Left Ventricular Lead Electrical Delay Is a Predictor of Mortality in Patients With Cardiac Resynchronization Therapy

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Background—Electric left ventricular lead position, assessed by the electric delay from the beginning of the QRS complex to the local LV electrogram (QLV), was found in previous studies to be a strong predictor of short-term response to cardiac resynchronization therapy. We hypothesized that suboptimum electric position of the left ventricular lead is associated with an excess of heart failure events and mortality.

Methods and Results—We analyzed the clinical outcome of patients with left bundle branch block or intraventricular conduction delay treated with cardiac resynchronization therapy at our institution during 9 years. Baseline clinical characteristics, QLV/QRS duration (QLV ratio) at cardiac resynchronization therapy implant, and data about heart failure hospitalization and mode of death were collected in 329 patients who were followed for a period of 3.3±1.9 years. Of them, 83 were hospitalized for heart failure and 83 died. Event rates for all-cause mortality, cardiac mortality, noncardiac mortality, heart failure mortality, and sudden death were 25.2%, 14.9%, 10.3%, 12.2%, and 2.1%, respectively. Patients with a QLV ratio ≤0.70 had significantly worse event-free survival for all study end points—hazard ratio, 1.6; 95% confidence interval, 1.0 to 2.4; *P*=0.05 for heart failure hospitalization; hazard ratio, 2.9; 95% confidence interval, 1.6 to 5.5; *P*=0.001 for heart failure mortality; hazard ratio, 1.8; 95% confidence interval, 1.1 to 2.7; *P*=0.01 for cardiac mortality; and hazard ratio, 2.1; 95% confidence interval, 1.2 to 3.7; *P*=0.01 for all-cause mortality. In multivariable analysis, QLV ratio ≤0.70 remained associated with all study end points.

Conclusions—Electric left ventricular lead position in cardiac resynchronization therapy patients was a significant predictor of heart failure hospitalization and mortality. **(*Circ Arrhythm Electrophysiol*. 2015;8:1113-1121. DOI: 10.1161/CIRCEP.115.003004.)**

Key Words: bundle-branch block ■ cardiac resynchronization therapy ■ heart failure ■ hospitalization ■ mortality

Cardiac resynchronization therapy (CRT) has become an established treatment strategy in chronic heart failure (HF) patients with left ventricular (LV) systolic dysfunction and a wide QRS complex.[1–3] It improves not only the symptoms of HF but also has the potential to reverse LV remodeling and decrease cardiac morbidity and mortality.[4,5] Unfortunately, ≈30% of patients fail to respond clinically to CRT.[6]

Electric LV lead position, assessed by the electric delay from the beginning of the native QRS complex to the local LV electrogram (QLV) or by QLV ratio defined as QLV over the QRS duration (QRSd), was found to be a predictor of symptomatic and structural response to CRT in several short-term (maximum 1-year follow-up) retrospective[7–9] and prospective studies.[10] Reverse LV remodeling after CRT is considered to be one of the strongest predictors of a good prognosis.[11] In our experience, the probability of reverse LV remodeling was 2-fold higher in patients in the upper versus lower tertile of QLV ratio.[9] Only 2 relatively small, single-center studies demonstrated that patients with poor LV lead position (QLV ratio <50%) presented with more HF hospitalizations and higher cardiac mortality as part of a combined clinical end point.[7,12]

We hypothesized that a study with sufficient statistical power could confirm and expand the current evidence with respect to the independent association of LV lead electric location with hard end points, such as cardiac or total mortality. Therefore, this study aimed to investigate the long-term predictive value of QLV for HF hospitalization and total or cardiac mortality.

Methods

Patient Cohort

We retrospectively analyzed data from a prospective database of patients with an implanted biventricular pacemaker or defibrillator at the Regional Hospital Liberec, Czech Republic, between June 2005 and

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WHAT IS KNOWN

- Optimum LV lead electric position is associated with better short-term response to CRT.
- Whether this is also associated with mortality benefit is largely unknown.

WHAT THE STUDY ADDS

- LV lead electric position within the terminal 30% of the intrinsic QRS complex is associated with a reduction in heart failure mortality and all-cause mortality during long-term follow-up.
- Maximum effort should be made to optimize the LV lead electric position during the implant procedure.

June 2013. CRT was indicated according to current guidelines of the European Society of Cardiology: symptomatic chronic HF despite optimal medical therapy, with LV ejection fraction ≤35% and QRSd≥120 ms.[13] Patients were included when they had spontaneous atrioventricular conduction, left bundle branch block (LBBB) or intraventricular conduction delay (IVCD) according to the Strauss criteria,[14] and when QLV measurement was available at the index CRT procedure. Several patients (n=14) with a surgically implanted LV lead were also included; these had either an LV lead implanted during previous open heart surgery or a video-thoracoscopically implanted LV lead because of technical failure of the transvenous approach. We excluded patients who underwent early (<1 year after the enrolment) reimplantation of the LV lead or electric reposition of the multipolar lead. Patients with delayed reimplantation of the LV lead (n=10) were included, and original QLV at the index implantation was considered relevant. All patients signed an informed consent with the procedure. The study was performed in accordance with the Declaration of Helsinki guidelines, and the analysis was approved by the local Ethics Committee.

Implant Procedure and LV Lead Positioning

Commercially available CRT systems were implanted at our center by 3 operators. The right ventricular (RV) lead was commonly placed in the midseptum region. The LV lead was inserted transvenously with a preference for lateral cardiac veins, followed by a posterolateral position. Whenever possible, attempts were made to maximize the QLV interval at implant.

