VENTRICULAR DYSSYNCHRONY IS COMMON AMONG HEART FAILURE PATIENTS WITH NARROW QRS COMPLEX

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ABSTRACT:

Current selection guideline for CRT uses broad QRS duration (>120 ms) as a marker for ventricular dyssynchrony. However, more recent data supports mechanical marker specifically measured by Tissue Doppler Imaging (TDI) as a better criterion to predict response to CRT. Sixty seven patients with significant left ventricular dysfunction (EF less than 40%) and narrow QRS complex were prospectively enrolled. They underwent Tissue Doppler Imaging (TDI) study to evaluate intraventricular mechanical dyssynchrony. Dyssynchrony index which is defined as standard deviation of time to peak systolic velocity in twelve ventricular segments was measured. A value greater than 32.6 is taken to reflect significant ventricular dyssynchrony. Overall 38 patients (56.7%) demonstrated significant dyssynchrony. There was no significant correlation between QRS duration and the Ts-SD-12 ($r = 0.14$, $p = 0.11$). Ventricular mechanical dyssynchrony is common in patients with normal QRS duration. Therefore, QRS duration alone will miss a substantial proportion of suitable patients for CRT and therefore deny them this adjunct therapy. We propose echocardiographic parameters, specifically TDI, to be included in patient selection criteria for CRT.
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KEYWORDS: *oab, luts, validation, translation, questionnaire*

Introduction

Cardiac Resynchronization Therapy (CRT) in the form of biventricular pacemaker has been shown to be an effective adjunct therapy in patients with drug-refractory heart failure and evidence of ventricular dyssynchrony (1-5). The current guidelines include broad QRS complex (greater than 120 milliseconds) as a marker for ventricular dyssynchrony (electrical dyssynchrony) (6). Nevertheless, emerging recent data support mechanical dyssynchrony as measured by Tissue Doppler Imaging (TDI) as a better predictor to CRT as compared to electrical dyssynchrony (7-11).

Aims

Our aims were to:

1. Determine the prevalence of ventricular dyssynchrony by using TDI among heart failure patients with narrow QRS complex.
2. Evaluate the correlation between QRS duration and ventricular dyssynchrony.

Methods

This study was approved by the University of Malaya Medical Centre research ethics committee.

Patients

The population consisted of 67 consecutive patients who were referred the echocardiography laboratory and who fulfilled the following criteria :

1. Age greater than 18 years old.
2. Left ventricular ejection fraction of less than 40%.
3. Narrow QRS complex as defined as less than 120 milliseconds.

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Patients with pacemaker or CRT were excluded from this study.

We did not include the functional class as one of the inclusion criteria because this was a study to specifically look at mechanical dyssynchrony as assessed by TDI. We felt functional class would be important if this were to assess the response of patients to CRT.

Echocardiography

Images were obtained with patients in the left lateral decubitus position using iE-33 (Phillips Medical System). Conventional 2-D M-Mode method was used to determine the ejection fraction, left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD). Aortic valve opening and closing time were measured from the apical 5-chamber view.

Tissue Doppler Imaging (TDI)

Tissue Doppler colour imaging was performed using 3.5-MHz transducer in apical long axis and apical 2- and 4-chamber views. Gain setting was adjusted accordingly to optimize colour saturation. Frame scanning rate of 100-140 Hz was used. At least three consecutive beats were stored and the images were digitalized and analyzed offline by using QLAB 5.0 (Phillips medical) software. Myocardial regional velocity curves were constructed from the digitalized images. The sampling was placed on the basal and middle segments of the septum and lateral walls (4-chamber view), inferior and anterolateral walls (2-chamber view) and posterior and anterior walls (apical long axis view). The beginning of QRS complex was taken as the reference point. The velocity curves from the three beats were averaged and the time to peak systolic velocity from the beginning of QRS complex was measured for each of the twelve segments. The standard deviations of the twelve segments peak velocities (Dyssynchrony index) were calculated and a value of greater than 32.6 ms was regarded as significant ventricular dyssynchrony.

