Correlation of Mechanical Dyssynchrony with QRS Duration Measured by Signal-Averaged Electrocardiography

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Background: Preimplantation left ventricular dyssynchrony is considered a prerequisite for a beneficial response to cardiac resynchronization therapy (CRT). However, electrical dyssynchrony estimated by QRS duration (QRSd) on ECG has not been proven to be an optimal surrogate of mechanical dyssynchrony. We evaluated the correlation of mechanical dyssynchrony with QRSd as measured by signal-averaged electrocardiography (SAECG) in comparison with measurements based on conventional surface ECG and with onscreen measurements based on digital ECG.

Methods: We included 49 consecutive patients with decompensated heart failure (40 men, aged 66.8 ± 9.5 years), New York Heart Association (NYHA) class II–IV, and LVEF $\leq 40\%$. QRSd was calculated by manual measurement of 12-lead ECG, on-screen measurement of computer-based ECG, and calculation of total ventricular activation time on SAECG.

Results: Only 60.4% of the studied patients had QRS ≥ 120 ms based on measurements derived by SAECG compared to 69.4% by using on-screen measurement of computer-based ECG and 73.5% based on surface ECG ($P = 0.041$). Interventricular but not intraventricular delay was correlated with QRSd. The correlation of interventricular dyssynchrony with QRSd was stronger when measured by SAECG than by surface ECG ($r = 0.45$, $P = 0.001$ vs $r = 0.35$, $P < 0.01$). Among patients with ischemic cardiomyopathy, no significant correlation was demonstrated between mechanical dyssynchrony and QRSd. In nonischemic patients, interventricular delay was significantly correlated with QRSd measured by surface ECG ($r = 0.45$, $P < 0.05$) and SAECG ($r = 0.46$, $P < 0.05$).

Conclusions: The use of SAECG results in different patient classification in wide QRS complex category as compared to surface ECG. Furthermore, QRSd measured by SAECG is correlated with interventricular but not intraventricular dyssynchrony in heart failure patients.

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Cardiac resynchronization therapy (CRT) is an established treatment for advanced, refractory to medical treatment heart failure.^{1,2} Despite compelling evidence confirming the morbidity and mortality benefit conferred by CRT, a major issue that still remains largely unresolved is the considerably high percentage of nonresponders, due to an impaired ability to prospectively discern the

subgroup of responders to CRT.³ This important caveat seems to reflect the modest discrimination performance of the usually implemented eligibility criteria for CRT.

The use of QRS duration as a consensus definition of cardiac dyssynchrony is based on the premise that heterogeneous electrical activation sequence (electrical dyssynchrony) results in

delayed regional contraction and ultimately in asynchronous and uncoordinated ventricular systole.⁴ However, several studies have demonstrated the dissociation between QRS duration and mechanical dyssynchrony.^{5–9}

The limited value of QRS duration as a surrogate marker of cardiac asynchrony may partly reflect the inability of conventional ECG to detect low-amplitude wavefronts in the terminal portion of the QRS complex. These late potentials that represent the delayed depolarization of certain myocardial loci due to lengthened excitation pathlength and/or slowed conduction velocity are major determinants of the total duration of ventricular activation. Thus, the accurate recording and inclusion of these minor depolarization currents in total QRS duration may represent a different paradigm of electrical dyssynchrony appraisal.

In the present study, we sought to investigate whether QRS duration estimated by SAECEG is correlated with echocardiographically documented mechanical dyssynchrony in heart failure patients.

METHODS

Patient Population

The study population included consecutive patients who were admitted to our hospital due to decompensated heart failure, with left ventricular ejection fraction (LVEF) $\leq 40\%$, New York Heart Association (NYHA) class II–IV, irrespective of QRS duration. Patients with a permanent pacemaker or intracardiac defibrillator were excluded from the study.

