Optimization of Repolarization during Biventricular Pacing: A New Target in Patients with Biventricular Devices?

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Background: Evaluation of repolarization during sequential biventricular pacing.

Methods: Patients with biventricular devices, and left ventricular leads placed to the basal part of lateral left ventricular wall were enrolled. QRS, QTc, JTc, and corrected Tpeak-Tend intervals were compared during sequential biventricular, left ventricular, and right ventricular pacing.

Results: Five patients with nonischemic and five with ischemic cardiomyopathy due to anterior myocardial infarction were enrolled. No correlation was observed between values of repolarization among patients. The optimal values of repolarization were significantly different from values of echocardiographically guided hemodynamic optimization. Two patients with biventricular pacing-induced ventricular fibrillation were successfully treated by reprogramming of V-V delay according to interventricular delay resulting in shorter Tpeak-Tend interval, although delayed effect of amiodarone in one of these patients cannot be ruled out.

Conclusions: Patients with biventricular devices may be prone to development of ventricular arrhythmias depending on programmed V-V interval. We suggest that optimization of repolarization may be performed in patients with biventricular pacemakers in the absence of backup ICD and those with frequent episodes of ventricular tachyarrhythmias, although this finding deserves further study.

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Cardiac resynchronization therapy (CRT) has been established as adjunctive therapeutic tool for patients with drug refractory heart failure. Symptomatic improvement and decrease in frequency of hospitalizations has been reported in patients with biventricular pacemakers. But it is still not well established, whether CRT reduces or increases susceptibility to potentially life-threatening arrhythmias. Both decrease and increase in frequency of ventricular arrhythmias were reported following initiation of biventricular pacing.^{1–5} In this study, we measured different repolarization indices during sequential biventricular, right ventricular endocardial, left ventricular epicardial pacing, and

sinus rhythm in patients with implanted biventricular pacemakers and ICDs.

METHODS

Both patients with ischemic and nonischemic cardiomyopathy were screened. To rule out possible effects of left ventricular pacing sites, only patients with epicardial leads implanted at the basal segments of lateral left ventricular wall were enrolled into the study. Location of the tip of LV lead was evaluated with conventional fluoroscopic examination. Localization of previous myocardial infarction could affect indices of repolarization.

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For this reason, only patients with previous anterior myocardial infarction were enrolled into the study.

Hemodynamic echo-guided optimization was performed according to best aortic tissue velocity integral (TVI) value, and optimal programmed V-V delays were noted for each patient.

Twelve-lead electrocardiograms were recorded in the cardiac electrophysiology (EP) laboratory setting with PC-controlled EP system (EP-Tracer/70, Cardiotek, Maastricht, the Netherlands).

QRS duration, QT, QTc, JT, JTc, Tpeak-Tend, and corrected Tpeak-Tend intervals were measured and calculated during sinus rhythm, right ventricular endocardial, left ventricular epicardial, simultaneous, and sequential biventricular pacing. Each pacing was maintained at a constant rate, above sinus rhythm for 5 minutes. QRS, QT, JT, and Tpeak-Tend intervals were measured during the last 10 seconds of each 5-minute pacing.

RESULTS

Ten eligible patients were enrolled. Five of them had nonischemic (patients 1–5) and another five had ischemic cardiomyopathy (patients 6–10). All of the study patients were CRT-responders. Left ventricular ejection fraction was not different between patients with ischemic and nonischemic cardiomyopathy (15 ± 5.6 vs 17 ± 8.3). Indexes of repolarization were measured for each study patient and these are presented in Tables 1–4.

There was no correlation among patients in respect to QRS width, shortest QTc, JTc, and corrected Tpeak-Tend intervals. Values varied significantly in the same patients at different programmed values of V-V delays. The shortest and longest values obtained for each patient are presented for comparison in Table 5. Comparison of programmed V-V delays in respect to optimal aortic TVI, narrowest QRS, shortest QTc, JTc, and corrected Tpeak-Tend intervals are presented in Table 6.

Two of the patients (patients 1 and 7), had frequent episodes of ventricular fibrillation following implantation of biventricular ICD. None of them had any episode of ventricular tachycardia or fibrillation prior to initiation of biventricular pacing. Note that for patient 7, best aortic TVI value was achieved during programmed left ventricular activation, which preceded right ventricular activation by 60 msec (LV60RV), while his narrowest QRS duration, and shortest QTc, JTc, and corrected Tpeak-Tend intervals were measured during simultaneous biventricular pacing (LV0RV) or when right ventricular activation preceded left ventricular activation by 20 msec (RV20LV). The same discrepancy was observed in patient 1. Patient 7 continued to develop frequent episodes of arrhythmia, despite intravenous loading dose of amiodarone. Abolishment of episodes of ventricular fibrillation was achieved by programming V-V delay according to optimal (shortest) Tpeak-Tend interval, although we cannot rule out possible delayed effect of amiodarone.

