QRS Fragmentation is Associated with Functional Mitral Regurgitation and Papillary Muscle Dyssynchrony in Patients with Non-ischemic Dilated Cardiomyopathy and Sinus Rhythm

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ABSTRACT

Aim: We investigated the impact of fragmented QRS (fQRS) complexes on ECG in predicting papillary muscle dyssynchrony and functional mitral regurgitation in patients with non-ischemic dilated cardiomyopathy with narrow QRS and sinus rhythm.
Methods: Thirty-one non-ischemic dilated cardiomyopathy patients with fQRS and 16 patients without fQRS were evaluated for intraventricular and papillary muscle dyssynchrony. All patients were in sinus rhythm and having narrow QRS intervals. Maximal Ts (duration between the beginning of the QRS complex and myocardial peak systolic velocity), difference between basal septal and lateral myocardial segments (ASE Sep-Lat Sys) and anterolateral and posteromedial papillary muscles (ASE Inter PAP Sys) were calculated to assess synchronicity.
Results: The patients with fQRS had significantly higher mitral regurgitant volume (p=0.043), shorter E wave deceleration (p=0.01) and isovolumetric relaxation time (p=0.044), lower basal septal (p=0.033) and lower basal lateral (p=0.007) TDI peak systolic velocities and higher ASE Sep-Lat Sys (p=0.041) and ASE Inter PAP Sys (p=0.033) values than patients without fQRS complexes.
Conclusion: fQRS was associated with intraventricular and papillary muscle dysssynchrony and more severe functional mitral regurgitation in patients with non-ischemic dilated cardiomyopathy and sinus rhythm. The presence of fQRS complexes may be useful in selecting patients for cardiac resynchronization therapy.

Key Words: Mitral stenosis, mitral balloon valvuloplasty, left ventricular function, tissue Doppler Imaging

ÖZET

Sinüs Ritmindeki Non-iskemik Dilate Kardiyomiyopatili Hastalarda EKG'de Fragmante QRS Varlığı Papiller Kas Dissenkronisi ve Fonksiyonel Mitral Yetersizliği ile İlişkilidir

Amaç: Çalışmamızda dar qrs'li non-iskemik dilate kardiyomiyopatili hastalarda ekg'de fragmante qrs varlığının fonksiyonel mitral yetersizliği ve papiller kas asenkroni ile ilişkisi incelendi.
Metodoloji: Sol ventrikül ejeksiyon fraksiyonu < %40 olan sinüs ritmindeki dar (<120msn) fragmante qrs'li 31 hasta ve bazal ekg'sinde fragmantasyon olmayan 16 dar qrs'li non-iskemik dilate kardiyomiyopatili hasta prospektif olarak çalışmaya dahil edildi. Senkronisite incelemesi için sol ventrikül bazal septal ve lateral segmentlerinin Ts (qrs kompleksinin başlangıcı referans noktası olarak alınarak miyokardiyal pik sistolik velositeye kadar geçen süre) değerleri arasındaki maksimal fark (ASE Sep-Lat Sys) ve anterolateral ve posteromedial papiller kasların Ts değerleri arasındaki maksimal fark (ASE Inter PAP Sys) hesaplandı. Fonksiyonel mitral yetersizliğinin derecesi PISA metodu ile değerlendirildi.
Bulgular: İstirahat ekg'sinde fargmantasyon olan hastaların mitral kaçak hacimleri anlamlı olarak yüksek (p=0.043), E dalga deselerasyon zamaları (p=0.01) ve izovolumetrik relaksasyon zamanları (p=0.044) anlamlı olarak kısa, bazal septum (p=0.033) ve bazal lateral (p=0.07) TDI pik sistolik velositeleri anlamlı olarak düşük, ASE Sep-Lat Sys (p=0.041) ve ASE Inter PAP Sys (p=0.033) anlamlı şekilde yüksek bulundu.

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Sonuç: Sinüs ritmindeki dar qrs'li non-iskemik dilate kardiyomiyopatili hastalarda bazal ekg'de fragmantasyon varlığı, intraventriküler ve papiller kas asenkronisi ve yüksek fonksiyonel mitral yetersizliği kaçak volümü ile ilişkilidir. Ekg'de fragmantasyon varlığı kardiyak resenkronizasyon tedavisinden fayda görebilecek, intraventriküler ve papiller kas asenkronisi yönünden araştırılması gereken dar qrs'li non-iskemik dilate kardiyomiyopatili hastaların belirlenmesinde önemli bir parametredir.