ECG Analysis

In all patients, maximal QRS duration was measured by two independent cardiologists who were unaware of patient's clinical status by using two different measurements: (a) manual measurement at standard speed (25 mm/s) from the printout of the 12-lead ECG (paper QRS—papQRS) and (b) on-screen measurement of computer-based ECG by using digital callipers (digital QRS—digQRS; CS 200, Schiller, Baar, Switzerland). Furthermore, SAECEG was performed in all patients by using a commercially available system (CS 200, Schiller). Two hundred cardiac cycles recorded from the standard Frank orthogonal X, Y, and Z leads were averaged and the noise level was less than 0.5 mV

in all cases. Analog to digital conversion was performed with a sampling rate of 2000 Hz and 16-bit accuracy, while a 40-Hz high-pass bidirectional filter was used. The following SAECEG parameters were calculated: (a) total duration of the filtered QRS complex (SAECEG-QRS), (b) the root-mean-square voltage of the last 40 ms of the filtered QRS complex (RMS40) and (c) the duration of the low amplitude signals at the terminal portion of the QRS complex with values less than 40 μ V (LAS).

Echocardiography and Assessment of Ventricular Dyssynchrony

The echocardiographic examination was performed with the patient tilted in the left lateral decubitus position by using a commercially available ultrasound system (Vivid 3, General Electric, Milwaukee, WI). All echocardiographic variables were measured twice in end-expiration and the mean values were included in the statistical analysis. Ejection fraction was calculated from the apical two and four chamber views by using the biplane Simpson's method.¹⁰

The estimation of interventricular dyssynchrony was based on the measurement of interventricular mechanical delay defined as the difference between the left and the right ventricular preejection period. The right ventricular preejection period (RVPEP) was measured by Doppler imaging in the basal short axis view as the time interval from the start of the QRS complex to the onset of flow through the pulmonary valve (beginning of the pulmonary artery flow envelope on the pulsed Doppler tracing). The left ventricular preejection period (LVPEP) was estimated in the apical five-chamber view as the time difference from the beginning of the QRS complex to the onset of aortic outflow (beginning of the aortic flow envelope on the pulsed Doppler tracing).¹¹ Values of interventricular delay higher than 40 ms have been proposed to be indicative of substantial interventricular dyssynchrony.¹²

Intraventricular dyssynchrony was assessed using tissue Doppler imaging (TDI) by measuring the time interval from the onset of the QRS to the occurrence of the peak systolic velocity of the interventricular septum (septal T_s) and the left ventricular lateral wall (lateral T_s) in the apical four-chamber view. The calculations of septal and lateral T_s were performed by placing the sample volume in the basal portions of the septum and

lateral wall. Septal to lateral wall delay defined as the difference between lateral T_s and septal T_s was used as an index of intraventricular dyssynchrony. Values of septal to lateral delay higher than 60 ms have been demonstrated to be indicative of significant intraventricular dyssynchrony.^{13,14}

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation. The Pearson's correlation coefficient was used to test the correlation between mechanical dyssynchrony and QRS duration. Pearson's chi-square test for categorical variables and Student's t-test for continuous variables were employed to compare baseline characteristics of the groups of interest. Comparisons of means of more than two groups were performed by one-way analysis of variance. All tests were considered to be significant at a 0.05 level of statistical significance. Statistical analyses were performed with SPSS statistical software (version 15.0, SPSS, Chicago, IL).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the article as written.

RESULTS

Baseline Parameters

A total of 49 patients (40 males, mean age 66.8 ± 9.5 years) were included in the study. The underlying etiology of heart failure was ischemic cardiomyopathy in 25 patients (51%) and nonischemic cardiomyopathy in 24 patients (49%). The majority of patients were in NYHA class III (46.9%), while 30.6% were in NYHA class II and 22.4% of patients were in NYHA class IV. Left ventricular ejection fraction was $28.4\% \pm 7.1\%$ (range 15–40%) and left ventricular end-diastolic diameter was 63.6 ± 8.0 mm. A complete right bundle branch block was present in five patients (10.2%), while 27 (55.1%) patients had a complete left bundle branch block and 4 (8.2%) patients had an undetermined pattern of conduction defect. Patients with nonischemic cardiomyopathy were significantly younger and had significantly lower ejection fraction in comparison to patients with ischemic cardiomyopathy (Table 1). The baseline characteristics of patients with or without intraventricular dyssynchrony (septal to lateral delay higher than the cutoff limit of 60 ms) are presented in Table 2.