Table 1. QRS Duration Measured during Sinus Rhythm, Right Ventricular Endocardial, Left Ventricular Epicardial, and Different Modes of Sequential Biventricular Pacing

Pt. No.	QRS (msec)											
	SR	RV endo	LV epi	LV80RV	LV60RV	LV40RV	LV20RV	LV0RV	RV20LV	RV40LV	RV60LV	RV80LV
1	186	192	207	198	216^b	195	171	165^a	177	177	186	192
2	99	159	186^b	183	165	147	147	129^a	135	150	153	168
3	123	207	174	180	162	174	165	156	153^a	177	183	186^b
4	153	213	189	180	180	171	153	147^a	156	165	183	195
5	147	228	228	234^b	228	207	189	177	171^a	180	195	216
6	183	198	159	147	156	153	153	141^a	141^a	162	186^b	180
7	228	294	312^b	237	210	207	204^a	204^a	207	227	228	240
8	198	288	216^a	252	282	246	246	240	246	246	258	282^b
9	147	150	150	162	156	156	144^a	168	162	144^a	162	186^b
10	NA	216	210^b	210	192	180	161	156	126^a	126^a	162	192

Shortest and longest QRS for each of the patients are presented as bold numerical values (^ashortest and ^blongest). Values obtained during sinus rhythm and right ventricular pacing are presented only for comparison. NA = not applicable.

Table 2. QTc Intervals Measured during Sinus Rhythm, Right Ventricular Endocardial, Left Ventricular Epicardial, and Different Modes of Sequential Biventricular Pacing

Pt. No.	QTc Interval (msec)											
	SR	RV endo	LV epi	LV80RV	LV60RV	LV40RV	LV20RV	LV0RV	RV20LV	RV40LV	RV60LV	RV80LV
1	530	520	570^b	540	535	520	480^a	490	485	489	489	530
2	420	490	530^b	495	460	460	490	450^a	460	470	495	530^b
3	430	500	510^b	500	465	470	430^a	440	440	470	470	485
4	475	500	475	465	450	460	450^a	460	470	475	480	495^b
5	530	550	655^b	595	535	510	500	490^a	520	520	520	570
6	520	535	530^b	450	515	525	480	445^a	490	490	515	520
7	515	620	875^b	660	620	560	515	480^a	570	610	665	650
8	650	625	580	580	625	625^b	590	580	560^a	580	600	610
9	517	514	535	550	564	571	550	492^a	578^b	542	578^b	571
10	NA	564	585^b	564	557	535	478	485	457^a	457^a	492	535

Shortest and longest QTc interval for each of the patients is presented as bold numerical value (^ashortest and ^blongest). Values obtained during sinus rhythm and right ventricular pacing are presented only for comparison.

NA = not applicable.

DISCUSSION

Some data suggest that CRT may reduce the risk of arrhythmias. However, proarrhythmia from CRT has also been reported. First, CRT has been associated with an increase in or new onset of monomorphic VT possibly related to site of stimulation with respect to site of infarction.¹⁻⁶ Second, CRT has appeared causative for polymorphic VT/VF as well, perhaps related to altered repolarization, including transmural dispersion of repolarization.^{1,7} However, some studies have shown no difference in dispersion of repolarization and microvolt T-wave alternans^{8,9} and even decrease

in ECG markers of ventricular dispersion of repolarization was reported¹⁰ in CRT recipients. Also several studies reported decrease in the frequency of VT/VF after initiation of biventricular pacing.¹¹ Theoretically, decrease in the frequency of ventricular arrhythmia in patients with CRT may be related to decrease in sympathetic tone secondary to improve in cardiac output, reduced wall stress, and electromechanical dyssynchrony, but findings of our study suggest that, repolarization-guided optimization of V-V delay may also decrease frequency of ventricular arrhythmias in patients with heart failure.¹²⁻¹⁵

Table 3. JTc Intervals Measured during Sinus Rhythm, Right Ventricular Endocardial, Left Ventricular Epicardial, and Different Modes of Sequential Biventricular Pacing

