<td>1.84</td>
<td>1.25–2.71</td>
</tr>
<tr>
<td>Blood urea nitrogen &lt;25 mg/dL</td>
<td>1.47</td>
<td>1.00–2.16</td>
</tr>
</tbody>
</table>

Derived from a single multivariable logistic regression model using a dichotomized CRT-D BIV pacing variable above or equal to 97%, with C-statistics = 0.71. Ectopy, atrial + ventricular ectopy, based on a 24 h Holter monitoring; BIV, biventricular pacing.

30.0 ± 18.7 vs. 31.1 ± 12.3, P = 0.718) or in any of the LVESV percentage reduction groups (Figure 4). Significant differences were evident between BIV 91–96% and BIV ≥97% both in the mean LVESV change (31.1 ± 12.3 vs. 36.8 ± 14.1, P < 0.001); and in the percentage of patients who achieved LVESV reductions of 30% or more (P ≤ 0.01).

Factors associated with high-biventricular pacing

A logistic regression model was used to identify baseline factors associated with high BIV pacing, defined as BIV pacing ≥97%. QRS prolongation ≥150 ms, no history of ventricular arrhythmias, blood urea nitrogen (BUN) <25 mg/dL, and a pre-implantation 24-h Holter monitoring with <10 ectopies/h were all associated with an increased probability of achieving high percentage of BIV pacing. Their respective odds ratios are listed in Table 3.

Discussion

In this study, we investigated the efficacy of CRT-D compared with ICD based on different levels of BIV pacing percentage. At BIV pacing <90%, the risk of HF/death was similar in the CRT-D- and ICD-treated patients. Increasing BIV pacing percentage was associated with a decrease in the risk of HF/death and an increase in LV reverse remodelling. Consistently, every 1% increase in BIV pacing percentage was associated with a 6% risk reduction in HF/death and a 10% risk reduction in death alone.

Our results are consistent with those of Koplan et al.,7 Hayes et al.,8 and Gasparini et al.,10 who found decreasing risk of HF/death and death with increasing BIV pacing. However, these studies only included CRT patients and defined their BIV pacing groups from arbitrary values found by either pre-specification or median/quartile values of BIV pacing. In the current study, we established an efficacy threshold for BIV pacing where CRT-D implantation had a similar effect on HF/death as an ICD device. We found that LBBB patients, who are in sinus rhythm at enrolment, require a BIV pacing percentage greater than 90% in order for CRT-D to be more beneficial than an ICD device. Furthermore, we observed a decrease in the risk of HF/death with increasing BIV pacing percentage, which is consistent with findings from previous studies.7,8

Even on the end-point of death alone we observed a 52% risk reduction in CRT-D patients with BIV ≥97%, when compared with

Figure 4 Echocardiographic reverse remodelling and biventricular pacing. Bar graph depicting the percentage of patients within each biventricular-pacing groups that achieve left ventricular end-systolic volume volume reductions >30, >35, and >40% from baseline to 1-year follow-up. For all levels of left ventricular end-systolic volume % reduction, there was a highly significant (P < 0.001) difference when comparing all four groups and within the cardiac resynchronization therapy-defibrillator groups.
ICD patients and an even further risk reduction when comparing with CRT-D patients with BIV pacing < 97%, which further emphasizes the importance of achieving high BIV pacing, even in a LBBB population of patients with a known high response to CRT-D.

Cardiac resynchronization therapy-defibrillator (CRT-D) patients who achieved BIV pacing ≥ 97% also exhibited a significantly higher level of LV reverse remodelling. Previous studies on BIV pacing did not include assessment of echocardiographic measurements, and this study shows a clear association between level of BIV pacing and CRT-D echocardiographic response. It has been shown that LBBB patients are the best responders to CRT-D treatment; however, we show that achieving high BIV pacing percentage can even further improve echocardiographic response, with >40% of all patients with BIV ≥ 97% achieving >40% reduction in LVESV volume from baseline to 1 year. Even though we do not find a difference in the risk of HF/death between CRT-D patients and patients with BIV ≤ 90%, there was still a significantly greater LV reverse remodelling in this BIV pacing group when compared with ICD patients. This confirms findings of previous studies, showing that a rather high level of reverse remodelling is required to see an effect on end-points such as HF/death and/or all-cause mortality.

Several hypotheses, related to cellular mechanisms, arrhythmias, and clinical optimization, could be employed to explain why even minimal changes in BIV pacing percentage results in significant changes in outcomes and reverse remodelling.