Empirical atrioventricular delay of 120 ms and zero V–V delay were programmed at implant and were not routinely optimized with echocardiography. When no clinical improvement was observed during follow-up visits, at least 1 echocardiographically guided optimization was performed.

Electrophysiological Measurements

The QLV interval was measured from the beginning of the native QRS complex to the local LV electrogram (EGM) from the implanted lead. A unipolar EGM from the electrode that was subsequently used for LV stimulation was preferentially used for this measurement. Alternatively, a bipolar EGM was used when a high quality unipolar EGM was not available. When a quadripolar lead was used, only unipolar EGMs were accepted for the measurement. The timing of local activation was considered to be at the fastest deflection (dV/dt minimum) of the unipolar EGM. For bipolar EGMs, local activation was annotated at the largest bipolar deflection crossing the isoelectric line or the first sharp spike of a signal if the crossing was not noticeable in case of more fragmented EGMs.[15] The local EGM was displayed simultaneously with a surface 12-lead ECG at a sweep speed of 200 mm/s on the electrophysiological recording system (Biotronik EP Control, Germany or Siemens Axiom Sensis XP, Germany). The QRSd and QLV interval were measured using electronic calipers, and the QLV ratio was assessed (Figure 1). All these measurements were performed prospectively at the time of implant.

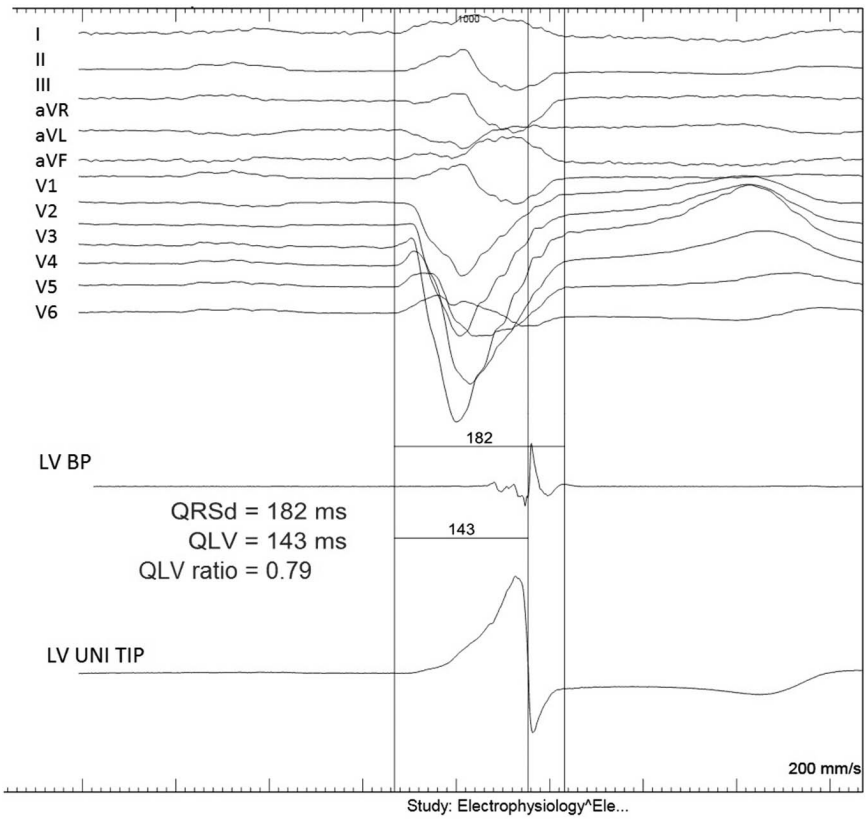

Figure 1. Measurement of the QLV. Printout of the electrophysiological recording system at 200mm/s paper speed showing the QRS duration and the QLV. LV-BP indicates left ventricular bipolar electrogram; LV UNI TIP, LV unipolar electrogram; QLV, left ventricular lead local electrogram delay from the beginning of QRS; and QRSd, QRS complex duration. QLV ratio was calculated as QLV/QRSd. Labels: Lead I, II, III…V5, V6 of the 12-lead surface ECG.

Follow-Up

All patients were followed in the local outpatient department every 6 months. During office visits, the results of clinical examination, standard ECG, CRT device settings, medical treatment, and echocardiographic findings were recorded prospectively into a dedicated database. Clinical outcome data were collected from the medical records and by contacting primary care physicians. Patients were classified as New York Heart Association (NYHA) responders when NYHA class decreased by ≥1 grade. Echocardiographic response was defined as a reduction of the LV end-systolic diameter ≥10%. When the proportion of ventricular pacing in patients with atrial fibrillation was <90% according to the device memory despite the rate control medical therapy, radiofrequency atrioventricular junction ablation was performed.

Study End Points

We defined 4 study end points for the follow-up: first HF hospitalization, HF mortality, cardiac mortality, and all-cause mortality. HF hospitalization was defined as an inpatient admission with overnight stay because of signs or symptoms of HF, including shortness of breath, peripheral edema, or congestion on chest radiograph, with subsequent improvement of these signs and symptoms with medical therapy. The cause of death was assessed by the consensus of 2 physicians, who were blinded to QLV interval. This was done by careful review of clinical, death, and necropsy reports and CRT device memory when available. Any sudden death of uncertain cause was considered sudden cardiac death. All the data were collected throughout the follow-up period in a dedicated database until the final lock. Patients with insufficient clinical data were considered as lost to follow-up.