Anahtar Kelimeler: Kardiyomiyopati, dissenkroni, fragmante QRS

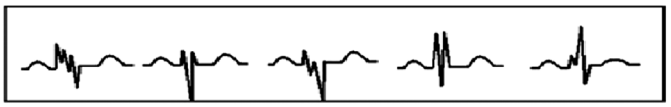
INTRODUCTION

Heart failure is an important health problem that affects many people.(1-3) Functional mitral regurgitation (FMR) indicates increased mortality in patients with dilated cardiomyopathy (DCM). (4,5) Functional mitral regurgitation is secondary to decreased transmitral pressure gardient, left ventricular dilatation and spherization, altered mitral annulus, papillary muscle, and mitral valve geometry, dyssynchronic left ventricular and papillary muscle contractions in patients with DCM. (6-12) Cardiac resynchronization therapy (CRT) improves functional capacity, functional mitral regurgitation, morbidity, and mortality in patients with heart failure. (9-11, 13-16) Improved coordination of papillary muscular contractions may be the reason of decreased functional mitral regurgitatant volume following CRT. Intraventricular dyssynchrony has been reported in patients with narrow QRS intervals as well. (17-21) However, the prevalence of dyssynchrony in patients with narrow QRS intervals is lower than patients with wide QRS complexes, hence CRT indications for patients with narrow QRS are limited. (17,18,20) The presence of fragmented QRS complexes (fQRS) in patients with coronary artery disease has been associated with regional myocardial damage, increased cardiac adverse events, and decreased event-free survival. (22-24) fQRS complexes are also seen in patients with left ventricular aneurysms. (25,26) We investigated the impact of fragmented QRS complexes on ECG in predicting papillary muscle dyssynchrony and functional mitral regurgitation in patients with non-ischemic dilated cardiomyopathy with narrow QRS and sinus rhythm.

METHODS

The present study was conducted at the heart failure clinic at the Kosuyolu Heart Education and Research Hospital. Forty-seven non-ischemic DCM patients with an LV ejection fraction less than 40% and sinus rhythm having narrow (less than 120 ms) are consecutively recruited. Thirty-one patients in this cohort were detected to have fQRS complexes and 16 patients did not have fQRS in their 12 lead ECGs. All patients had heart failure symptoms and were receiving beta-blockers, angiotensin converting enzyme inhibitors, diuretics and digoxin. All patients included in this study were diagnosed with LV dysfunction for at least two years, were using the above-mentioned medications for at least six months, and were symptomatic for at least the previous six months. Patients with organic valvular heart disease, a history of myocardial infarction, ischemic ECG findings, angiographically significant coronary artery disease (more than 50% stenosis in any epicardial coronary artery), atrial fibrillation, chronic liver or kidney failure, as well as patients with permanent pacemakers were excluded from the study. The study protocol was approved by the institutional review board and the subjects gave written informed consent for their participation in the study.

ECG: The resting 12-lead ECG (0.5 to 150 Hz, 25 mm/sec, 10 mm/mV) was analyzed by two independent clinicians who were blinded to echocardiographic data. There was 99.5% concordance for ECG signs. In case of disagreement, the final diagnosis was achieved by mutual agreement. The fragmented QRS (fQRS) included various RSR' patterns and was defined by the presence of an additional R wave (R' prime), notching in nadir of the S wave, notching of R wave, or the presence of more than one R prime (fragmentation) in two contiguous leads corresponding to a major myocardial segment as previouslu described (22) (Figure-1).



RSR' Patterns in various morphologies with or without Q wave	fQRS >2 contiguous anterior leads (V1-V4) assigned to Anterior Segments
Presence of an additional R wave (R')	fQRS >2 contiguous lateral leads (I, aVL, V5-6) assigned to Lateral Segments
Notching in the nadir of S wave	fQRS >2 contiguous inferior leads (II, III, aVF) assigned to Inferior Segments
Notching in the nadir if R wave	
Presence of >1 R' (Fragmentation)	

Figure 1: Definition of fragmented QRS complexes and corresponding myocardial segments on surface ECG.

