



Precision and reproducibility of non-automatic measurement of the QRS complex in potential candidates for cardiac resynchronization therapy



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ABSTRACT

Background: Accurate measurement of QRS complex duration (QRSd) remains crucial for the selection of patients for cardiac resynchronization therapy (CRT). However, assessment of QRSd on conventional surface electrocardiograms (ECG), especially when performed without computer assistance, may be challenging due to the limited accuracy of the human eye to discriminate differences in the range of 10 ms at 25 mm/s. The value and reproducibility of visual assessment of QRSd at 25 mm/s on conventional ECGs was compared to those obtained using an electrophysiology recording system (EPRS) with simultaneous 12 lead traces at 100 mm/s, which was considered the gold standard. **Methods:** The ECGs of 102 consecutive patients with left ventricular dysfunction undergoing electrophysiological evaluation were collected. Two sets of measurements were obtained: 1) QRSd-25 measured on conventional 12-lead ECGs printed at 25 mm/s with standard amplification (10 mm/mV) by 4 different observers, and 2) QRSd-100 measured on simultaneous 12-lead traces at 100 mm/s and 40 mm/mV by 2 different observers using electronic callipers.

Results: Significant differences were observed between QRSd-100 and QRSd-25 measurements (19.3 ± 9.9 ms, range 1.0–47.5, $p < 0.001$). QRSd-25 showed significant inter and intra-observer variability. When categorizing individual ECGs in three QRSd-25 subgroups (<120 ms, 120–149 ms and ≥ 150 ms), low concordance was observed between both techniques (kappa index 0.25, $p < 0.001$). The sensitivity and specificity of QRSd-25 to detect QRSd-100 ≥ 150 ms was 36.6% and 100.0% respectively.

Conclusions: Visual measurement of QRSd at 25 mm/s often underestimates its magnitude and presents significant inter and intraobserver variability.

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Introduction

Measurement of QRS complex duration (QRSd) using the 12-lead ECG remains the cornerstone for patient selection for cardiac resynchronization therapy (CRT). Patients enrolled in all pivotal clinical trials of CRT had a wide QRS complex regardless its morphology or the presence of bundle branch block [1–4]. According to these trial results, CRT is currently recommended in patients with QRSd over 150 ms, may be considered when the QRSd is 120–150 ms and is contraindicated in patients with QRSd <120 ms [5]. Visual assessment of the QRSd on conventional ECG traces is often used as an alternative to automatic ECG interval measurement by the ECG machine when this feature is not available or considered unreliable. However, estimating differences in the range of 10 ms on the basis of visual assessment of QRS

complexes printed at 25 mm/s speed on different and often non-simultaneous leads, can be challenging and may have low reproducibility. Conventional ECG traces were used in all pivotal CRT trials to determine the QRSd and it is unclear whether visual estimation, automatic interval measurement by the ECG machine, or both were performed for the latter determination.

The aim of the present study was to investigate the accuracy and reproducibility of visual measurement of QRSd on conventional 12 lead ECG tracings printed at 25 mm/s.

Methods

Patients

We retrospectively selected a sample of consecutive patients with left ventricular dysfunction (left ventricular ejection fraction $\leq 35\%$) undergoing electrophysiological evaluation. The duration of the QRS was not considered an inclusion or exclusion criterion in the study because

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the rationale was to evaluate the performance of visual assessment among different ranges of QRSD. Therefore, both patients with QRS complexes considered narrow and wide were included. Persistent non-supraventricular conduction (incessant ventricular tachycardia or ventricular pacing) during the study and channelopathies or other repolarization abnormalities that may limit the quantification of QRSD were considered exclusion criteria. The study protocol was approved by the Institutional Ethics Committee.

Data collection

Stored ECGs from a multichannel electrophysiology recording system (LabSystem© Pro EP recording System, Boston Scientific, Boston, MA, USA) were printed at 25 mm/s and 10 mm/mV amplification using a conventional format of 4 columns each of them presenting 2.5 s of 3 simultaneous ECG leads. In addition, the same tracings were displayed on the EP recording system at 100 mm/s and 40 mm/mV amplification. Subsequently, the following measurements of the QRSD were performed:

- Assessment on the printed ECGs (QRSD-25) by 4 independent observers blinded to each others' measurements: 2 clinical cardiologists (CAR1 and CAR2) and 2 cardiology fellows (FLW1 and FLW2). The interobserver reproducibility of QRSD-25 measurement was calculated with these 4 values. In addition, a senior medical student (MED) completed two sets of measurements on different days to determine if there was significant intraobserver variability of QRSD-25 measurement (QRSD-25-MED).
- Assessment on the EP recording system using electronic callipers with an accuracy of ±1 ms (QRSD-100) by 2 independent observers blinded to the others' measurements: an electrophysiologist (EP) and a senior medical student (MED). The interobserver reproducibility of QRSD-100 measurement was calculated with these 2 values. The latter observer completed two sets of measurements on different days to analyse if there was significant intraobserver variability of QRSD-100 measurement. The QRSD-100 was considered the gold standard of QRSD in this study.