ECG analysis

Standard 12-lead electrocardiograms were acquired at a paper speed of 25mm/second and a scale of 10 mm/mV. Prolonged QRS duration is defined as greater than 120 milliseconds.

Lead II was used to measure the QRS duration. Five QRS complexes were measured manually using standard ruler and the average value was taken as the final QRS duration.

Statistical analysis

Data were analyzed using statistical SPSS software (version 14.0, SPSS Inc., Chicago, Illinois). All parametric variables were compared using independent *t*-test. For comparison between more than two variables analysis of variance (ANOVA) was used. Pearson's correlation was used to examine the relationship of two continuous variables. Non-parametric variables were analyzed using Pearson's $\chi 2$ test. A probability value of $p < 0.05$ (2-sided) was considered to be significant. The measurement of dyssynhcrony index was performed by single investigator and the intraobserver variability was expressed as Pearson's correlation coefficient.

Results

Baseline characteristics are listed in Table I. The "uncertain" aetiology represented those patients who were newly diagnosed to have impaired left ventricular function and were still under investigation at the time of this study. We found 38 out of 67 (56.7%) patients had significant ventricular dyssynchrony. There was no significant correlation between QRS duration and dyssynchrony index ($r=0.09$ $p=0.47$) (Figure 1). The comparison of characteristics of patients and echocardiographic parameters between those with and without LV dyssynchrony is illustrated in Table II. The intraobserver correlations for 10 randomly selected patients for dyssynhcrony index is 0.98 ($p < 0.001$).

Discussion

Different methods are currently being used to assess mechanical ventricular dyssynchrony (7-11). The dyssynchrony index, introduced by Yu (9), is thought to be the best method since it has shown excellent sensitivity and specificity in predicting response to CRT (10-11). The cut-off 32.6 millisecond is derived from the mean plus two standard deviation of the normal population in the study conducted by Yu and his colleagues (9).

The finding of the presence of ventricular dyssynchrony among heart failure patients with narrow QRS complex in this study is consistent with other studies around the world (9, 12-14). Unfortunately, these patients were excluded from CRT based on the current selection criteria.

The QRS complex represents the vectorial sum of electrical forces generated by myocardial masses over time. It is unable to convey the presence and severity of electrical delay in all ventricular segments and correlates particularly poorly with disturbance of distal conduction tissue. Furthermore, since QRS duration is only influenced by significant myocardial masses, regional changes represented by small vectors are inadequately displayed.

Interestingly, Auricchio *et al* documented heterogeneous left ventricular (LV) activation among heart failure patients with left bundle branch block morphology via LV endocardial mapping (15). Functional lines of block with different anatomic location within the LV were demonstrated and surface ECG recordings were unable to predict location and extent of ventricular conduction delays. This was compatible with tissue Doppler imaging (TDI) findings of variable location as well as extent of mechanical LV dyssynchrony that could not be predicted from QRS duration of a surface ECG.

In short, electrical dyssynchrony may well be linked to mechanical dyssynchrony but surface ECG is not sensitive enough to detect regional electrical delays as TDI does for regional mechanical delays. Secondly, some of these patients may have mechanical dyssynchrony without significant electrical delay in the presence of myocardial disease which does not involve the conduction pathway.

Moreover, Achilli *et al* demonstrated that clinical and functional benefit of CRT was similar in patients with wide or narrow QRS complex (16). It was the first study that included patients with mechanical dyssynchrony demonstrated by echocardiography but narrow QRS complex in looking for the benefit of CRT. Another more recent and larger study by Yu *et al* also showed CRT for heart failure patients with narrow QRS complex and coexisting mechanical dyssynchrony by TDI resulted in left ventricular reverse remodeling and improvement of clinical status (17). The extent of the benefit was similar to that of wide QRS complex group.