Presence of fQRS in >2 contiguous anterior leads (V1 to V5) were assigned to anterior myocardial segments, in lateral leads (I, aVL, and V5,V6) to the lateral myocardial segments, in inferior leads (II, III, and aVF) to the inferior myocardial segments, and in V1,V2 to the posterior myocardial segments. The fQRS also was seen in more than one myocardial segments in some patients.

Echocardiography: Standard echocardiography with Doppler studies were performed by using a commercially available system (System 5, Vingmed-General Electric, Horten, Norway). Two echocardiographers who are unaware of the study performed the examinations and they were blinded for the ECG's and clinical status of the patients. LV dimension and ejection fraction were measured by two dimensional guided M-mo-

de echocardiography according to the guidelines of the American Society of Echocardiography.(27) The maximal rate of LV systolic pressure increase (LV dP/dt) was used as an index of LV systolic performance and was estimated from the steepest increasing segment of the continuous wave Doppler of the mitral regurgitation velocity spectrum. (28) Tissue Doppler imaging was performed in the apical views (four chamber, two chamber, and long axis) for the long axis motion of the LV. (29) Two-dimensional echocardiography with tissue Doppler color imaging was performed with a 2.5 MHz phase array transducer. The system was set by bypassing the high pass filter, while the low frequency Doppler shifts were input directly into an autocorrelator. Gain settings, filters, and pulse repetitive frequency were adjusted to optimize color saturation, and a color Doppler frame scanning rate of 100– 140 Hz was used. At least three consecutive beats were stored and the images were digitised and analysed off-line by a computer (EchoPac 6.3, Vingmed-General Electric). Myocardial regional velocity curves were constructed from the digitised images. For detail assessment of regional myocardial function, 7x7 mm of sampling window was placed at the myocardial segment of interest. In each view, both the basal and mid segments were assessed. In this way septal, anteroseptal, anterior, lateral, inferior, posterior segments at both basal and middle levels and anterolateral and posteromedial papillary muscles were interrogated. For the measurement of timing, the beginning of the QRS complex was used as the reference point, where the time to peak myocardial sustained systolic (TS) was quantified. For each segment and papillary muscle. (30) (Figure 2)

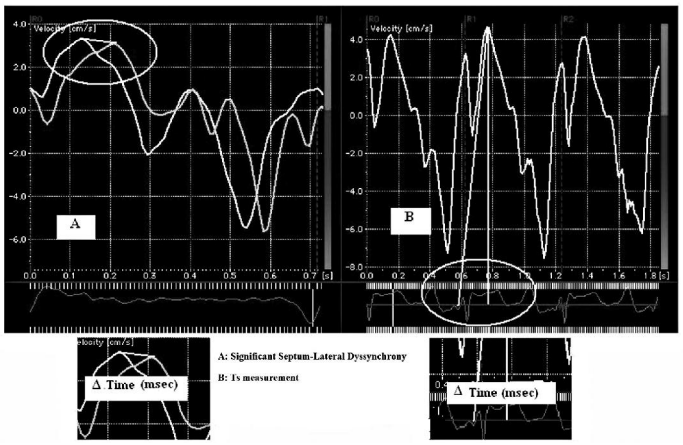


Figure 2: Tissue Doppler derived myocardial velocity curves demonstrating significant septum-lateral systolic dyssynchrony and Ts measurement.

The estimated interobserver and intraobserver variabilities were 4.3% and 3.7% respectively. All echocardiographic studies were performed by an experienced echocardiographer who was blinded for the ECG data. For the assessment of synchronicity the maximal difference in Ts between basal and lateral segments (ASE Sep-Lat Sist) and between anterolateral and posteromedial papillary muscles (ASE Inter PAP Sist) were calculated. To assess global cardiac function, the myocardial sustained systolic (S), early diastolic (E) and late diastolic (A) velocities from the basal septal and basal lateral segments were calculated. Significant systolic dyssynchrony was defined as ASE Sep-Lat Sist > 60 msn and ASE Inter PAP Sist > 60 ms. (31,32) FMR was graded according to "proximal isovelocity surface area" (PISA) method. (33) Mitral regurgitant volume (FMR Vol ml) was defined as the variable determining the severity.