The ECG signal was filtered between 0.01 and 100 Hz for both the QRSD-25 and QRSD-100 measurements. The average of the QRSD-25 values measured by the 4 observers was compared with the QRSD-100 values measured by the EP (QRSD-100-EP). The correlation between both values was studied.

Statistical analysis

Quantitative variables are presented as mean ± standard deviation, and categorical variables as counts and percentages. The Student-Fisher *t*-test and the ANOVA test were used to compare two or more means, respectively. Categorical variables were analysed using the chi-square test, and the Kappa index was employed as a measure of agreement. The correlation between quantitative variables was estimated with the Pearson correlation coefficient. Prior to data collection, we estimated a sample size of 99 patients to detect a difference of at least 10 ms in the QRSD between ECGs conventionally measured at 25 mm/s and those measured in the EP recording system at 100 mm/s, for a standard deviation of 20 ms, an alpha error of 0.05 and a beta error of 0.10 (estimation of exclusion of 15% ECGs). According to the study protocol, the results were stratified in three categories of QRSD (<120 ms, 120–149 ms and ≥150 ms). A two-sided *p* value of <0.05 was considered statistically significant. All analyses were performed using the SPSS 22.0 computer package, IBM, Armonk, NY, USA.

Table 1
Interobserver variability of the QRSD-ECG25 and QRSD-EPS100 assessment (milliseconds).

	CAR1	CAR2	FLW1	FLW2	ECG-25	EPS-100
Mean	128.2	126.9	126.3	111.8	123.3	141.8
SD	27.9	29.0	30.2	21.2	26.0	26.9
Minimum	90.0	80.0	80.0	80.0	85.0	94.0
Maximum	230.0	260.0	240.0	195.0	222.5	224.0

Abbreviations: CAR clinical cardiologists, FLW cardiology residents, ECG-25 mean assessment performed by all observers. EPS-100 measurement performed by an experienced electrophysiologist using an electronic polygraph.

Results

Baseline characteristics

ECGs from 102 patients were finally included in the analysis. Eighty-four (82.4%) were men and had a mean age of 65.0 ± 16.8 years. Left ventricular ejection fraction was 27 ± 7% (range 10–35). Ischemic heart disease was the most frequent aetiology among the study population (45.1%) and nearly one third of the patients presented a history of myocardial infarction. Idiopathic dilated cardiomyopathy was the second most frequent cause (28.4%). Regarding heart rhythm, 66 patients (64.5%) were in sinus rhythm, 19 (18.6%) in atrial fibrillation and 17 (16.9%) in atrial flutter. Sixty-five percent of the patients had normal intraventricular conduction, while 17% presented left bundle branch block (LBBB), 9% complete right bundle branch block (RBBB) and the remaining 9% had RBBB and left anterior hemiblock.

QRSD-25 vs QRSD-100 difference

Mean QRSD-25 was 19.3 ± 9.9 ms (range 1.0–47.5) shorter than QRSD-100 (*p* < 0.001) (Table 1). The observers consistently selected the precordial leads V2 and V4 as those in which the longer QRSD-25 was most apparent (Table 2).

The electrocardiograms were classified into three subgroups (<120 ms, 120–149 ms and ≥150 ms) according to the results obtained using both types of measurements (QRSD-25 and QRSD-100-EP). A weak concordance between both techniques was noted (Kappa index 0.25, *p* < 0.001). Only 31.6% and 36.6% of the tracings with QRSD-100 of 120–149 ms and ≥150 ms respectively were identified as such by QRSD-25 (Table 3).

Table 4 and Fig. 1A show the results obtained when categorizing the measurements into two unique groups, <150 ms and ≥150 ms. The sensitivity and specificity to detect QRS complexes ≥150 ms by QRSD-25 was 36.6% and 100.0% respectively. No statistically significant relationship was observed between the different baseline cardiac rhythm and the leads with the longer QRSD. There were also no significant differences between the baseline cardiac rhythm and the mean difference between QRSD-25 and QRSD-100.