We certainly need RCT to evaluate the response of the patients with narrow QRS complexes to CRT. Although studies so far have not shown favourable response to CRT for patients with narrow QRS complexes but those studies were small and from single centre trials. We need more evidence to illustrate convincingly ventricular dyssynchrony is common in patients with normal QRS duration. Ultimately, in order to change the practice, we need trials with large number of patients that include those with narrow QRS complex for CRT and show its benefits to them.

Table 1: *Patient Characteristics and Echocardiographic Data (n = 67)*

Variables	Value (n=%)
1. Gender	
Male	53 (79.1%)
Female	14 (20.9%)
2. Mean Age	59.1 (27.0-92.0)
3. Aetiology	
Ischaemic	37 (55.2%)
Non Ischaemic	11 (16.4%)
Uncertain	19 (28.4%)
4. Diabetes Mellitus	37 (55.2%)
5. Hypertension	40 (59.7%)
6. New York Heart Association Class	
Ii	33 (49.3%)
Iii	31 (46.3%)
Iv	3 (4.5%)
7. Medications	
Acei	49 (73.1%)
Beta-Blocker	29 (43.3%)
Digitalis	12 (17.9%)
Diuretics	44 (65.7%)
Statin	44 (65.7%)
Aspirin	52 (77.6%)
Anticoagulants	7 (10.4%)
8. Mean Lv Ejection Fraction (Ef) (Range)	25.4% (10.0-40.0%)
9. Mean Lv End Systolic Diameter (mm) (Range)	50.8 (30.0-78.0)
10. Mean Lv End Diastolic Diameter (mm) (Range)	59.1 (43.0-85.0)
11. Rhythm	
Sinus	61 (91.0%)
Atrial Fibrillation	6 (9.0%)
12. Mean Qrs Duration (Ms) (Range)	94.6 (74.0-117.0)

Table 2: *Univariate analysis of lifestyle factors between cases and controls*

Variables	Patients with LV dyssynchrony (n)	Patients without LV dyssynchrony (n)	*p* value
Gender			
Male	29	24	0.52
Female	9	5	
Age (mean ± SD)	58.2 ± 13.1	60.1 ± 12.8	0.55
Aetiology			
Ischaemic	18	19	0.29
Non-ischaemic	8	3	
Uncertain	12	7	
NYHA class			
II	22	11	0.21
III	14	17	
IV	2	1	
Diabetes Mellitus	19	18	0.32
Hypertension	23	17	0.88
Medications			
ACEI	28	21	0.91
B-blocker	18	11	0.44
Rhythm			
Sinus	36	25	0.23
Atrial Fibrillation	2	4	
Ejection Fraction (%) (mean ± SD)	26.1 ± 7.6	24.5 ± 7.6	0.39
LVESD (mm) (mean ± SD)	51.6 ± 11.0	49.6 ± 8.3	0.42
VEDD (mm) (mean ± SD)	60.0 ± 10.7	57.9 ± 7.1	0.36

Although several studies have consistently shown that TDI improves patient selection for CRT, the lack of uniformity of the method used to assess ventricular dyssynchrony limits its function at present. Different centers have their own method and technique to define ventricular dyssynchrony. Although the standard deviation of peak systolic velocity of twelve left ventricular segments (Dyssynchrony index) seems promising, but more data is needed to support its use as a standard method.

Our limitation is that, although the dyssynchrony index value of 32.6 is a reasonable value to be used in this study since our local population are not very dissimilar in term of ethnic or geographical background to that in Yu's study, inclusion of normal controls to determine our own cut-off value and test its sensitivity and specificity for patient selection for CRT would be ideal. However, the number of our new CRT patients is relatively small; thus such study would take quite a long period to reach a reasonable target number of patients.

Conclusion

Ventricular dyssynchrony is common in heart failure patients with normal QRS duration. QRS duration

alone is not predictive of mechanical dyssynchrony as detected by TDI. Further studies especially large RCT's are needed to evaluate the response of heart failure patients with narrow QRS complexes to CRT. The selection criteria for cardiac resynchronization therapy may need to include echocardiographic parameters so that the benefit of this technology may be extended to a greater population.

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