Changes in left ventricular synchrony and systolic function in dilated cardiomyopathy patients with fragmented QRS complexes

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Aims
Fragmented QRS (f-QRS) complexes are associated with adverse cardiovascular events in patients with coronary heart disease; however, the effects on patients with dilated cardiomyopathy (DCM) remain elusive. This study is to investigate the changes of left ventricular (LV) synchrony and systolic function in DCM patients with f-QRS complexes.

Methods and results
Twenty DCM patients with f-QRS complexes and 29 DCM patients without f-QRS (n-QRS) complexes were enrolled. The LV segmental longitudinal, radial and circumferential time to peak strain and general longitudinal systolic strain, radial strain, circumferential strain were measured, respectively, by speckle tracking imaging. The LV segmental standard deviations and maximal differences were also calculated. The LV dyssynchrony was defined as the time in peak anteroseptal wall to posterior wall strain > 130 ms or longitudinal strain delay index > 25%. The mean QRS durations in f-QRS and n-QRS groups were not different (P = ns). The incidence of LV dyssynchrony was 15/20 (75%) vs. 5/29 (17%) in two groups (P < 0.01). Two patients died of sudden death in f-QRS group during 2 years follow-up; however, no death in n-QRS group (P < 0.05). Patients in f-QRS group showed worsening LV dyssynchrony in f-QRS group after 2 years follow-up (P < 0.05). Overall, LV function was comparable at baseline (P = ns), but had significantly worsened only in the f-QRS group (P < 0.05).

Conclusion
The f-QRS complex is significantly associated with LV dyssynchrony in DCM patients and can be used as a reliable index to evaluate ventricular synchrony and predict the prognosis in DCM patients with narrow QRS complexes.

Keywords
Fragmented QRS complex • Dilated cardiomyopathy • Ventricular dyssynchrony • Speckle tracking imaging

Introduction
Dilated cardiomyopathy (DCM) is characterized by ventricular dilation and reduced systolic function. Patients with DCM usually manifest with progressive heart failure, arrhythmias, and/or sudden cardiac death. Some DCM patients have intra-ventricular conduction block or bundle branch conduction block, displaying a wide QRS complex on surface electrocardiograms (ECGs). In the last decade, cardiac resynchronization therapy (CRT) has been established as one of the important therapeutic strategies for DCM patients with wide QRS and heart failure; however, CRT guidelines emphasize that the patients undergoing CRT must have inter- or intra-ventricular dyssynchrony, as demonstrated by a wide QRS complex on ECGs, preferably with complete left bundle branch block. According to these criteria, only a relative small proportion of DCM patients with heart failure are suitable candidates for CRT. On the other hand, many studies have shown that 20 to 50% patients with heart failure and normal QRS complex (n-QRS) have mechanical ventricular dyssynchrony. These data suggest that using QRS duration as the only criterion to detect dyssynchrony may have limitations. Recent trials (RETHinQ, Echo-CRT, etc.) attempting to use echocardiographic criteria for selection of patients with narrow QRS for CRT have not been promising, and therefore current CRT guidelines limit clinicians to selecting patients with wide QRS complexes.

In recent years, fragmentation of the QRS complex has been studied in many cardiovascular diseases. It has been reported that a fragmented QRS (f-QRS) complex in patients with coronary heart disease is associated with adverse cardiovascular events, and some
What’s new?

- This is the first assessment on left ventricular (LV) synchrony and systolic function in idiopathic dilated cardiomyopathy (DCM) patients with fragmented QRS (f-QRS) complexes in 2 years follow-up by speckle tracking echocardiography (STE) technique.
- The study confirms that f-QRS complex is significantly associated with LV dyssynchrony in idiopathic DCM patients and may be used as a reliable electrocardiography clue to assess LV dyssynchrony and predict prognosis in patients with idiopathic DCM.
- The results show that the percentage of LV dyssynchrony in f-QRS group is remarkably higher than that in control group. More importantly, the results assessed by STE are quite consistent with the clinical evaluations. Speckle tracking echocardiography may accurately assess the LV synchrony and systolic function in DCM patients with f-QRS complexes.

studies have demonstrated that f-QRS complex may be used as a predictor of LV dyssynchrony in non-ischaemic DCM. In assessing LV dyssynchrony, tissue Doppler imaging is usually used in clinical practice; however, there are no data that report on assessment of LV synchrony and systolic function by speckle tracking echocardiography (STE) in DCM patients with f-QRS complexes. Therefore, we investigated the relationship between f-QRS complex and LV dyssynchrony in DCM patients with STE.