Statistical Analysis

The follow-up database was locked in May 2014. Continuous variables were expressed as a mean±SD or median (25th–75th percentiles, ie, interquartile range [IQR]) and compared by 2-tailed *t* test for independent samples or Mann–Whitney *U* test for clearly nonnormally distributed data. Categorical variables were expressed as percentages and compared by χ^2 test. Based on our previous experience from the short-term CRT response study,[9] the QLV ratio cutoff value of 0.70 (approximately lower tertile boundary) was considered a reasonable risk stratifier. Occurrence of study end points in empirical categories by QLV ratio were expressed as percentages with 95% confidence intervals (modified Wald method). The effect of selected baseline factors on QLV ratio was analyzed by main effects ANOVA with full-factorial scheme of interactions. Associations of baseline variables with all study end points were investigated by Cox proportional hazards regression analysis. Likewise QLV ratio, other continuous and nonbinary categorical variables were dichotomized by their high-risk tertile boundaries or other clinically meaningful/suitable values. All factors that were univariably associated ($P<0.10$) with at least 1 study end point were entered into the multivariable Cox regression models and investigated by stepwise-forward method. Schoenfeld residuals were used to test for proportionality assumption. Kaplan–Meier curves were used to display cumulative event-free survival. Multivariable models were used to demonstrate the hypothetical benefit from a better LV lead position. Life months gained were computed by comparing the survival curves in high-risk subgroup (QLV ratio ≤0.7) with those when QLV ratio was fixed to low-risk value (>0.7). A *P* value ≤0.05 was considered significant. All analyses were performed using the STATISTICA Version 12 software (Statsoft Inc.).

Results

A total of 410 consecutive CRT patients with preserved atrioventricular conduction were available. Some of them were excluded because of the presence of right bundle branch block (RBBB; n=42) or QLV measurement missing (n=37). The latter subgroup differed from the main population in prevalence of coronary artery disease (76% versus 56%, P=0.02), mitral

Table 1. Baseline Characteristics in Total Population and in Subgroups by QLV Ratio

Variable	All, n=329	QLV Ratio ≤0.7, n=97	QLV Ratio >0.7 , n=232	*P* Value (QLV Ratio ≤0.7 vs >0.7)
Age, y	67.6±9.3	67.7±9.8	67.6±9.1	0.98
Women, %	24.6	17.5	27.6	0.053
ICM,%	56.2	67.0	51.7	0.01
AF, %	15.5	18.6	14.2	0.32
Biventricular pacing, %*	99 (97–99)	99 (95–99)	99 (97–100)	0.12
LBBB, %	90.9	84.5	93.5	0.01
ICD, %	76.0	78.4	75.0	0.52
NYHA class	3 (3–3)	3 (3–3)	3 (3–3)	0.72
Creatinine, μmol/L	96 (79–116)	100 (79–114)	92 (78–117	0.27
LVEF, %	26.2±5.6	25.4±6.1	26.5±5.3	0.11
LVEDd, mm	65.7±7.3	66.3±6.8	65.4±7.6	0.31
LVESd, mm	56.2±8.2	57.1±7.5	55.9±8.5	0.24
MR (grade)	1 (1–2)	1 (1–2)	1 (1–2)	0.92
QRSd, ms	160±20	152±20	163±20	<0.001
QRSd ≤150 ms, %	30.1	47.4	22.8	<0.001
QLV, ms	122±30	89±19	136±22	<0.001
QLV ratio	0.76±0.14	0.58±0.1	0.84±0.1	n/a

The values are expressed as a mean±SD or median (interquartile range). QLV ratio was calculated as QLV/QRSd. AF indicates atrial fibrillation (persistent or permanent) at implant; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; LBBB, left bundle branch block; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic diameter; LVESd, left ventricular end-systolic diameter; MR, mitral regurgitation; QRSd, QRS complex duration; and QLV, left ventricular lead local electrogram delay from the beginning of QRS.

*Assessed at the last contact.

regurgitation grade (median: 2, IQR: 1–3 versus median: 1, IQR: 1–2; $P<0.001$), and NYHA class (median: 3, IQR: 3–4 versus median: 3, IQR 3–3; $P<0.01$). A total of 331 patients were analyzed.

Patient baseline characteristics, including the indices of the LV lead electric position, are shown in Table 1. Prevalence of coronary artery disease was higher in men than in women (61% versus 42%, $P=0.003$). Prevalence of IVCD was higher in ischemic versus nonischemic cardiomyopathy (12% versus 6%, $P=0.04$). As a result, the prevalence of suboptimal implants (QLV ratio ≤0.70) was the highest (67%) in men with coronary artery disease and IVCD QRS pattern and the lowest (17%) in women with nonischemic cardiomyopathy and LBBB QRS pattern. When the effects of 3 factors—sex, cause of cardiomyopathy, and QRS pattern—were analyzed by ANOVA, QLV ratio ≤0.70 was significantly influenced by the presence of coronary artery disease ($P=0.04$) only. The distribution of patients by NYHA class II to IV was 8.5%, 73.5%, and 18.0%, respectively. Mitral regurgitation grade 1 to 4 was present in 57.1%, 21.0%, 14.0%, and 7.9% of patients, respectively.

The majority of patients were treated with β-blockers (96%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (99%), loop diuretics (91%), and mineralocorticoid receptor antagonists (89%). Atrioventricular junction ablation was performed in 54 subjects (16.4%). A quadripolar LV lead was used only in small proportion of patients (n=11), and none of them required electric reposition during follow-up.