Interobserver and intraobserver variability

The correlation between QRSD-100-EP and QRSD-25 ranged from 0.80 to 0.90 (Table 5). The results obtained by the CAR observers were more concordant with QRSD-100 than those obtained by the FLW observers. Interobserver variability between QRSD-100-EP and the QRSD-100 measured by the senior medical student (QRSD-100-MED) was very low and the correlation was excellent (*r* = 0.993, *p* < 0.001).

Table 2
Leads with the broader QRS complex as assessed by the observers.

	I	II	III	aVR	aVL	aVF	V1	V2	V3	V4	V5	V6
Frequency	12	12	18	0	5	10	30	98	73	105	31	6
Percentage	3.0	3.0	4.5	0.0	1.25	2.5	7.5	24.5	18.25	26.25	7.75	1.5

Table 3
ECG categorization using visual assessment of ECGs previously analyzed using the poligraph (gold standard).

		QRSd-EPS100 (n, %)		
		<120 ms	120-149 ms	>150 ms
QRSd—ECG25 (n,%)	<120 ms	22 (95.7)	26 (68.4)	3 (7.3)
	120-149 ms	1 (4.3)	12 (31.6)	23 (56.1)
	>150 ms	0 (0.0)	0 (0.0)	15 (36.6)

Table 4
Contingency table for the duration of the QRS categorized in <150 ms and ≥150 ms (considering QRSd-EPS100 the reference technique).

		QRSd-EPS100 (n, %)		
		<150 ms	≥150 ms	Total
QRSd-ECG25 (n,%)	<150 ms	61 (100.0)	26 (63.4)	87
	≥150 ms	0 (0.0)	15 (36.6)	15
	Total	61	41	102

With regard to intraobserver variability, the correlation of the two measurements performed by the medical student of the QRSd-25-MED and QRSd-100-MED were 0.94 and 0.99 respectively. The mean difference between both measurements of QRSd-25-MED and QRSd-100-MED was 8.3 ± 7.3 ms (range 0–20) and 2.9 ± 2.0 ms (range 0–8) respectively. The mean difference between QRSd-25-MED and

QRSd-100-MED was similar to that obtained by the other observers (20.1 ± 10.3 ms, range 0–49). Categorization of QRSd in <120 ms, 120–149 ms and ≥150 of the measurements performed by the medical student also showed poor concordance between QRSd-25 and QRSd-100 (Kappa index 0.22, $p < 0.001$, Table 6 and Fig. 1B).

Discussion

CRT has been tested in different randomized clinical trials showing remarkable improvements in dyssynchrony, left ventricular systolic function and the whole natural history of patients with heart failure and reduced ejection fraction. However, approximately 30% of implanted patients are finally considered non-responders to this therapy [6]. Thus, it is essential to improve the work-up process for the selection of potential CRT candidates. QRS duration is considered the key parameter with the closest relationship to clinical and echocardiographic outcomes, even above asynchrony markers reported from different imaging techniques. Therefore, it is important to improve accuracy and reproducibility of QRSd assessment, in order to avoid unnecessary indications of CRT and not to lose appropriate indications. The present study tried to evaluate a wide range of QRS durations and not only those which were broader in order to test if there is underestimation or overestimation of the true QRSd by conventional measurement. Both possibilities are relevant and have significant clinical implications.

Our study demonstrated that both the accuracy and reproducibility of conventional visual QRSd measurement is suboptimal. Conventional QRSd-25 assessment failed to identify 26 of the 41 patients who presented QRSd ≥150 ms when measured by an optimized method using simultaneous leads at 100 mm/s and electronic callipers. Only one patient with QRSd-100 between 120 and 149 ms had LBBB morphology, which may have justified by itself the indication for CRT therapy. These findings suggest that conventional selection of CRT candidates performed in daily clinical practice might be inadequate in a significant number of patients. These findings are aligned with those found in several papers reporting significant differences between QRSd measured visually by human observers and automatically by the electrocardiographic machine, or between different commercially available electrocardiographs [7–11]. However, little is known about inter- and intra-observer variability of QRSd measured visually by different observers, or the magnitude of differences when compared to a more precise method of measurement such as the one used in this report (simultaneous tracings of all 12 leads at 100 mm/s with voltage amplification and the aid of electronic callipers). The precision of this specific method

