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Pathophysiological links, echocardiographic characteristics, and clinical implications of QRS morphology in patients with dilated cardiomyopathy

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***Abstract*:** Heart failure is an important clinical problem worldwide. There is great interest in evaluating the relationship between electrocardiographic variations and dilated cardiomyopathy (DCM) since it has been used as a predictor of increased morbidity and mortality. The presence of fragmentation in the QRS complexes on 12-lead electrocardiogram (ECG) was reported as a marker of depolarization abnormality in patients with DCM. Previous studies have investigated the relation between QRS morphology and DCM. QRS morphology and duration are associated with clinical deterioration and increased mortality in patients with DCM. Although surface ECG provides valuable information on prognosis of these patients, echocardiographic methods have been used for further investigation of patients with DCM. The aim of the present review is to provide an overview of the pathophysiological links, echocardiographic characteristics and clinical implications of QRS morphology in patients with DCM.

Keywords: dilated cardiomyopathy, echocardiography, electrocardiography, fragmented QRS, prognosis, QRS morphology

Introduction

Heart failure (HF) is an important clinical problem worldwide [Williams *et al.* 1995]. HF is a progressive disease and results in decreased functional capacity, as well as hemodynamic and neurohormonal abnormalities [Topol, 1998]. Dilated cardiomyopathy (DCM) is associated with increased morbidity and mortality due to progressive HF and sudden cardiac death [Torp-Pedersen *et al.* 2005]. There is great interest in evaluating the relationship between electrocardiographic variations and DCM since it has been used as a predictor of increased morbidity and mortality [Sha *et al.* 2011]. There is a close relationship between QRS morphology and DCM. The presence of fragmentation in the QRS complexes on 12-lead electrocardiogram (ECG) was reported as a marker of depolarization abnormality [Das *et al.* 2008]. Fragmented QRS (f-QRS) was defined according to QRS duration as narrow QRS complexes (QRS $<$120 ms) or wide QRS complexes (QRS $\geqslant$120 ms). Das and colleagues originally defined f-QRS as narrow QRS complexes with the presence of an additional R wave (R′), notching in the S wave, or the presence of $>$1 R′ fragmentation in 2 contiguous leads without a typical bundle branch block (BBB) pattern (QRS $\geqslant$120 ms) and incomplete right BBB (Figure 1). f-QRS was defined in a wide QRS complex ($\geqslant$120 ms) as the QRS complex with $>$2 R′ waves or notches in the R or S wave in a wide QRS complex of BBB, or paced QRS, or premature ventricular complexes (PVC) in two contiguous leads. If the QRS complex of PVC only has two notches in the R waves, they considered the QRS complex to be f-QRS-positive when the notches were $>$40 ms apart and present in 2 contiguous leads [Das *et al.* 2008]. Although wide QRS complexes are common in patients with organic heart disease, f-QRS complexes can be a prognostic marker in patients with DCM [Sha *et al.* 2011; Das *et al.* 2008; Ozcan *et al.* 2013].

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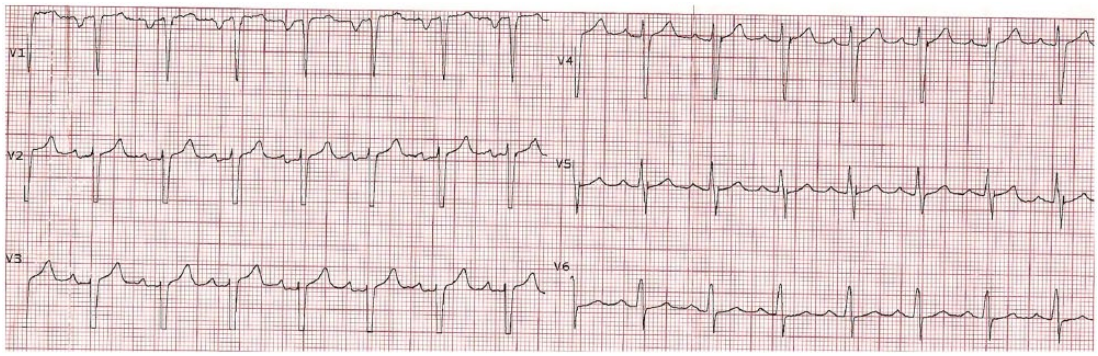

Figure 1. Surface electrocardiogram shows a fragmented QRS pattern in a patient with dilated cardiomyopathy.