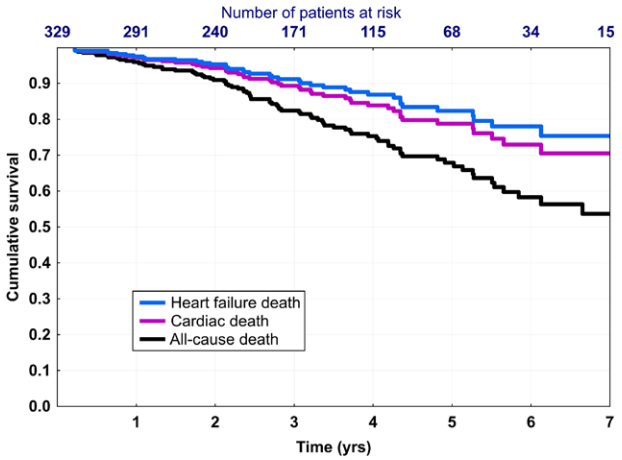

Figure 2. Cumulative survival by mode of death.

At 12-month follow-up, 240 (79.5%) patients were classified as NYHA responders and 164 (55.6%) as echocardiographic responders. Two patients were lost to follow-up.

Clinical Outcomes

During the mean follow-up period of 3.3±1.9 years (range, 0.5–8.8 years; median, 3.1 years; IQR, 1.9–4.7 years), a total of 83 (25.2%) patients died from cardiac (n=49, 14.9%) or

Table 2. Comparison of Baseline Characteristics in Patient Subgroups by Clinical Outcome After Cardiac Resynchronization Therapy (n=329)

	HF Hospitalization			HF Death			Cardiac Death			All-Cause Death		
	Yes	No		Yes	No		Yes	No		Yes	No	
Variable	(n=83)	(n=246)	*P* Value	(n=40)	(n=289)	*P* Value	(n=49)	(n=280)	*P* Value	(n=83)	(n=246)	*P* Value
Women, %	19.3	26.4	0.19	15.0	26.0	0.13	16.3	26.1	0.14	18.1	26.8	0.11
Age, y	67.9±0.3	67.5±8.9	0.76	68.3±10.2	67.5±9.2	0.64	69.0±10.0	67.4±9.1	0.25	70.1±9.0	66.8±9.2	<0.01
ICM, %	62.7	54.1	0.17	72.5	54.0	0.03	69.4	53.9	0.04	69.9	51.6	<0.01
SR, %	85.5	84.1	0.76	87.5	84.1	0.58	89.8	83.6	0.27	81.9	85.4	0.46
Biventricular pacing, %*	99 (96–99)	99 (97–100)	0.10	98 (94–99)	99 (97–100)	0.10	99 (95–99)	99 (97–100)	0.21	99 (95–100)	99 (97–99)	0.36
LBBB, %	86.7	92.3	0.13	92.5	90.7	0.71	93.9	90.4	0.43	94.0	89.8	0.26
ICD, %	71.1	77.6	0.23	77.5	75.8	0.81	67.3	77.5	0.13	67.5	78.9	0.04
QRSd, ms	157±21	160±20	0.21	158±21	160±20	0.56	160±21	160±20	0.93	161±21	159±20	0.34
QRSd≤150 ms, %	42.2	26.0	<0.01	37.5	29.1	0.28	32.7	29.6	0.67	27.7	30.9	0.59
MR (grade)	2 (1–3)	1 (1–2)	<0.01	2 (1–3)	1 (1–2)	0.13	2 (1–3)	1 (1–2)	0.06	2 (1–3)	1 (1–2)	0.01
NYHA class	3(3–4)	3 (3–3)	<0.001	3 (3–4)	3 (3–3)	0.01	3 (3–4)	3 (3–3)	<0.01	3 (3–4)	3 (3–3)	0.01
Creatinine, µmol/L	99 (80–127)	94 (78–114)	0.16	104 (84–130)	94 (78–114)	0.06	104 (81–138)	93 (78–114)	0.02	103 (81–130)	92 (77–114)	0.02
LVEF, %	24.4±5.4	26.8±5.5	0.001	23.4±5.3	26.6±5.5	<0.001	24.3±5.7	26.6±5.5	0.01	25.1±6.1	26.5±5.3	0.04
LVEDd, mm	66.6±8.1	65.4±7.0	0.2	67.3±6.9	65.5±7.4	0.14	66.7±7.6	65.5±7.3	0.31	66.4±7.8	65.5±7.2	0.32
LVESd, mm	57.7±9.1	55.8±7.9	0.07	58.8±7.7	55.9±8.2	0.04	57.6±9.3	56.0±8.0	0.22	57.3±8.9	55.9±8.0	0.20
QLV, ms	115±32	124±29	0.02	112±32	124±30	0.02	116±31	123±30	0.12	120±31	123±30	0.33
QLV ratio	0.73±0.16	0.77±0.13	0.04	0.70±0.15	0.77±0.14	<0.01	0.72±0.15	0.77±0.14	0.03	0.74±0.14	0.77±0.14	0.05

The values are expressed as mean±SD or median (interquartile range). QLV ratio was calculated as QLV/QRSd. AF indicates atrial fibrillation (persistent or permanent) at implant; HF, heart failure; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; LBBB, left bundle branch block; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic diameter; LVESd, left ventricular end-systolic diameter; MR, mitral regurgitation; QRSd, QRS complex duration; and QLV, left ventricular lead local electrogram delay from the beginning of QRS; and SR, sinus rhythm at implant.