Pt. No.	JTc interval (msec)											
	SR	RV endo	LV epi	LV80RV	LV60RV	LV40RV	LV20RV	LV0RV	RV20LV	RV40LV	RV60LV	RV80LV
1	310	300	320^b	320	280^a	280^a	280^a	310	280	305	295	300
2	290	280	275	265^a	270	285	290	285	275	275	280	320^b
3	300	295	335^b	320	305	300	260^a	285	285	300	295	300
4	280	270	260	245	240^a	265	285	285	300^b	295	280	290
5	380	320	425^b	360	300^a	300^a	305	305	335	330	330	330
6	310	315	325	315	335	340^b	315	300	315	250^a	305	315
7	280	330	552^b	435	400	345	320	300^a	370	390	420	395
8	435	320	340^b	300^a	320	340^b	310	310	300^a	305	310	310
9	332	321	342^a	357	364	378	385	350	400^b	378	385	350
10	NA	326	278^a	307	321^b	321	285	314	285	314	300	321^b

Shortest and longest JTc interval for each of the patients is presented as bold numerical value (^ashortest and ^blongest). Values obtained during sinus rhythm and right ventricular pacing are presented only for comparison.

NA = not applicable.

Table 4. Corrected Tpeak-Tend Intervals Measured during Sinus Rhythm, Right Ventricular Endocardial, Left Ventricular Epicardial, and Different Modes of Sequential Biventricular Pacing

Pt. No.	Corrected Tpeak-Tend Interval (msec)											
	SR	RV endo	LV epi	LV80RV	LV60RV	LV40RV	LV20RV	LV0RV	RV20LV	RV40LV	RV60LV	RV80LV
1	162	137	181^b	151	144	129	107^a	137	114	129	125	133
2	90	167	144	110	116	125	120	101^a	112	120	148	175^b
3	108	153	114	99	84^a	84^a	99	120	114	129	132	147^b
4	198	212	188	171	158^a	171	171	178	185	182	209^b	205
5	186	159	192^b	159	123^a	123^a	129	132	141	135	132	153
6	185	169	140	120	133	146^b	114	94^a	130	124	130	140
7	144	150	354^b	168	160	144	120^a	120^a	150	174	198	192
8	143	300	208^a	260	267	280	254	254	254	287	300	306^b
9	164	171	114^a	128	164	157	121	142	200^b	178	192	164
10	NA	178	164	171^b	164	128	121	121	107^a	135	121	164

Shortest and longest Tpeak-Tend interval for each of the patients is presented as bold numerical value (^ashortest and ^blongest). Values obtained during sinus rhythm and right ventricular pacing are presented only for comparison. NA = not applicable.

Biventricular pacing was reported to have minimal effects on parameters of ventricular repolarization, when compared to left ventricular epicardial pacing.¹⁶ But we have observed that individual patient may have shortest Tpeak-Tend interval during left ventricular pacing.

Previously, effect of biventricular and left ventricular pacing on QT interval was investigated as an index of ventricular repolarization. But in our opinion QT and QTc interval should not be considered as a marker of repolarization in patients with implantable pacemakers. This point of view was supported by observation of other investigators and is related to fact that pacing-induced prolongation of ventricular depolarization frequently results in prolongation of QT interval, making it inaccurate parameter of ventricular repolarization.^{1,7,17,18} Absence of correlation between pacing-induced prolongation of QT interval and torsades de pointes, in addition, supports the above-mentioned effect.¹⁹ We suggest, that measurement of corrected JT and preferably Tpeak-Tend interval may be more appropriate in this setting.

Previous studies, which aimed investigation of repolarization abnormalities in patients with biventricular pacemakers, performed comparison of various indices of repolarization obtained during sinus rhythm, right ventricular endocardial, left ventricular epicardial, and simultaneous biventricular pacing modes. But there was lack of data obtained during sequential biventricular pacing.

In this study, we proposed that different programmed V-V intervals in the same patient may

result in deterioration or improvement of repolarization abnormalities. For this reason, we enrolled patients with both ischemic and nonischemic cardiomyopathy, with left ventricular leads implanted to the basal part of lateral left ventricular wall (nine of them were implanted percutaneously via branches of coronary sinus and one was implanted with minithoracotomy in patient 10). Patients with ischemic cardiomyopathy, all had previous anterior myocardial infarction. This strict selection method was performed to avoid potential effect of pacing site and localization of infarction on indices of ventricular repolarization. At the end of study, we have observed no correlation between optimal echo-guided V-V delays, optimal QTc, JTc, and Tpeak-Tend intervals. This surprising finding suggests that individual patient may require optimization of repolarization indices to avoid occurrence of PMVT or VF, as it was observed in patients 1 and 7. However, possible delayed effect of amiodarone could contribute to the abolishment of VF episodes in patient 7.