The present review provides an overview the pathophysiological links, echocardiographic characteristics and clinical implications of QRS morphology in patients with DCM.

Pathophysiological links between QRS morphology and DCM

The pathogenesis of DCM is important to understanding the relationship between QRS morphology and DCM. Previous studies have demonstrated that DCM is associated with organic abnormalities of the ventricular myocardium [Dec and Fuster, 1994]. Intramyocardial inflammation, myocyte degeneration and intramyocardial fibrosis are common in patients with DCM [Timonen *et al.* 2008]. Myocardial fibrosis is an important factor in the development of HF and is also associated with decreased survival in these patients [Babür *et al.* 2011]. While transmural and subendocardial fibrosis is often associated with ischemic cardiomyopathy, patchy or midwall fibrosis is usually associated with nonischemic DCM [McCrohon *et al.* 2003]. Genetic predisposition, environmental factors such as toxins and pathogens, metabolic factors and immune response are some of the underlying factors of midwall fibrosis in these patients [McCrohon *et al.* 2003; Izawa *et al.* 2005].

Although previous studies have proposed several pathophysiological links to the occurrence of f-QRS, the exact mechanism of f-QRS remains unclear. Previous studies have demonstrated that the fragmentation of QRS complexes is shown to be associated with intraventricular systolic dyssynchrony and subendocardial fibrosis in patients with non-ischemic DCM [Basaran *et al.* 2011; Tigen *et al.* 2009]. Myocardial scars usually occur in the midmyocardial or subepicardial layer of the myocardium. Patchy involvement is more common in these patients. Unorganized activation of the myocardium due to myocardial scarring leads to f-QRS complexes in these patients. f-QRS is also common in patients with ischemic DCM. Myocardial infarction is associated with f-QRS complexes on electrocardiogram (ECG) due to regional or transmural fibrosis [Das *et al.* 2008]. Left ventricular hypertrophy, T-wave inversions, Q waves in precordial leads, left axis deviation and left BBB are common ECG findings in patients with DCM. Although patients with DCM usually have wide QRS complexes, f-QRS can be detected in both forms of QRS complexes as wide or narrow f-QRS. There are several explanations about why some patients have wide f-QRS or narrow f-QRS. Disease duration, severity, and the extension and/or pattern of myocardial scarring may contribute to the occurrence of QRS morphology [Das *et al.* 2008].

Echocardiographic characteristics of QRS morphology in DCM

Wide QRS complexes are frequently seen due to prolonged ventricular activity in patients with DCM. Prolonged ventricular activity may lead to left ventricular (LV) dyssynchrony in these patients. Intramyocardial fibrosis usually results in myocardial dyssynchrony in patients with DCM. LV dyssynchrony is common in patients with HF [Ghio *et al.* 2004], especially in patients with wide QRS complexes [Yu *et al.* 2003]. Approximately 50% of HF patients have intraventricular conduction delay, which leads to ventricular dyssynchrony [Grines *et al.* 1989]. In a

previous study, Karaahmet and colleagues showed that cardiac fibrosis correlated with impaired LV diastolic function and functional capacity, elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) levels, and adverse cardiac remodeling in patients with nonischemic DCM [Karaahmet *et al.* 2010]. In another study, Tigen and colleagues showed that patients with nonischemic DCM and prominent cardiac fibrosis had significant intraventricular systolic dyssynchrony [Tigen *et al.* 2010]. Previous studies have demonstrated that transthoracic echocardiography provides valuable information about LV dyssynchrony. Several echocardiographic methods have been used for the evaluation of LV dyssynchrony [Sutherland *et al.* 2000; Rouleau *et al.* 2001]. Echocardiographic methods provide accurate information about the importance and localization of the dyssynchronic segments of the LV myocardium. The evaluation of longitudinal LV velocities using tissue Doppler imaging is the main clinical method for the assessment of myocardial dyssynchrony in these patients.