Statistical Analysis: Analysis was performed using a statistical software program (SPSS forWindows, version 13.0; SPSS Inc, Chicago, Illinois, USA). Data are presented as mean ± SD, controlled for normal distribution by Kolmogorov-Smirnov test, and compared by using paired student t-test. Finally, nonparametric tests, such as Mann-Whitney U test, were used when the distribution was not normal. Categorical data between two or more groups were compared by the Pearson ¯ 2 test. Sensitivity was defined by the number of true positives for the presence of fQRS complexes and

Table 1: Demographical, clinical and echocardiographic characteristics of the study patients

Gender (F/M)	**11/36**
Age	**38±15**
NYHA (I-II / III-IV)	**33/14**
Left atrium (cm)	**4.9±0.8**
LVESD (cm)	**6.2±0.7**
LVEDD (cm)	**7.1±0.8**
IVS (cm)	**1±0.28**
PW (cm)	**1±0.26**
EF (%)	**26.6±8**
EPSS (cm)	**2.4±0.5**
dP/dt (mmHg/msn)	**511±153**
FMR Vol (ml)	**24±15**
Mitral E Vel (m/sn)	**0.9±0.26**
Mitral A Vel (m/sn)	**0.4±0.17**
E/A	**2.4±1.1**
EDT (msn)	**127±64**
IVRT (msn)	**91±33**
PAP (mmHg)	**52±14**
RV TDI s (cm/sn)	**7±2.2**
Sep TDI s (cm/sn)	**2.9±1.1**
Sep TDI e (cm/sn)	**3.3±1.9**
Sep TDI a (cm/sn)	**3.4±1.7**

LVESD: Left ventricular end systolic diameter; LVEDD:Left ventricular end diastolic diameter; IVS:Interventricular septum; PW:Posterior wall; EF:Left ventricular ejection fraction; EPSS:End point septal seperation; EDT: E wave deceleration time; IVRT:Isovolumetric relaxation time; PAP: Pulmonary artery systolic pressure. FMR Vol: Functional mitral regurgitant volume

a corresponding intraventricular dyssynchrony for suitable myocardial segments. Specificity was defined as the number of true negatives with no fQRS complexes and normally defined synchronicity. A P-value < 0.05 was considered to be significant.

RESULTS

Study group included 11 females (%23), 36 males (%77). Mean age was 38±15. Demographical, clinical, and echocardiographic characteristics of the study population and the differences between two groups are shown in Table-1 and Table-2.

Table 2: Demographical, clinical and echocardiographic characteristics of the patients with and without fragmented QRS complexes

	Fragmented QRS (N=31)	Normal QRS (N=16)	P
Gender (F\M)	6/25	5/11	NS
Age	40±15	35±15	NS
NYHA (I-II / III-IV)	20/11	13/3	NS
Left atrium (cm)	5±0.7	4.8±1	NS
LVEDD (cm)	7.2±0.9	6.8±0.7	NS
LVESD (cm)	6.3±0.7	6±0.7	NS
IVS (cm)	1.1±0.3	1±0.3	NS
PW (cm)	1±0.2	1±0.3	NS
EF (%)	27±8	26±7	NS
EPSS (cm)	2.4±0.5	2.3±0.4	NS
dP/dt (mmHg/msn)	493±159	539±143	NS
FMR Vol (ml)	27.5±16	17±9	0.043
E/A	2.6±0.9	2.4±1.2	NS
EDT (msec)	103±58	140±64	0.01
IVRT (msec)	78±28	98±33	0.044
PAP (mmHg)	48±9	52±17	NS
RV TDI s (cm/sn)	7.2±2.4	6.7±1.8	NS
Sep TDI s (cm/sn)	2.6±1.2	3.3±0.9	0.033
Sep TDI e (cm/sn)	2.9±1.6	3.9±2.3	NS
Sep TDI a (cm/sn)	3.7±1.8	2.7±1.5	NS
Lat TDI s (cm/sn)	2.4±0.7	3.6±1.6	0.007
Lat TDI e (cm/sn)	4.2±2.3	6±3.6	NS
Lat TDI a (cm/sn)	3.2±2	2.6±1.5	NS
ASE Sep-Lat Sys (msn)	72±48	46±24	0.041
ASE Inter Pap Sys (msn)	48±36	26±22	0.033

LVESD: Left ventricular end systolic diameter; LVEDD:Left ventricular end diastolic diameter; IVS:Interventricular septum; PW:Posterior wall; EF:Left ventricular ejection fraction; EPSS:End point septal seperation; EDT: E wave deceleration time; IVRT:Isovolumetric relaxation time; PAP: Pulmonary artery systolic pressure. FMR Vol: Functional mitral regurgitant volume.