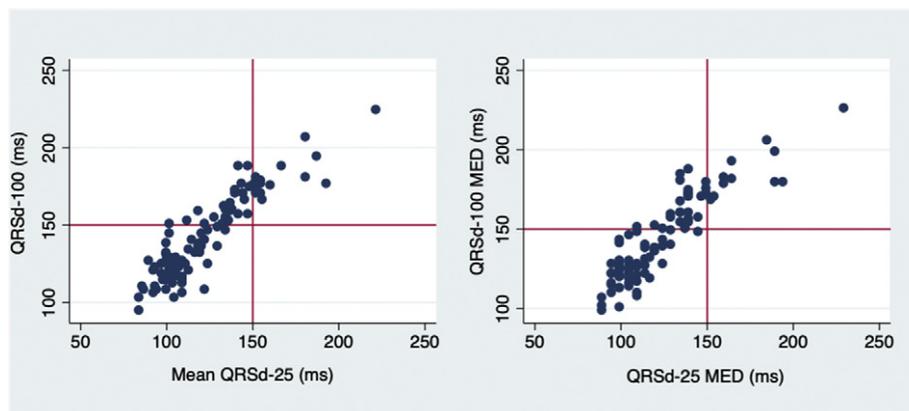


Fig. 1. Correlation of QRSd conventionally measured with that using a more precise methodology by an electrophysiology recording system. Each point in the graph corresponds to a single patient and illustrates the measurement of the QRSd obtained by both methods. Left panel displays the dot plot regarding measurements performed by the clinical cardiologists and the electrophysiologist. Right panel shows the same measurements performed by the medical student. All patients who are located in the upper left quadrant of the graph had a QRSd ≥150 ms when measurement by the electrophysiology recording system but <150 ms when measured conventionally. These patients may potentially benefit from CRT therapy but are not classified as such by conventional visual ECG QRSd measurement.

Table 5
Correlation matrix including the measurements performed by all observers.

	CAR1	CAR2	FLW1	FLW2	EPS
CAR1	1	0.930 p < 0,001	0.917 p < 0,001	0.855 p < 0,001	0.906 p < 0,001
CAR2	0.930 p < 0,001	1	0.927 p < 0,001	0.856 p < 0,001	0.894 p < 0,001
FLW1	0.917 p < 0,001	0.927 p < 0,001	1	0.873 p < 0,001	0.876 p < 0,001
FLW2	0.855 p < 0,001	0.856 p < 0,001	0.873 p < 0,001	1	0.800 p < 0,001
EPS	0.906 p < 0,001	0.894 p < 0,001	0.876 p < 0,001	0.800 p < 0,001	1

Abbreviations: CAR clinical cardiologists, FLW cardiology fellows, EPS measurement performed by an electrophysiologist using an electronic polygraph.

Table 6
Categorization of the QRSD as measured by the medical student using conventional manual assessment in the electrocardiograms previously quantified with the polygraph (considered the reference technique).

QRSD-MED-EPS100 (n, %)

QRSD-MED-ECG25 (n, %)

	<150 ms	120-149 ms	≥150 ms
<150 ms	19 (100.0)	31 (72.1)	1 (2.5)
120-149 ms	0 (0.0)	12 (27.9)	24 (60.0)
≥150 ms	0 (0.0)	0 (0.0)	15 (37.5)

is supported by the high inter and intraobserver reproducibility found in the study. Interestingly, this reproducibility was also found when comparing the best possible observer (a senior electrophysiologist) with one with little ECG experience (a medical student). Conventional visual measurement of the QRSD-25 showed better correlation with QRSD-100

in the measurements performed by the senior cardiologists than those performed by the cardiology fellows and, therefore, may be more dependent on the training of the individual observer.

Definition of the onset and ending points of the QRS complex may be the main source of error when using conventional QRSD-25 assessment [12]. The QRS vector reflects the sum of the myocardial electrical forces that fluctuate during electrical systole and, therefore, may result in low amplitude or even isoelectric deflections in some leads when these forces are opposed and neutralized by others. Most digital electrophysiology recording systems implement amplification of electric forces, decreasing the chances of them going unnoticed. In addition, they also allow simultaneous assessment of all 12 leads, preventing inadequate measurement of the beginning or end of the QRS complex in a lead where the initial or terminal forces are isoelectric. In addition, higher resolution at 100 mm/s and the use of electronic callipers consistently increases the accuracy of the measurement (Fig. 2). The 4-column display of the 12 lead ECG is the most commonly used in clinical practice. For this reason, this was the selected format in order to assess differences in QRSD-25 complex duration between different operators.