Methods

Study population

Forty-nine consecutive patients with idiopathic DCM were recruited in this study. The inclusion criteria for DCM were as follows: (i) patients with cardiac enlargement, reduced LV systolic function, with or without clinical congestive heart failure; (ii) x-ray and echocardiographic evidence for cardiac enlargement, with LV dilation defined as LV end-diastolic diameter > 55 mm, LV ejection fraction (LVEF) ≤ 50%, and globally reduced ventricular wall motion; (iii) patients with secondary causes of cardiomyopathy, such as ischaemic DCM, perinatal cardiomyopathy, valvular disease, alcoholic cardiomyopathy, and others caused by metabolic or secretory diseases, were excluded. Ischaemic DCM was excluded by coronary angiography or coronary computer tomography. Other secondary cardiomyopathies were excluded by a combination of detailed patient histories, physical examination findings, and by coronary angiography or coronary computerized tomography. All patients when enrolled were in sinus rhythm and those in atrial fibrillation were excluded. However, patients with a history of atrial fibrillation who were in sinus rhythm at the time of enrolment were also included in the study. The protocol was approved by the Institutional Review Board for Biomedical Research of Wuxi People’s Hospital affiliated to Nanjing Medical University, and all patients gave informed consents consistent with this protocol.

ECG analysis

The resting 12-lead surface ECGs (recorded at filter settings of 0.5–150 Hz, paper speed 25 mm/s, voltage standardization 10 mm/mV) were independently analysed by two experienced electrocardiographers who were blinded to the echocardiographic data. In case of disagreement, the final diagnosis was achieved by mutual agreement and confirmed by a third ECG reviewer. An f-QRS complex was defined as the presence of various RSR’ patterns in two or more than two contiguous leads,

including the presence of an additional R wave (R’) or more than one R’, or notchting in the upstroke of the R wave or nadir of the S wave. The inclusion criteria for ECGs with f-QRS complex were as follows: (i) QRS duration < 120 ms, (ii) one or more than one notch of Qr or QR patterns in the QRS complex, (iii) absence of complete or incomplete bundle branch block or left anterior/left posterior fascicular block (Figure 1). The patients were categorized into f-QRS group and n-QRS group according to whether there were f-QRS complexes in 12-lead surface ECGs or not.

Echocardiographic examination

Philips IE33 color Doppler ultrasound instrument and two-dimensional cardiac probe (Philips Ultrasound, 22100 Bothell-Everett Highway Bothell, WA, USA) with frequency 2.0–3.5 MHz and frame rate (75 ± 8) frames/s were used in this study. The instrument was equipped with a QLAB multi-parameter analysis workstation. Echocardiography examinations were performed in all patients with left lateral decubitus position and ECGs were recorded simultaneously. Patients breathed normally during the image acquisition. Left ventricular end-diastolic diameter (LVEDD), LV end systolic diameter (LVEDS), LV end systole volume (LVESV), LV end-diastolic volume (LVEDV), and LVEF were measured in apical four- and two-chamber views with the Simpson method. Mitral regurgitant volume was determined using semi-quantitative and quantitativecolour Doppler-based parameters. Two-dimensional images were acquired and stored in LV apical long-axis four- and two-chamber views and in the para-sternal short-axis mitral valve, papillary muscle, and apical levels for three cardiac cycles. Repeat imaging was obtained in all patients after 2 years follow-up. Measurement was performed by two experienced echocardiographers who were blinded to the clinical and ECG data. All data were stored on hard disk, and the images with source formatting were copied to the workstation for off-line analysis.

Two-dimensional speckle tracking echocardiographic examination and analysis

Speckle tracking echocardiography technique is dependent on frame rate and image resolution. Two-dimension STE examination and analysis were performed as reported in previous studies.