Patients were categorized into two subgroups according to having (n=31; 66%) and not having (n=16; 34%) f QRS complexes in their basal ECGs. Patients with fQRS had more ASE Sep-Lat Sist than patients without fQRS (18 vs 4; p=0.031). There was no statistical difference between the prevalence of ASE Inter PAP Sist between the two groups. Patients with fQRS had higher FMR regurgitant volumes (p=0.043), shorter E wave deceleration (p=0.01) and isovolumetric relaxation time (p=0.044), lower basal septal (p=0.033) and basal lateral (p=0.007) TDI peak systolic velocities. Patients with fQRS had higher ASE Sep-Lat Sys (p=0.041) and ASE Inter PAP Sys (p=0.033) values than without fQRS. The remaining parameters between the two groups were similar.

DISCUSSION

Our study revealed that presence of fQRS complexes in ECG is associated with intraventricular and papillary muscle dysynchrony in patients with narrow QRS intervals and sinus rhythm. This group of patients were also having higher FMR than the patients without fQRS complexes. Although it did not reach statistical siginficance, patients with fQRS complexes were having higher NYHA class, larger left atrial diameter, and lower dP/dt values suggesting this finding may be associated with the severity of heart failure. Tissue Doppler derived peak systolic velocities obtained from the septum and lateral wall were significantly lower in these patients supporting this hypothesis.

FMR is a common finding in congestive heart failure. It has been associated with worse prognosis, therefore its treatment is one of the goals of the medical and surgical management options of heart failure. (34,35) Surgical treatment of FMR aims to decrease the mitral annular diameter, however mitral regurgitation persists or recurs in many cases. (36,37) On the other hand, CRT improves FMR in the early and late setting. (9-11, 15-16, 38) This is most likely secondary to the improved coordination of papillary muscular contractions following the CRT. (10,15,16) However, FMR does not improve in all the patients following CRT. One possible explanation for this finding is papillary muscle dyssynchrony. (16) Recently, intraventricular dyssynchrony has been reported in patients with narrow QRS intervals and these patients may benefit from CRT. (17,18,23,31,39) Soyama and coworkers reported that the dyssynchronous activation of myocardial segments adjacent to papillary muscles resulted mitral regurgitation in DCM patients with narrow QRS intervals. (12) Therefore, simple indicators in determining the presence of intraventricular and papillary muscle dyssynchrony may be useful for the clinicians in DCM patients with narrow QRS intervals. The presence of fragmented QRS in 12-lead ECG is associated with increased adverse cardiac events and mortality in patients with coronary artery disease. (23) Das, et al. reported that the presence of fragmented QRSs has a better sensitivity and negative predictive value than Q waves in ECG for detection of myocardial scar in patients with narrow QRS complexes. (22) Myocardial scar and/or ischemia cause nonhomogenous ventricular activation which results in fragmentation in ECG (40,41). Dyssynchronic contraction pattern might be secondary to nonhomogenous intraventricular activation and uncoordinated

depolarization of viable myocyte groups which are surrounded by fibrotic tissue (23). Presence of intraventricular and papillary muscle dyssynchrony in patients with fQRS complexes in our study is also a finding suggesting this hypothesis.

Surgical treatment of mitral regurgitation is associated with significant morbidity and mortality. Therefore, alternative treatment options such as CRT is crucial in the management of heart failure. (42) Achilli and coworkers demonstrated the reduction of FMR by CRT in 14 patients with intraventricular dyssynchrony and narrow QRS intervals. (39) We suggest that presence of fQRS may be useful in detection of intraventricular and papillary dyssynchrony as well as estimate which patients have significant FMR in the non-ischemic DCM population. Hence, this finding can be helpful in patient selection for CRT.

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