Our findings raise concerns about present patient selection for CRT by conventional QRSD measurement. It may be argued that the current indications for CRT are based on the results of the pivotal studies which used conventional measurement of QRSD at 25 mm/s. However,

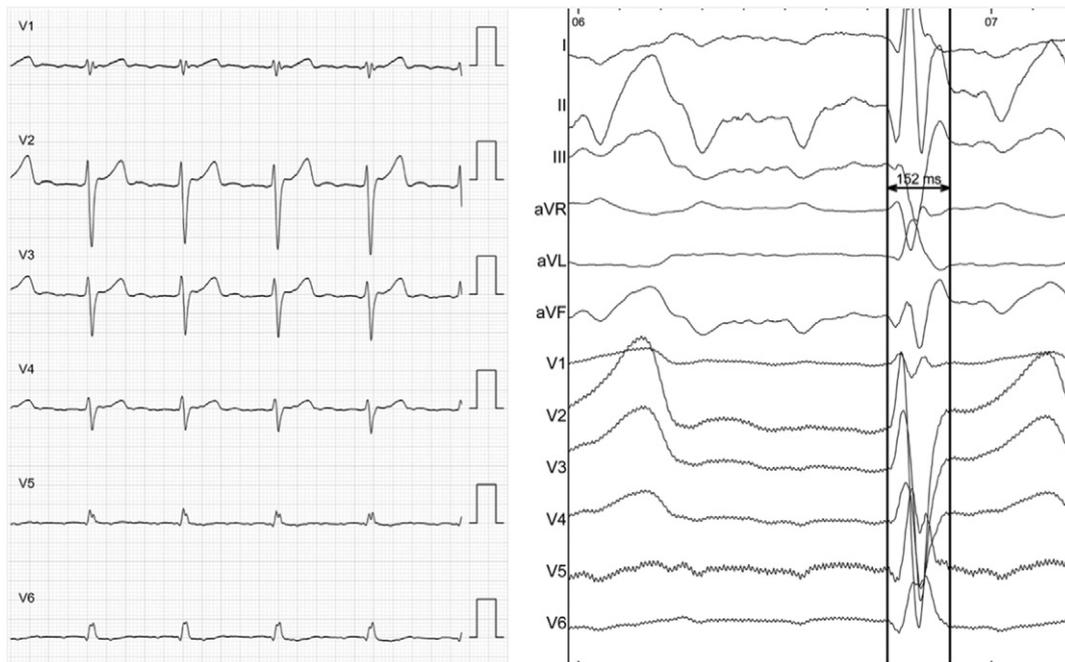


Fig. 2. QRSD measurement conventionally at 25 mms (left) and at 100 mm/s and high amplification with the assistance of an electrophysiology recording system (right) in the same patient. The mean QRSD-25 measured by the four clinical observers was 126 ms (CAR1 130, CAR2 130, FLW1 122 and FLW2 120 ms) while the QRSD-100 measured by the electrophysiologist was 152 ms.

whether visual measurement or automatic measurement by the ECG machine was used is not explicitly reported in any of them. This question is relevant according to our results and should be incorporated to future trials or recommendations in order to improve patient selection for CRT.

Limitations

This is a retrospective study, with the inherent limitations of this type of design. However, consecutive patients were selected in order to minimize possible enrolment biases. Although the study population may be considered small, it was determined by the sample size calculation performed during the design phase. In fact, observed differences in the sample exceeded those initially predicted. On the other hand, the time and motivation that observers had to perform all QRSd measurements are probably different than those employed in daily clinical practice and may have resulted in smaller differences between QRSd-25 and QRSd-100. Although QRSd is an important factor to set the indication for CRT, other factors such as the QRS complex configuration, are also important and have not been fully evaluated in this study. Another limitation is the involvement of a medical student to assess the interobserver variability of the QRSd-100 and intraobserver variability of both techniques. However, this condition was intentionally included in the protocol in order to compare the most favourable (senior electrophysiologist) and unfavourable (medical student) scenarios in term of ECG experience for the measurement of the QRSd-100. Despite this, the correlation of both observers was excellent and supported the use of QRSd-100 as the gold standard measurement of the QRSd.

Conclusions

Precision and reproducibility of conventional visual QRSd assessment at 25 mm/s are low. This methodology often leads to underestimation of the QRSd duration and is influenced by the observer experience. These findings may have relevant implications in the way contemporary CRT candidates are selected.

Author contributions

All authors have made substantial contributions to: (1) the conception and design of the study, or acquisition of data, or analysis and

interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Declaration of competing interest

There are no conflicts of interests related to this work. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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