Echocardiographic optimization of both A-V and V-V delays in patients with biventricular pacemakers was frequently performed to achieve best hemodynamic response and clinical improvement. Results of our study suggest that, not only echocardiographic optimization, but also optimization of repolarization may be performed in selected group of patients. Taking into account the fact that optimization of repolarization is a time-consuming method, it may be difficult to apply this technique to all patients following implantation of

Table 5. Shortest and Longest Values of Repolarization Measured at Different Programmed V-V Delays are Presented for Comparison

Pt. No.	Shortest QTc (msec/V-V delay)	Longest QTc (msec/V-V delay)	Shortest JTc (msec/V-V delay)	Longest JTc (msec/V-V delay)	Shortest Tp-Te (msec/V-V delay)	Longest Tp-Te (msec/V-V delay)
1	480/LV20RV	570/LVepi	280/LV20RV and LV40RV and LV60RV and LV80RV	320/LVepi	107/LV20RV	181/LVepi
2	450/LV0RV	530/LVepi and RV80LV	265/LV80RV	320/RV80LV	101/LV0RV	175/RV80LV
3	430/LV20RV	510/LVepi	260/LV20RV	335/LVepi	84/LV40RV and LV60RV	147/RV80LV
4	450/LV20RV	495/RV80LV	240/LV60RV	300/RV20LV	158/LV60RV	209/RV60LV
5	490/LV0RV	655/LVepi	300/LV40RV and LV60RV	425/LVepi	123/LV40RV and LV60RV	192/LVepi
6	445/LV0RV	530/LVepi	250/RV40LV	340/LV40RV	94/LV0RV	146/LV40RV
7	480/LV0RV	875/LVepi	300/LV0RV	552/LVepi	120/LV0RV and LV20RV	208/LVepi
8	560/RV20LV	625/LV40RV	300/LV80RV and RV20LV	340/LVepi and LV40RV	208/LVepi	306/RV80LV
9	492/LV0RV	578/RV20LV and RV60LV	342/LVepi	400/RV20LV	114/LV epi	200/RV20LV
10	457/RV20LV and RV40LV	585/LVepi	278/LVepi	321/LV60RV	107/RV20LV	171/LV80RV

Table 6. Optimal Values of Echo-Guided V-V Delay are Compared to Interventricular Delays, which Result in Narrowest QRS, and Shortest QTc, JTc, and Tpeak-Tend Intervals

Patient No.	Optimal Echo-Guided V-V Delay	Optimal V-V Delay for QRS Width	Optimal QTc Interval	Optimal JTc Interval	Optimal Corrected Tpeak-Tend
1	LV0RV	LV0RV	LV20RV	LV20RV LV40RV LV60RV RV20LV	LV20RV
2	LV0RV	LV0RV	LV40RV LV60RV LV80RV	LV60RV	LV0RV
3	LV0RV	RV20LV	LV20RV	LV20RV	LV40RV LV60RV
4	LV0RV	LV20RV	LV20RV	LV60RV	LV60RV
5	LV0RV	RV20LV	LV0RV	LV40RV LV60RV	LV40RV LV60RV
6	LV0RV	LV0RV RV20LV	LV0RV	RV40LV	LV0RV
7	LV60RV	LV0RV	LV0RV	LV0RV	LV0RV LV20RV
8	LVP only	LVP only	LVP only LV0RV LV80RV	LV80RV RV20LV	LVP only
9	LV0RV	LV20RV RV40LV	LV0RV	LVP only	LVP only
10	LV0RV	RV20LV RV40LV	RV20LV RV40LV	LVP only	RV20LV

biventricular devices. Another important aspect is presence of discrepancy between echo-guided and repolarization-guided optimal V-V delays. Thus, routine optimization of repolarization will result in increased number of nonresponders. In our opinion, patients with biventricular pacemakers (not ICDs) and those with frequent episodes of ventricular tachyarrhythmias should undergo optimization of repolarization indices and simultaneous echocardiographic assessment. In patients with frequent ventricular tachyarrhythmias, V-V values should be programmed according to optimal Tpeak-Tend interval. Otherwise in patients without back-up ICD therapy, V-V delays should be programmed to values, which result in shortest Tpeak-Tend intervals and TVI values, which are better than those obtained during sinus rhythm. However, all of these above-presented suggestions deserve further investigation. Additionally, we would like to remind that optimal A-V and V-V delays are not stable and tend to change over time. So, results of this study do not provide us with information about stability of repolarization values over long periods of time.

STUDY LIMITATION

The main limitation of this study is small number of patients. However, we tried to exclude possible effect of lead position and infarct location on values of ventricular repolarization. Another important limitation is absence of proof that just reprogramming of V-V delay alone will always result in termination of CRT-related ventricular arrhythmias.

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