Kirk et al. recently provided strong evidence that CRT alters myocardial function on a cellular level. In a canine heart, they showed that in dysynchronous hearts, CRT activates the glycogen synthase kinase 3β, mediating recovery of the myofilament function, which results in increased Ca2+ sensitivity, known to be the determinant factor for contractile function of the myocytes. One could speculate that only a minimal increase in BIV pacing percentage could result in significant changes in the glycogen synthase kinase 3β activation, which in turn would lead to reductions in HF/death and increased reverse remodelling.

Furthermore, one could speculate that patients in the higher spectrum of BIV pacing are subject to better monitoring by their physician, with regular optimizations in regards to both CRT-D programming to optimize BIV pacing percentage, but also in regards to medication.

Finally, patients with BIV pacing 91–96%, might have had more episodes with low BIV pacing, maybe due to arrhythmias, which might have resulted in decompensation and HF hospitalization.

When investigating factors associated with high BIV pacing percentage in the CRT-D population, we found that patients with preserved kidney function, longer QRS durations, no history of ventricular tachyarrhythmia, and minimal ectopy burden on pre-implantation Holter were more likely to achieve BIV pacing ≥ 97%. These factors are consistent with factors other studies have found to be associated with a better CRT-D outcome. The fact that low ectopy burden and no prior ventricular tachyarrhythmias were both highly associated with increased probability of achieving high BIV pacing percentage is consistent with the notion that these two factors might affect BIV pacing capture, and with previous findings. Interestingly, the presence or absence of history of atrial tachyarrhythmias before enrolment was not a factor associated with higher likelihood of achieving high BIV pacing. Furthermore, it did not enter the model for estimating risk of HF/death. As predefined in the MADIT-CRT trial, all patients in the MADIT-CRT trial had to be in sinus rhythm at enrolment and could not have had any atrial tachyarrhythmia within 1 month prior to enrolment. This eliminated all patients with permanent or persistent atrial fibrillation. These findings are consistent with results from a recently published study from the MADIT-CRT population, showing that intermittent atrial tachyarrhythmia does not result in an attenuated effect on CRT-D efficacy. Furthermore, we have previously shown that percentage of patients who achieved BIV pacing ≥ 92% was similar regardless of both prior history of intermittent atrial tachyarrhythmia and in-trial intermittent atrial tachyarrhythmia.

Clinical impact

Previous studies have shown high CRT-D efficacy with increasing BIV pacing. This study established a BIV pacing threshold at which the implantation of a CRT-D device is superior to an ICD device. Furthermore, our study population was limited to patients in sinus rhythm with LBBB QRS morphology which is in accordance to the current class I guideline indications for CRT-D implantation. Even though the apparent threshold for CRT-D efficacy seems to be a BIV pacing percentage > 90%, we observed further highly significant risk reductions in both HF/death and all-cause mortality, along with more pronounced reverse remodelling, with increasing BIV pacing.

Our study further emphasizes the importance of achieving very high BIV pacing (> 97%) in CRT-D patients, who are in sinus rhythm at the time of CRT-D implantation. Measures for optimizing BIV pacing percentage in terms of optimizing pharmacological therapy, AV-delay and minimizing atrial, and ventricular tachyarrhythmias along with ectopy burden, should be made when physicians encounter a CRT-D patient with < 97% BIV pacing.

Limitations and strengths

In the current study, information on average percentage of BIV pacing throughout the follow-up was derived from the last interrogation strip in the study or prior to death, as we did not have information on BIV pacing at different time points throughout the study. Our patient population consisted solely of patients with HF symptoms corresponding to NYHA class I/II, and therefore the current results cannot be extrapolated to patients with more severe HF. Further studies are needed to establish the BIV pacing threshold for CRT-D efficacy in these patients. Furthermore, the results from this study may not be generalizable to other populations, due to the potential for overfitting the models, by utilizing best subset regression to identify adjustment variables. Given the retrospective nature of the data and analyses, it is difficult to establish non-inferiority; therefore, the results should be interpreted in that context.

Conclusion

In NYHA class I and II, HF patients with LBBB QRS morphology, who were in sinus rhythm at enrolment, BIV pacing percentages that exceeds 90% are associated with reduction in the risk of HF/death, when compared with an ICD control population. Further increasing BIV pacing percentage was associated with increased reverse remodelling and decreased risk of HF/death. Biventricular pacing ≥ 97% was associated with significant 52% reduction in all-cause mortality. Physicians should be aware of patients with suboptimal BIV pacing to...
implement preventive and optimizing measures to improve the outcome and prognosis in these patients.

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No other potential conflict of interest relevant to this article was reported.

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