Table 1. Baseline Characteristics of Patients in the Ischemic and Nonischemic Subgroups

	Ischemic Cardiomyopathy (n = 25)	Nonischemic Cardiomyopathy (n = 24)	P Value
Age (years)	69.4 ± 8.4	64 ± 9.9	0.045
Female gender (%)	12%	25%	N.S.
NYHA class	2.9 ± 0.9	2.9 ± 0.6	N.S.
LVEF (%)	30.4 ± 6.7	26.2 ± 6.9	0.035
LVEDD (mm)	64.1 ± 9.3	63.1 ± 6.4	N.S.
LVPEP (ms)	114 ± 27	130 ± 29	N.S.
SAECG (ms)	135 ± 33	137 ± 35	N.S.
SAECG > 120 ms (%)	58%	63%	N.S.
RMS40 (μ V)	28 ± 17.7	28.8 ± 22.6	N.S.
LAS (ms)	56.5 ± 28.8	52.1 ± 31.8	N.S.
papQRSmax (ms)	149 ± 34	149 ± 32	N.S.
papQRSmax > 120 ms (%)	68%	79%	N.S.
digQRSmax (ms)	151 ± 37	145 ± 33	N.S.
digQRSmax > 120 ms (%)	72%	67%	N.S.
Interventricular delay (ms)	14 ± 30	28 ± 27	N.S.
Intraventricular delay (ms)	74 ± 35	62 ± 39	N.S.

Values of continuous variables are mean $\pm$ SD.

LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVPEP = left ventricular preejection period.

Table 2. Baseline Characteristics of Patients with or without Intraventricular Dyssynchrony (Septal to Lateral Delay > 60 ms)

	With Intraventricular Dyssynchrony (n = 29)	Without Intraventricular Dyssynchrony (n = 20)	P Value
Age (years)	67.3 ± 10.3	66 ± 8.3	N.S.
Female gender (%)	24%	10%	N.S.
NYHA class	3.1 ± 0.7	2.7 ± 0.7	N.S.
LVEF (%)	28.1 ± 7.8	28.7 ± 6.1	N.S.
LVEDD (mm)	62.8 ± 7.1	64.8 ± 9.3	N.S.
LVPEP (ms)	118 ± 27	126 ± 31	N.S.
SAEKG (ms)	135 ± 33	137 ± 35	N.S.
SAEKG > 120 ms (%)	54%	70%	N.S.
RMS40 (μV)	28.3 ± 19.2	28.5 ± 21.7	N.S.
LAS (ms)	53.5 ± 27.5	55.4 ± 34.1	N.S.
papQRSmax (ms)	149 ± 31	149 ± 37	N.S.
papQRSmax > 120 ms (%)	72%	75%	N.S.
digQRSmax (ms)	148 ± 35	149 ± 35	N.S.
digQRSmax > 120 ms (%)	69%	70%	N.S.
Interventricular delay (ms)	15 ± 31	28 ± 25	N.S.

Values of continuous variables are mean ± SD.

LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVPEP = left ventricular preejection period.

Indices of Electrical and Mechanical Dyssynchrony

In the total population, SAEKG-QRS was shorter than papQRS and digQRS (136 ± 33 ms vs 149 ± 33 ms and 148 ± 35 ms, respectively). The use of the three different methods of QRS duration measurement resulted in different classification of patients in relation to QRSd greater than 120 ms. Using papQRS, 73.5% of the studied patients were classified as having QRS > 120 ms, while 69.4% by using digQRS and only 60.4% by using SAEKG-QRS. Between papQRS- and SAEKG-QRS-based classification, the difference reached statistical significance (paired chi-square with Yates correction, $P = 0.041$). The mean LVPEP was 121 ± 29 ms, while in 22.4% of patients LVPEP was higher than 140 ms. Interventricular dyssynchrony was 21 ± 29 ms in the total population while in 11 patients (22.4%) it was higher than 40 ms. In addition, 59.2% of patients had a significant intraventricular delay, as documented by a septal to lateral delay exceeding the cut-off limit of 60 ms. The electrocardiographic and echocardiographic parameters of patients in the ischemic and nonischemic subgroups are presented in Table 1. The percentages of ischemic and nonischemic patients with mechanical dyssynchrony are presented in Figure 1.