The timing of the aortic valve opening and closing was determined by analysis of the aortic blood flow spectrum. Endocardium was manually traced with appropriate software. The tracked myocardial segment strain curve, strain peak, and the time to peak strain were automatically recorded with software. The durations from the start of the QRS complex to systolic 1 longitudinal peak strain in LV apical long-axis view, and systolic radial and circumferential peak strains in parasternal short-axis view were measured and analysed. The magnitude of strain in each segment was also measured at the same time as follows: (i) The LV global longitudinal, radial, and circumferential strains were calculated, respectively. Eighteen-segment mean strain peaks in long-axis view were defined as global longitudinal strain (GLS), whereas global circumferential strain and global radial strain were both obtained in short-axis views; (ii) standard deviations of LV systolic longitudinal strain, radial strain, circumferential strain, and the segmental maximal difference were also calculated; (iii) the presence of LV dyssynchrony was defined if the time from peak anteroseptal wall to posterior wall strain was ≥ 130 ms; (iv) longitudinal strain delay index (LSDI) was defined as the sum of 18-segment longitudinal peak strain and end systolic strain difference when the aortic valve was closed; LSDI ≥ 25% was considered as LV dyssynchrony.

In order to eliminate the effects of different heart rates on patient examination results, all time parameters were divided by the RR interval and expressed as a percentage.

Follow-up

All patients in both groups remained on optimal medical therapy during the 2 years of follow-up. Patients had follow-up evaluations in our
cardiovascular clinic every month for the first 6 months and every 3 months thereafter. Follow-up in all patients consisted of clinical evaluation and repeat echocardiographic assessment. Clinical evaluation included New York Heart Association (NYHA) heart functional class, the distance covered in 6-min walk test, and the quality-of-life scores using the Minnesota Living with Heart Failure questionnaire. Echocardiographic assessment included conventional echocardiography examination and STE. Left ventricular GLs, radial strain, circumferential strain, and LV systolic function were analysed. Follow-up ECG evaluations included QRS morphology and QRS duration. All patients in both groups were followed up for 2 years. The changes of LV synchrony and systolic function between and within two groups were compared at the end of follow-up.

Statistical analysis
Statistical analysis was performed using SPSS17.0 statistical software (SPSS Inc., Chicago, IL, USA). All values are presented as mean ± standard deviation (±). The categorical data are expressed as rates or percentages. Numerical data with normal distribution were compared using Student t-test between two groups and paired t-test within two groups. The nonparametric test (Mann–Whitney U) was applied to numerical variables with skewed distributions. Dichotomous variables were compared with χ² test or Fisher exact probability method. P-value of <0.05 was considered statistical significance.

Results
Baseline characteristics of the two groups and the distribution of f-QRS complexes on 12-lead surface ECG in DCM patients
There were 49 DCM patients, including 29 males and 20 females. There were 20 patients in f-QRS group (13 males and 7 females), and 29 patients in the n-QRS group (16 males and 13 females). There were no significant differences in sex, age, heart rate, NYHA heart function class, left atrial diameter, LVEDD, LVESD, LVEF, and mitral regurgitant in two groups (Table 1). In patients in the f-QRS group, QRS fractionation appeared in two or more contiguous 12-lead surface ECG leads (as grouped by coronary blood supply regions). The anterior chest leads (V1–V6) were assigned as anterior wall; Leads I, aVL, V5, and V6 reflected the lateral wall; Leads II, III, and aVF reflected the inferior wall. Leads V1 and V2 reflected the anterior septum. In some patients, f-QRS complexes could be seen in many myocardial segments (Figure 2); however, the percentage of f-QRS complexes in inferior leads was the highest. The distribution of f-QRS complexes in 20 DCM patients was as follows: 7 in inferior segment, 3 in septal segment, 2 in anterior segment, 2 in lateral segment, 1 in posterior segment, 1 in anterior and lateral segments, 1 in inferior and lateral segments, 1 in posterior and lateral segments, 1 in inferior and posterior segments, and 1 in septal, anterior, inferior, and lateral segments.

The comparative results of clinical and echocardiographic assessment between f-QRS group and n-QRS group after 2 years follow-up
At baseline, there were four patients with LV dyssynchrony (as defined in Methods) in the f-QRS group and none in the n-QRS group. After 2 years, 11 of 16 patients (69%) developed LV dyssynchrony in the f-QRS group; whereas only 5 of 29 patients (17%) developed LV dys-synchrony in the n-QRS group (P = 0.001). Similarly, LV systolic function in f-QRS group and n-QRS group was not different at enrolment, but LV systolic function in f-QRS group declined remarkably when compared with n-QRS group after 2 years follow-up (P < 0.05).
There were three patients who developed new-onset atrial fibrillation in the f-QRS group after 2 years follow-up; whereas none of the patients in the n-QRS group developed atrial fibrillation after 2 years follow-up ($P = 0.062$). Two patients (both with low LVEF, significant LV dyssynchrony, and frequent ventricular ectopy at baseline) died suddenly in f-QRS group; however, no patients died in n-QRS group ($P < 0.05$). No new changes in QRS morphology and QRS duration appeared in either group; i.e. no patients in n-QRS group developed new QRS fractionation or bundle branch block, and no patients in f-QRS group developed bundle branch block. None of the patients in either group received a pacemaker, an ICD or CRT-P/D during the 2 years follow-up (Table 2).