Although cardiac resynchronization therapy (CRT) is a useful treatment method for HF patients [Cleland *et al.* 2005; Kadish *et al.* 2004], some of patients with CRT remain nonresponders to CRT [Abraham *et al.* 2002]. Previous studies have shown that CRT has been associated with functional improvement and decreased mortality in HF patients [Cleland *et al.* 2005; Kadish *et al.* 2004; Abraham *et al.* 2002]. Hence, identification of those patients is important due to the high risk of complications and increased cost of this device. Therefore, echocardiographic methods may be a good guide for CRT implantation in these patients. In particular, echocardiographic methods are recommended in borderline patients selected for CRT [Gorcsan *et al.* 2008].

Besides the close relationship between wide QRS complexes and LV dyssynchrony, narrow QRS complexes are also associated with LV dyssynchrony. In a previous study, Basaran and colleagues showed that fragmentation in baseline ECG was associated with intraventricular systolic dyssynchrony and subendocardial fibrosis in nonischemic DCM patients with narrow QRS intervals and sinus rhythm [Basaran *et al.* 2011]. In another study, Tigen and colleagues showed that fragmentation in resting ECG was associated with significant intraventricular dyssynchrony in patients with nonischemic DCM, narrow QRS and sinus rhythm [Tigen *et al.* 2009]. Consistent with previous reports, Yusuf and colleagues also demonstrated that fragmented QRS was a marker of electrical dyssynchrony, which results in significant intraventricular dyssynchrony in patients with nonischemic DCM and a narrow QRS interval [Yusuf *et al.* 2013]. Those studies have demonstrated that fibrotic myocardial tissue may trigger the dyssynchronic contraction pattern of the myocardium in patients with DCM.

Clinical implications of QRS morphology in DCM

Previous studies have reported that prolonged QRS duration is a predictor of increased risk of mortality and decreased functional capacity in patients with DCM [Amiya *et al.* 2006]. Intraventricular dyssynchrony not only associates with wide QRS complexes, but also associates with narrow QRS intervals [Yu *et al.* 2003; Bleeker *et al.* 2005]. Approximately 27–56% of patients with narrow QRS intervals have intraventricular dyssynchrony [Cazeau *et al.* 2001]. The prognostic value of ventricular dyssynchrony using QRS duration has been demonstrated in several studies. Karaahmet and colleagues demonstrated that increased intraventricular delay was associated with increased risk for death in patients with nonischemic DCM, independent from the QRS duration and LV ejection fraction [Karaahmet *et al.* 2009]. In contrast to this report, previous studies have shown that wide QRS intervals are also associated with increased mortality and morbidity in patients with HF [Fosbøl *et al.* 2008]. Ozcan and colleagues reported that the presence of narrow f-QRS is associated with worse New York Heart Association functional class in patients with decompensated HF. In addition, narrow f-QRS predicts cardiovascular mortality patients with systolic HF [Ozcan *et al.* 2013].

It is well known that left BBB is associated with clinical deterioration and increased mortality in patients with DCM [Koga *et al.* 1993]. Prolonged QRS duration (>120 ms) with complete left BBB has been proposed as the most important selection criteria for the determination of patients who have a favorable effect from CRT [Abraham *et al.* 2002; Cazeau *et al.* 2001]. In a previous study, Fauchier and colleagues showed that left BBB on the left axis reflected a high intraventricular dyssynchrony [Fauchier *et al.* 2003]. They also showed a relation between left anterior hemiblock and intraventricular dyssynchrony in 48% of their

study population. Therefore, they proposed that patients with left anterior hemiblock and severe HF may also benefit from CRT. In a recent study, Zareba has proposed more attention to QRS morphology than QRS duration for the selection of patients who benefit from CRT [Zareba, 2013]. Two large clinical trials – the MADIT-CRT [Zareba *et al.* 2011] and RAFT studies [Tang *et al.* 2010] – demonstrated that only patients with left BBB responded to CRT. In the RAFT study, patients with right BBB morphology did not respond to CRT although those patients had prolonged QRS duration (QRS >150 ms).

Conclusion

Echocardiography and 12-lead surface ECG are important diagnostic tools in the clinical settings of DCM patients. Echocardiographic characteristics and QRS morphologies provide valuable information about cardiovascular morbidity and mortality in patients with DCM. Therefore, clinicians should pay more attention to evaluating patients who have f-QRS.

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Conflict of interest statement

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