*Assessed at the last contact.

noncardiac (n=34, 10.3%) causes. The majority (82%) of cardiac deaths occurred because of HF (n=40, 12.2%). Other cardiac deaths included sudden death (n=7, 2.1%), myocardial infarction (n=1), and aortic stenosis (n=1). Noncardiac deaths occurred because of malignancy (n=16), infection (n=12), aortic aneurysm rupture (n=2), aortic bifurcation thrombosis (n=1), stroke (n=1), myasthenia gravis (n=1), and suicide (n=1). Event rates for all-cause mortality, cardiac mortality, noncardiac mortality, HF mortality, and sudden death were 25.2%, 14.9%, 10.3%, 12.2%, and 2.1%, respectively. Cumulative survival by the mode of death during 7-year follow-up is shown in Figure 2. A total of 83 (25.2%) patients were hospitalized for HF. All but one patient with HF death had prior hospitalization for HF.

Differences between subgroups of patients defined by clinical outcome are shown in Table 2. For all study end points, higher NYHA class, lower LVEF, and lower QLV ratio at implant were consistently associated with adverse outcomes. Survivors were more likely to have received an implantable cardioverter defibrillator (ICD); however, cardiac mortality was comparable between ICD and non-ICD groups.

Risk Prediction by QLV Ratio

In order not to miss clinically relevant QLV ratio dichotomies, we investigated the occurrence of study end points in 4 subgroups defined by QLV ratio boundaries of 0.60 (≈15% percentile), 0.70 (approximately lower tertile), and 0.80 (approximately median). Visual analysis of the corresponding data (Figure 3) suggested again an optimum QLV ratio cut-off of 0.70 for predicting study end points, and thus this value was used for further analysis.

There were 97 patients (30%) with a QLV ratio ≤0.70 (approximately lower tertile boundary). The differences between patients with a QLV ratio ≤0.70 and a QLV ratio >0.70 are shown in Table 1. Compared with the rest of the population, patients with a QLV ratio ≤0.70 had significantly worse event-free survival for all study end points (Table 3; Figure 4). With the QLV ratio dichotomy of ≤0.70, survival curves separated early after CRT implantation for HF hospitalization. This occurred no earlier than after 2 years for mortality end points.

Multivariable Risk Prediction

All continuous or ordinal baseline factors were dichotomized as follows: age>72 years (n=113; 34%), LVEF<25% (n=111; 34%), QRSd ≥170ms (n=107; 33%) or QRSd ≤150ms (n=99; 30%), biventricular pacing <98% (n=95; 29%), mitral regurgitation grade ≥2 (n=141; 45%), NYHA class=4 (n=59; 18%), serum creatinine >107 μmol/L (n=109; 33%), LV end-diastolic diameter >68 mm (n=108; 33%), and LV end-systolic diameter >60 mm (n=82; 25%). The results of both univariable and multivariable Cox regression analysis are shown in Tables 4 and 5 only for those factors that were univariably associated (P<0.10) with at least 1 study end point. All factors conformed to an assumption of proportionality. A QLV ratio ≤0.70 was the only factor independently associated with all study end points. Other factors (age, coronary artery disease, NYHA class, QRSd, percentage of biventricular pacing, serum creatinine, and LVEF) were not (or not consistent) predictors of study end points either in univariable or multivariable analysis. Sudden death occurred in 7 patients (including 5 patients with CRT-P). The only predictor of sudden death was the absence of ICD (relative risk, 5.5; 95% confidence interval, 1.0–28.9; P=0.046).

After adjustment for other clinical confounders, it was demonstrated that better LV lead position alone (>0.70 versus

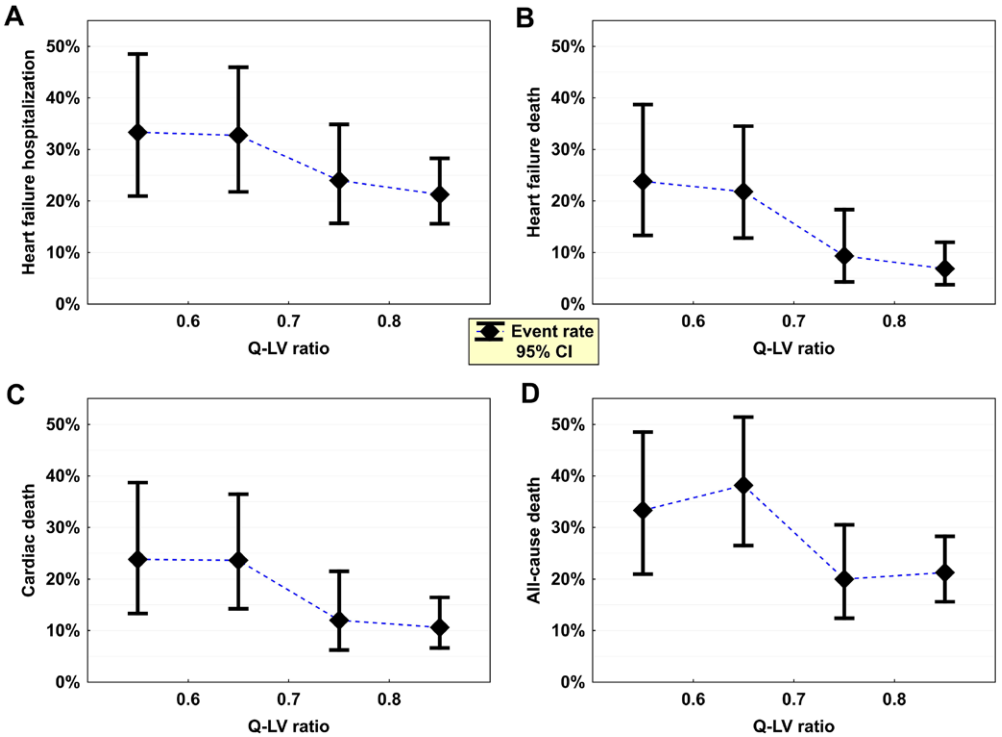

Figure 3. Event rates for individual end points in 4 subgroups by QLV ratio. Event rates with 95% confidence interval (CI) for (**A**) heart failure hospitalizations, (**B**) heart failure death, (**C**) cardiac death, and (**D**) all-cause death in 4 QLV ratio subgroups defined by boundaries of 0.60, 0.70, and 0.80. QLV indicates left ventricular lead local electrogram delay from the beginning of QRS.