Correlation between QRS Duration and Mechanical Dyssynchrony

Interventricular delay was significantly correlated with QRS duration as evaluated by both paper- and computer-based ECG ($r = 0.33$, $P < 0.05$ and $r = 0.30$, $P < 0.05$, respectively). Total QRS duration estimated by signal-averaged ECG was also significantly correlated with interventricular delay at a higher level of statistical significance ($r = 0.41$, $P = 0.004$). In the total population, papQRS, digQRS, and SAEKG-QRS were not correlated with intraventricular delay. The scatter plots of SAEKG-QRS with interventricular and intraventricular delay are presented in Figures 2 and 3 respectively.

In the patients with ischemic cardiomyopathy, no significant correlation was demonstrated between interventricular or intraventricular dyssynchrony with QRS duration as measured with any of the three implemented methods. However, in patients with nonischemic cardiomyopathy, interventricular delay was significantly correlated with papQRS ($r = 0.45$, $P < 0.05$), filQRS ($r = 0.61$, $P < 0.01$), and SAEKG-QRS ($r = 0.46$, $P < 0.05$). In the nonischemic subpopulation, intraventricular delay was not significantly correlated with papQRS, filQRS, or SAEKG-QRS.

Figure 1. Percentage of patients with ischemic and nonischemic cardiomyopathy presenting significant interventricular (>40 ms) and intraventricular (>60 ms) mechanical dyssynchrony.

Figure 2. Scatter plot of total QRS duration as evaluated with signal-averaged ECG (SAECG-QRS) with interventricular delay. The fit line as estimated by the linear fit method is also presented.

Figure 3. Scatter plot of total QRS duration as evaluated with signal-averaged ECG (SAECG-QRS) with intraventricular delay. The fit line as estimated by the linear fit method is also presented.

DISCUSSION

The superiority of QRS duration in comparison to echocardiographically documented mechanical dyssynchrony for optimal prediction of eligibility and response to CRT represents a long-prevalled debate and a topic of intense research with profound implications in clinical practice. Despite the fact that the latest guidelines recommend the use of wide QRS as an index of dyssynchrony,⁴ several arguments cast doubt on the reliability and accuracy of electrocardiographic criteria. The main concerns pertain to the existing dissociation between electrical and mechanical dyssynchrony and the limited ability of QRS duration to predict a favorable response to CRT.¹⁵ Bader et al. reported that major intraventricular dyssynchrony was an independent predictor of severe cardiac events independent of the QRS width and was detectable in 56% of heart failure patients with narrow QRS.⁵ Yu et al. also demonstrated that QRS duration was not a determinant of significant systolic mechanical asynchrony, while among patients subjected to CRT intraventricular asynchrony but not QRS duration was a significant independent predictor of reverse remodeling and clinical improvement.^{6,7}

Badano et al. recently showed that intraleft ventricular dyssynchrony was frequently present in patients with narrow (<120 ms) as well as normal QRS (<100 ms), while it was not detectable in up to 40% of LBBB patients.⁸ Accordingly, Bleeker et al. have reported that although about one-third of patients with wide QRS complex did not display substantial dyssynchrony, it was present in 27% of patients with narrow QRS.⁹