The comparative results of clinical and echocardiographic assessment within f-QRS group and n-QRS group after 2 years follow-up

In addition to the comparison of clinical and echocardiography assessment between f-QRS group and n-QRS group after 2 years follow-up,
we also performed the comparison of clinical and echocardiographic assessment within the f-QRS and n-QRS groups individually. The results showed that both LV synchrony and systolic function worsened significantly only in f-QRS group at 2 years of follow-up (Table 3 and Figure 3).

### Discussion

#### Main findings

In this prospective study, we investigated the effect of f-QRS complex on the development of LV dyssynchrony and systolic dysfunction in
49 patients with idiopathic DCM who were followed up for 2 years. The major findings of this study are: (i) LV dyssynchrony was more often present in patients with f-QRS complexes than in patients with n-QRS complexes; (ii) overall, LV systolic function and LV dyssynchrony were more likely to worsen in patients with f-QRS complexes after 2 years follow-up, compared with patients with n-QRS complexes; and (iii) idiopathic DCM patients with f-QRS complexes were more likely to experience adverse cardiovascular events. These results, if replicated, suggest that an f-QRS complex is significantly associated with intra-ventricular dyssynchrony in idiopathic DCM patients, and may be a reliable ECG clue to predict prognosis in patients with idiopathic DCM.

The potential role of f-QRS complex in clinical practice

It is now clear that CRT performs best in patients with electrical evidence of dyssynchrony—a wide QRS complexes especially complete left bundle branch block.1,16 However, wide QRS complexes occur in only 20–30% patients with heart failure; whereas mechanical intra-ventricular dyssynchrony can be present in 27–56% of patients with narrow QRS complexes.2,17,18 Therefore, it may be of clinical value to find alternate methods to accurately assess LV dyssynchrony, and possibly identify additional patients who may benefit from CRT.

Das et al.7 were the first to report that f-QRS complex was related to myocardial scars and fibrosis. In recent years, clinical studies have demonstrated that f-QRS complex can be used to predict the risk of sudden cardiac death in patients with coronary heart diseases, arrhythmias in patients with right ventricular cardiomyopathy,8 and for risk stratification in patients without cardiac valvular surgery.9 Therefore, f-QRS complex may be valuable in clinical practice.

The clinical implications of f-QRS complex in patients with DCM

The mechanisms underlying idiopathic DCM incompletely explained. Many studies have demonstrated that idiopathic DCM may be associated with myocardial inflammation, necrosis and fibrosis,8,9,19–22 interspersed with viable myocardial cells. It is possible that ventricular dyssynchrony in idiopathic DCM may be related to discordant

Figure 3  The representative changes of LV dyssynchrony in short-axis papillary muscle level in fragmented QRS complex group and normal QRS complex group after 2 years follow-up. The LV dyssynchrony in fragmented QRS complex group was aggravated after 2 years follow-up (A and B); however, there were no significant changes in normal QRS complex group (C and D). The curves with six different colours represent the strain directions of six myocardial segments in short-axis papillary muscle level, respectively. The longitudinal axis is the scale of the strain and expressed as a percentage. The horizontal axis is time scale and the unit is in second. (A) Fragmented QRS complex group at study enrolment. (B) Fragmented QRS complex group after 2 years. (C) Normal QRS complex group at study enrolment. (D) Normal QRS complex group after 2 years.
intra-ventricular depolarization as a result of non-uniform impulse propagation in the surviving myocardial cells which are surrounded by fibrous tissue. The hypothesis may explain the association of f-QRS complex and ventricular dyssynchrony in idiopathic DCM patients. Currently, there are few published data regarding the effects of f-QRS complex on LV synchrony and systolic function in idiopathic DCM patients.\textsuperscript{12,13} Tigen et al.\textsuperscript{12} who first reported this relationship, showed that an f-QRS complex could predict intra-ventricular dyssynchrony in idiopathic DCM patients. More recently, Yusuf et al.\textsuperscript{13} have also reported that f-QRS complex is a marker of ventricular dyssynchrony.