Table 3. Event Rates for QLV Ratio Subgroups

Event	Group by QLV Ratio	Deceased, n	Surviving, n	Total Event Rate, %
HF hospitalization	>0.7	51	181	22.0
	≤0.7	32	65	33.0
HF death	>0.7	18	214	7.8
	≤0.7	22	75	22.7
Cardiac death	>0.7	26	206	11.2
	≤0.7	23	74	23.7
All-cause death	>0.7	48	184	20.7
	≤0.7	35	62	36.1
Noncardiac death	>0.7	22	210	9.5
	≤0.7	12	85	12.4
Sudden death	>0.7	6	226	2.6
	≤0.7	1	96	1.0

HF indicates heart failure; and QLV, left ventricular lead local electrogram delay from the beginning of QRS.

≤0.70), the only modifiable baseline factor, is associated with the gain of 3.0, 2.8, 3.2, and 3.3 event-free months of life for all-cause mortality, cardiac mortality, HF mortality, and HF hospitalization, respectively.

Discussion

In this long-term follow-up study, we have demonstrated for the first time that electric LV lead position assessed by QLV ratio is a strong predictor of HF hospitalization and cardiac mortality in LBBB/IVCD patients receiving CRT. Suboptimal QLV ratio ≤0.70 was associated with more than doubled cardiac mortality, which was driven predominantly by a 3-fold higher HF mortality compared with the rest of the population. Unfavorable outcomes in this subgroup also resulted in significantly higher all-cause mortality.

Interestingly, risk prediction by QLV ratio did not apply to sudden death. This mode of death was associated only with the absence of ICD. Sudden death did not influence overall cardiac mortality, most likely because the presence of ICD changed the mode of cardiac death from sudden to HF death.

The LV assist device implantation and heart transplant have usually been part of a composite end point in previous CRT studies. None of our patients was transplanted, although some of them died while on the waiting list for transplantation. Only 1 patient received an LV assist device, which was implanted after the database lock.

Both the QLV interval and the QLV ratio were found to be predictors of short-term CRT response.[7–10,12] Only the QLV ratio was used in clinical outcome studies.[7,12] There are several reasons why the use of the QLV ratio (instead of QLV) may be preferable. First, the QLV ratio represents a pure index of LV lead location. Second, the QLV interval principally correlates with the QRSd. Although both variables (QLV and QRSd) act in a synergic manner in prediction models of short-term CRT response, prolonged QRSd is a risk factor for cardiac mortality in HF patients.[16] This may attenuate the risk-predictive power of the QLV interval in long-term trials investigating clinical outcomes. Indeed, patients in the upper tertile of QRSd in our