An issue that has not been addressed in the literature is whether the shortcoming of 12-lead surface ECG to accurately reflect the presence of dyssynchrony is at least partly attributed to its inherent inability to incorporate the delayed electrical activation of certain myocardial segments, which may still contribute to mechanical dyssynergy. This argument provided the rationale for our study hypothesis that the QRS duration as measured by the high-resolution analysis of SAECD may be better correlated with the presence of mechanical dyssynchrony. According to our results, the percentage of patients in the wide QRS complex category is significantly lower when QRSd is measured using SAECD as compared to surface ECG. It is thus evident that the implementation of this alternate method of QRSd measurement would differentiate

the heart failure patients considered eligible for CRT on the basis of electrical dyssynchrony as compared to the traditional surface ECG method. Furthermore, total ventricular activation time calculated by SAECC was shown to be significantly correlated with interventricular but not intraventricular dyssynchrony in the total patient population. In addition, the correlation of electrical and interventricular mechanical dyssynchrony was stronger when QRS duration was measured with SAECC as compared to conventional measurement or digital calculation of 12-lead surface ECG.

The premise of using the SAECC for measurement of total ventricular activation time is also supported by *ex vivo* studies that have demonstrated that mechanical dyssynchrony causes disparities in conduction velocity, action potential duration, and refractoriness.¹⁶ The induced electrophysiological remodeling and heterogeneity provide the necessary underlying milieu for the generation of fragmented potentials in the terminal portion of the QRS complex, which are not detectable by the conventional ECG. Furthermore, SAECC may blunt the discrepancy of electrical and mechanical asynchrony by enabling the electrical representation of myocardial areas with an abnormal kinesis detectable by imaging methods, which would have been excluded by the standard ECG because of their small mass.¹⁷

In the present study we also analyzed the relationship of electrical and mechanical dyssynchrony based on the type of underlying cardiomyopathy. According to our results, in the ischemic subgroup of patients mechanical dyssynchrony was not correlated with QRS duration as measured by either SAECC or 12-lead surface ECG. On the contrary, among patients with nonischemic cardiomyopathy, QRS duration was significantly correlated with interventricular but not intraventricular delay. Tournoux et al. have elegantly demonstrated the absence of correlation between electrical and mechanical dyssynchrony in ischemic patients, while in nonischemic patients both intra- and interventricular delay were correlated with QRS duration.¹⁸ Furthermore, Bleeker et al. also demonstrated no relation between QRS duration and intraventricular delay in patients with ischemic cardiomyopathy, while in nonischemic patients a weak correlation was demonstrated.⁹ Thus, the underlying cardiomyopathy seems to modify the relationship between QRS duration and mechanical dyssyn-

chrony, which is weaker among patients with heart failure of ischemic aetiology.

The poor correlation of QRS duration with mechanical dyssynchrony and response to CRT may also be to some extent attributed to the crude and inaccurate measurement of QRS duration on 12-lead surface ECG, resulting in the erroneous classification of candidates in the wide QRS complex category. Therefore, in the present study we compared the conventional method of QRS duration measurement on the 12-lead ECG with the on-screen measurement of computer-based ECG by using digital callipers, and we evaluated potential discrepancies in QRS duration values. Based on our findings, the two methods resulted in similar values of QRS duration and similar percentages of patients with wide QRS complex. However, this was not the case with the SAECC, which resulted in lower values of QRS duration and smaller percentage of patients classified in the broad QRS category.

Our study is mainly limited by the small number of included patients and the observational study design. The method used for assessment of intraventricular dyssynchrony is a TDI parameter examining the time to peak systolic contraction between two myocardial segments. Although this index of dyssynchrony is simple, easily applicable in everyday clinical practice and has been shown to be highly predictive of response to CRT,¹⁴ it appraises dyssynchrony only in the longitudinal axis without differentiating passive motion and true myocardial deformation.

In conclusion, the use of SAECC results in different patient classification in the wide QRS complex category as compared with surface ECG. Furthermore, QRS duration as measured by SAECC is correlated with interventricular but not intraventricular dyssynchrony in heart failure patients. The potential superiority of SAECC versus 12-lead surface ECG needs to be further addressed by large prospective trials focusing not only on the existing correlation with mechanical dyssynchrony but mainly on the prediction of response to CRT, which represents whatsoever the ultimate clinical target. In this context, the implementation of this alternate method of electrical dyssynchrony evaluation may improve our selection criteria and increase the response rate to CRT.

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