In this study, unlike previous studies, we prospectively report on detailed echocardiographic characteristics at baseline and at 2 years of follow-up for all idiopathic DCM patients with f-QRS complexes and n-QRS complexes. Clinical assessment including NYHA heart function class, quality-of-life scores, and distance covered in 6-min walk test are also reported at study enrolment and after 2 years. Patients in f-QRS group showed worsening LV synchrony especially in myocardial territories localized by f-QRS complexes, declining LV systolic function, poor life quality and increased sudden death, suggesting that if proven in additional studies, an f-QRS complex may be a reliable marker of worse prognosis in idiopathic DCM patients.

**Ventricular dyssynchrony assessment by STE**

In addition to serial clinical evaluations in this study, echocardiography was also performed to assess LV synchrony and systolic function in all patients with and without f-QRS complexes. Tissue Doppler imaging is a technique that has been widely applied to quantify LV dyssynchrony\textsuperscript{12,13} and predict response to CRT. However, there are no reports about using STE to assess LV dyssynchrony in idiopathic DCM patients with systolic dysfunction and f-QRS complexes. Our results showed that the percentage of LV dyssynchrony in f-QRS group was significantly higher than that in n-QRS group (75 vs. 17\%) at baseline, and STE findings were quite consistent with clinical evaluations, suggesting that STE can assess LV dyssynchrony in idiopathic DCM patients with f-QRS complexes.

**Study limitations**

We had relatively small numbers of patients enrolled, 20 DCM patients with f-QRS complexes and 29 DCM patients with n-QRS complexes, although we performed 2 years follow-up evaluations for all patients. These results will need to be validated in larger studies. Speckle tracking echocardiography analysis is dependent on frame rates and image resolution, and represents another limitation to the technique; low frame rates result in greater changes in speckle patterns, and prevent the precise characterization of regional myocardial motion and global temporal resolution of the regional strain map. If the frame rates are increased excessively, the scan-line density and image resolution are reduced. In this study, the frame rates were chosen in the range of 40–90 Hz with a mean of 75 Hz suitable for STE analysis. Most importantly, although f-QRS complexes identify DCM patients with worse prognosis, it remains to be proven that CRT will improve outcomes in patients selected on the basis of f-QRS complexes.

**Conclusions**

In summary, the presence of f-QRS complexes is significantly associated with LV dyssynchrony in idiopathic DCM patients. An f-QRS complex may be used as a reliable marker of LV dyssynchrony and predicts a worse prognosis. The presence of f-QRS complexes on 12-lead ECGs may help us to identify idiopathic DCM patients who may benefit from CRT and possibly guide LV lead placement, although this remains to be validated by future studies.

**Conflict of interest:** none declared.

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**References**


A 66-year-old female patient with severe dilated cardiomyopathy reports about alarm sounds from her cardiac resynchronization therapy-defibrillator (CRT-D) device, occurring several times over the last months. She had received a Medtronic Viva XT CRT-D device 2 months earlier; due to end-stage heart failure, a HeartWare® Ventricular Assist Device was subsequently implanted as demonstrated in the chest X-ray.

During a comprehensive assessment, we were able to induce the alarm sound by moving the Assist Device’s Controller (in its bag) close to the implanted CRT-D. The same alarm (same tone, same duration) was repeated by placing a magnet in the vicinity of the CRT-D device. Analysis of the device by the manufacturer finally confirmed the CRT-D’s magnet field approach alarm as the reason for the observed alarms, triggered by the magnetic field of the assist device’s controller.

Interactions between a left ventricular assist device and implantable cardioverter-defibrillators (ICDs) have been described, including changes in lead impedances, sensing, and capture threshold as well as interference with ICD’s telemetry. Furthermore, one inappropriate shock has been reported due to noise of the LVAD battery system.

To the best of our knowledge, this represents the first interaction between a left ventricular assist device’s controller and a CRT-D device due to magnetic field interference.

The full-length version of this report can be viewed at: http://www.escardio.org/Guidelines-&-Education/E%E2%80%93learning/Clinical-cases/Electrophysiology/EP-Case-Reports.

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