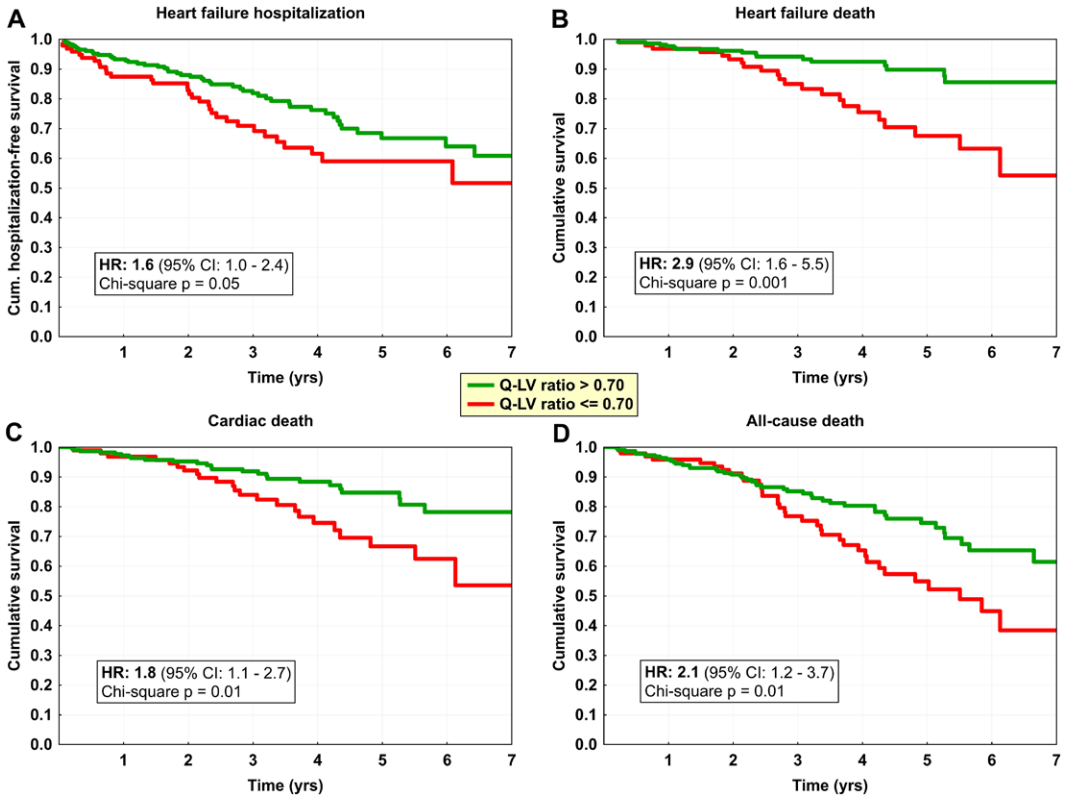

Figure 4. Event-free survival in subgroups by QLV ratio. Kaplan–Meier curves for the (**A**) first heart failure hospitalization, (**B**) heart failure death, (**C**) cardiac death, and (**D**) all-cause death in subgroups by the QLV ratio dichotomy (≤0.7 vs >0.7). CI indicates confidence interval; HR, hazard ratio; and QLV left ventricular lead local electrogram delay from the beginning of QRS.

Table 4. Univariable and Multivariable Risk Prediction (Cox Regression Models of Proportional Hazards)

	HF Hospitalization						HF Death					
	Univariable			Multivariable			Univariable			Multivariable		
Definition of Risk	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age >72 y	1.4	0.9–2.2	0.12				1.7	0.9–3.1	0.11			
Ischemic cardiomyopathy	1.5	0.9–2.3	0.08				2.4	1.2–4.7	0.02	2.4	1.2–5.0	0.02
Biventricular pacing <98%	1.5	1.0–2.4	0.07				1.9	1.0–3.5	0.06			
IVCD	3.4	1.8–6.6	<0.001	3.6	1.8–7.1	<0.001	1.7	0.5–5.6	0.38			
QRSd ≥170 ms	1.1	0.7–1.8	0.62				1.5	0.8–2.8	0.23			
QRSd ≤150 ms	1.8	1.1–2.7	0.01				1.4	0.7–2.7	0.31			
NYHA=4	2.2	1.4–3.6	<0.001	2.5	1.6–4.1	<0.001	2.1	1.1–4.1	0.03	2.9	1.4–5.8	<0.01
Creatinine >107μmol/L	1.2	0.8–1.9	0.36				1.8	0.9–3.3	0.08			
LVEF<25%	1.7	1.1–2.6	0.02				2.5	1.3–4.7	<0.01	2.2	1.2–4.2	0.02
LVESd>60 mm	1.7	1.0–2.6	0.03	1.6	1.0–2.6	0.05	1.2	0.6–2.5	0.55			
QLV ratio≤0.70	1.6	1.0–2.4	0.05	1.6	1.0–2.6	0.04	2.9	1.6–5.5	0.001	3.1	1.6–6.0	<0.001

CI indicates confidence interval; HF, heart failure; HR, hazard ratio; IVCD, intraventricular conduction delay; LVEF, left ventricular ejection fraction; LVESd, left ventricular end-systolic diameter; NYHA, New York Heart Association; QLV indicates left ventricular lead local electrogram delay from the beginning of QRS; and QRSd, QRS complex duration.

study had a statistically worse prognosis in terms of cardiac mortality despite the presence of CRT.

The first report on the impact of LV lead electric location was published by Singh et al[7] in 2006. They analyzed the clinical outcome after 1 year of CRT in 71 patients with LBBB. Those with suboptimal LV lead position (QLV/QRSd<0.5) presented with increased all-cause mortality and hospitalization rate for HF in a combined end point. However, patients with a QLV ratio<0.5 were rare in our cohort (5%) in contrast to a study by Singh et al[7] (38%). The majority of our high-risk patients had a QLV ratio in the range of 0.50 to 0.70, better representing the contemporary population of CRT patients and our LV lead implant strategies.

A recent article from Kandala et al[12] investigated the impact of LV lead electric location in a mixed population of 144 CRT patients. They demonstrated that a QLV ratio ≥0.5 in each of the 3 nonexclusive subgroups, consisting of patients with LBBB (n=82), non-LBBB (n=62), and RBBB (n=18) QRS configuration, was associated with better clinical outcome according to a composite end point of all-cause mortality, HF hospitalization, LV assist device implantation, and heart transplantation. The event-free survival was driven by freedom from HF hospitalization. As the authors noted, the study was underpowered to detect any survival benefit from better LV lead location. It is likely that not only the relatively small population but also short mean follow-up of no >2 years (derived from survival curves; not exactly stated) played a role.

Compared with these studies, we investigated a larger and homogeneous population of 329 LBBB/IVCD patients. The vast majority of our study population (91%) had true complete LBBB. Importantly, our study also had longer follow-up,

Table 5. Univariable and Multivariable Risk Prediction (Cox Regression Models of Proportional Hazards)

	Cardiac Death						All-Cause Death					
	Univariable			Multivariable			Univariable			Multivariable		
Definition of Risk	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age >72 y	2.1	1.4–3.2	<0.001	2.0	1.2–3.6	0.01	2.0	1.1–3.5	0.02	1.9	1.3–3.0	<0.01
Ischemic cardiomyopathy	2.1	1.3–3.4	<0.01				2.0	1.1–3.7	0.02	2.1	1.3–3.4	<0.01
Biventricular pacing <98%	1.5	0.9–2.7	0.16				1.4	0.9–2.2	0.14			
IVCD	1.4	0.6–3.5	0.47				1.4	0.4–4.5	0.60			
QRSd ≥170 ms	1.8	1.1–2.7	0.01	1.9	1.0–3.3	0.04	1.5	0.9–2.7	0.14			
QRSd ≤150 ms	1.0	0.6–1.9	0.88				0.8	0.5–1.4	0.48			
NYHA=4	1.4	0.9–2.4	0.14				2.1	1.2–3.8	0.02	1.9	1.1–3.1	0.02
Creatinine >107 μmol/L	1.9	1.1–3.3	0.03				1.5	1.0–2.4	0.06			
LVEF<25%	1.5	1.0–2.3	0.07	1.8	1.1–3.2	0.03	1.9	1.1–3.3	0.03			
LVESd>60 mm	1.4	0.9–2.3	0.12				1.3	0.7–2.4	0.42			
QLV ratio ≤0.70	1.8	1.1–2.7	0.01	2.3	1.3–4.1	<0.01	2.1	1.2–3.7	0.01	1.8	1.1–2.8	0.01

CI indicates confidence interval; HR, hazard ratio; IVCD, intraventricular conduction delay; LVEF, left ventricular ejection fraction; LVESd, left ventricular end-systolic diameter; NYHA, New York Heart Association; QLV indicates left ventricular lead local electrogram delay from the beginning of QRS; and QRSd, QRS complex duration.

which reached an average of 3.3 years. This seems to be critical because survival curves for mortality end points (unlike the curve for HF hospitalization) start separating no earlier than 2 years after CRT implantation, according to our assessment. This observation is also in line with the absence of a mortality difference between QLV-ratio strata in the study of Kandala et al.

It is obvious that not only the QLV ratio but also the type of electric dyssynchrony is prognostically important. We decided to exclude patients with RBBB from our analysis. In our opinion, the QLV ratio in RBBB does not properly reflect optimum electric LV lead position because the total QRSd is significantly influenced by variable left-to-right transseptal conduction together with the RV activation time. We think that the QLV ratio in RBBB patients should be optimized during RV pacing instead of during intrinsically conducted beats.

In our study, the IVCD pattern was predictive of HF hospitalizations only, whereas other studies have identified an association between IVCD and outcome.[3,5] This is certainly because of the low proportion (9%) of IVCD patients in our population. Therefore, any conclusions cannot be drawn from our study about the impact of the IVCD on event-free survival either alone or in combination with other risk stratifiers like electric LV lead position.

When comparing previously published CRT studies, which investigated QLV, an apparent temporal trend of improvement in electric position of the LV lead can be observed. Although more than one third of patients in the first published study had a QLV ratio<0.50,[7] the mean QLV ratios in newer studies reached 0.63 in the SmartDelay determined atrioventricular optimization (SMART-AV) trial (a mixed population including RBBB),[17] 0.73 in the LBBB subgroup from the study by Kandala et al,[12] and 0.78 in our subgroup of transvenously implanted LBBB patients. Possible explanations for this trend include better instrumentation for LV lead implantation and the growing intention to guide the CRT implant procedure not only anatomically but also based on recorded LV EGMs. In this regard, our study benefited from standardized measurements of the QLV performed using an electrophysiological recording system and both bipolar and unipolar EGMs. This approach is more precise compared with the use of device programmer readings.

Study Implications

This study expands the evidence that suboptimum LV lead position in CRT patients is associated with adverse outcome. Importantly, the QLV ratio cutoff value of 0.70 used to define high-risk patients is considerably higher than cutoff values used in previously published studies. Our data suggest that patients with a QLV ratio ≤0.70 may be considered candidates for reintervention. Since transvenous LV lead reimplantation is frequently not feasible because of the anatomy of the coronary sinus and its tributaries, the benefits and risks of a surgical procedure should be considered.[18] We have recently developed a simple technique of thoracoscopic epicardial mapping during LV lead implantation,[19] which seems safe and efficacious for improvement of LV lead electric position. Whether such an intervention should be performed and when—that is, either early after suboptimum transvenous LV lead implant in all patients or reserved for those with subsequent absence of clinical and echocardiographic response to CRT—remains to be established in future prospective studies.

Study Limitations

Although the data in our CRT database were collected prospectively, the hypotheses were defined post hoc and data analyzed retrospectively. Therefore, the results should be interpreted with caution. A cutoff value of 0.70 for the QLV ratio was chosen more or less empirically and may not be the optimal choice. However, an appropriate search for the most applicable dichotomy would require a much larger patient population. In addition, the LV lead positions were not recorded on cine-loops systematically. Therefore, we could not evaluate the potential impact of a given LV lead anatomic position on outcome measures. The amount and the distribution of LV scar tissue, which may interfere with the CRT response, were also not assessed. We did not collect data on Echo-guided CRT optimization which was performed only in early nonresponders to CRT, more likely in those with QLV ratio <0.70. This consequently might influence the results of our study, but with the effect of diminishing rather than strengthening the association of LV lead electric position with clinical end points.

Conclusions

Electric LV lead position assessed by QLV ratio was found to be a significant predictor of mortality in CRT patients with LBBB/IVCD. Therefore, maximum effort should be made to optimize the LV lead electric position during the implant procedure. Patients with suboptimal transvenous LV lead position may be considered candidates for surgical intervention.

Disclosures

Dr Kautzner is a member of scientific advisory board for Biosense Webster, Boston Scientific, Medtronic, St Jude Medical, and received speaker's honoraria from Biosense Webster, Biotronik, Boston Scientific, Hansen Medical, Medtronic, and St Jude Medical. Dr Polasek reports receiving lecture fees from St. Jude Medical and Medtronic. The other authors report no conflicts.

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Left Ventricular Lead Electrical Delay Is a Predictor of Mortality in Patients With Cardiac Resynchronization Therapy

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