Papillary muscle dyssynchrony as a cause of functional mitral regurgitation in non-ischemic dilated cardiomyopathy patients with narrow QRS complexes

Dar QRS'li non-iskemik dilate kardiyomiyopatili hastalarda fonksiyonel mitral yetersizliğinin nedeni olarak papiller kas dissenkronisi

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ABSTRACT

Objective: Mitral regurgitation (MR) increases mortality in dilated cardiomyopathy (DCM). We investigated the prevalence of functional MR in non-ischemic DCM patients with narrow QRS intervals and its association with papillary muscle dyssynchrony.
Methods: Ninety-three patients were enrolled consecutively in this cross-sectional study. Patients were evaluated for the presence of intraventricular (DYS Sep-Lat Sys) and papillary muscle (DYS Inter PAP Sys) systolic dyssynchrony using tissue Doppler echocardiographic imaging (TDI). Two-dimensional and Doppler echocardiography were used for quantification of MR. Statistical analyses were performed using unpaired t test, Mann-Whitney U test, correlation and logistic regression analyses.
Results: Thirty-seven patients (39%) had significant DYS Sep-Lat Sys and 25 patients (26%) had DYS Inter PAP Sys. Patients with DYS Inter PAP Sys had lower basal septum systolic (p=0.007) and late diastolic velocities (p=0.049), greater MR volume (p=0.01), effective regurgitant orifice (ERO) (p=0.01), and E/A ratios (p=0.03) than the patients without DYS Inter PAP Sys. Fifty-five patients with narrow QRS intervals were also evaluated for DYS Inter PAP Sys. Patients with DYS Inter PAP Sys and narrow QRS had lower basal septum TDI peak systolic velocities (p=0.038), higher MR volume (p=0.03) and ERO (p=0.03). Logistic regression analysis revealed that NYHA Class III-IV (OR=6.4, 95% CI: 1.1-37.1, p=0.038) and DYS Inter PAP Sys (OR=9.5, 95% CI: 1.17-75.78, p=0.034) were the independent predictors of functional MR >20 ml.
Conclusion: Papillary muscle systolic dyssynchrony is common and correlated with functional MR in non-ischemic DCM patients with sinus rhythm and narrow QRS. Papillary muscle systolic dyssynchrony may help predict patients who will benefit from cardiac resynchronization therapy.
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Key words: Dyssynchrony, cardiomyopathy, papillary muscle, mitral regurgitation, logistic regression analysis

ÖZET

Amaç: Mitral yetersizliği, dilate kardiyomyopatili hastalarda prognozu olumsuz etkiler. Bu çalışmada dar QRS'li non-iskemik dilate kardiyomyopatili (NDKM) hastalarda fonksiyonel mitral yetersizliği sıklığı ve bunun papiller kas dissenkronisi ile ilişkisi araştırıldı.
Yöntemler: Doksan üç hasta ardışık olarak enine kesitli çalışmaya alındı. Hastalar septum-lateral sistolik (DYS Sep-Lat Sys) ve papiller kas sistolik (DYS Inter PAP Sys) dissenkronisi varlığı açısından doku Doppler ekokardiyografi (TDI) ile araştırıldı. Mitral yetersizliği ve sol ventrikül diyastolik fonksiyonu iki-boyutlu ve Doppler ekokardiyografi ile incelendi. İstatistiksel analizler eşleştirilmemiş t testi, Mann-Whitney U testi, korelasyon ve lojistik regresyon analizleri ile yapıldı.
Bulgular: Doksan üç NDKM'li hastadan 37'sinde (39%) belirgin DYS Sep-Lat Sys ve 25'inde (26%) belirgin DYS Inter PAP Sys saptandı. Belirgin papiller kas dissenkronisi olan hastalarda bazal septum TDI sistolik (p=0.007) ve geç diyastolik (p=0.049) velositeleri daha düşük, mitral regurjitan volüm (p=0.01), efektif regürjitan orifis alanı (p=0.01) ve E/A oranı (p=0.03) ise daha yüksek saptandı. Dar QRS'li 55 hasta DYS Inter PAP Sys varlığı yönünden incelendi. Belirgin DYS Inter PAP Sys olan hastaların mitral regurjitan volüm (p=0.03) ve efektif regürjitan orifis alanı (p=0.03) yüksek bazal septum TDI pik sistolik hızları (p=0.038) düşük bulundu. Lojistik regresyon analizinde NYHA Sınıf III-IV (OR=6.4, %95GA: 1.1-37.1,

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p=0.038) ve DYS Inter PAP Sys (OR=9.5, %95GA: 1.17-75.78, p=0.034) varlığı fonksiyonel mitral yetersizliğinin 20 ml'nin üzerinde olmasının bağımsız belirteçleri olarak saptandı.
Sonuç: Papiller kas sistolik dissenkronisi, sinus ritmindeki dar QRS'li non-iskemik dilate kardiyomyopatili hastalarda yaygındır ve fonksiyonel mitral yetersizliği ile ilişkilidir. Papiller kas sistolik dissenkronisi, kardiyak resenkronizasyon tedavisinden fayda görecek hastaların öngörülmesinde kullanılabilir. *(Anadolu Kardiyol Derg 2009; 9: 196-203)*
Anahtar kelimeler: Dissenkroni, kardiyomiyopati, papiller kas, mitral yetersizliği, lojistik regresyon analizi

Introduction

Functional mitral regurgitation (MR) is associated with a worse prognosis in patients with dilated cardiomyopathy (DCM) (1, 2). The suggested mechanisms for functional MR in DCM are the decreased transmitral pressure gradient, which effects mitral valve closure, geometrical changes in the mitral annulus, papillary muscles, and mitral valve, and the dyssynchronic left ventricular and papillary muscular contractions (3-9). Cardiac resynchronization therapy (CRT) has been demonstrated to improve heart failure symptoms, exercise capacity, mortality, and functional MR in patients with heart failure (6-8, 10-12). Reduced MR volume seems to be secondary to the improved coordination of papillary muscular contractions following CRT (8, 11, 12). Intraventricular dyssynchrony has been demonstrated in patients with narrow QRS intervals (13-15). However, the association between papillary muscle dysfunction and functional MR has not been established in patients with DCM who have narrow (<120 ms) QRS complexes on the electrocardiogram (ECG). We investigated the severity of functional MR in non-ischemic DCM patients with narrow QRS intervals and its association with papillary muscle dyssynchrony.

Methods

Patient population

The study population was selected from the patients who were evaluated in Kartal Koşuyolu Heart Education and Research Hospital cardiology outpatient clinic between January 2004 and June 2007. All patients who met the inclusion criteria were asked to participate the study, and the ones who accepted to participate were enrolled prospectively (93 non-ischemic DCM patients with left ventricular systolic ejection fraction <40%). Patients with organic heart valve disease that may cause mitral regurgitation (rheumatic or degenerative heart valve disease, mitral annular calcification, mitral valve prolapsus, chordae tendinea rupture), history of acute coronary syndrome, ischemic ECG findings, significant coronary artery disease in coronary angiography (>50% luminal stenosis), permanent pacemakers, and chronic renal failure that may hinder coronary angiographic study were excluded from the study. Local ethics committee approved the protocol of this cross-sectional study.

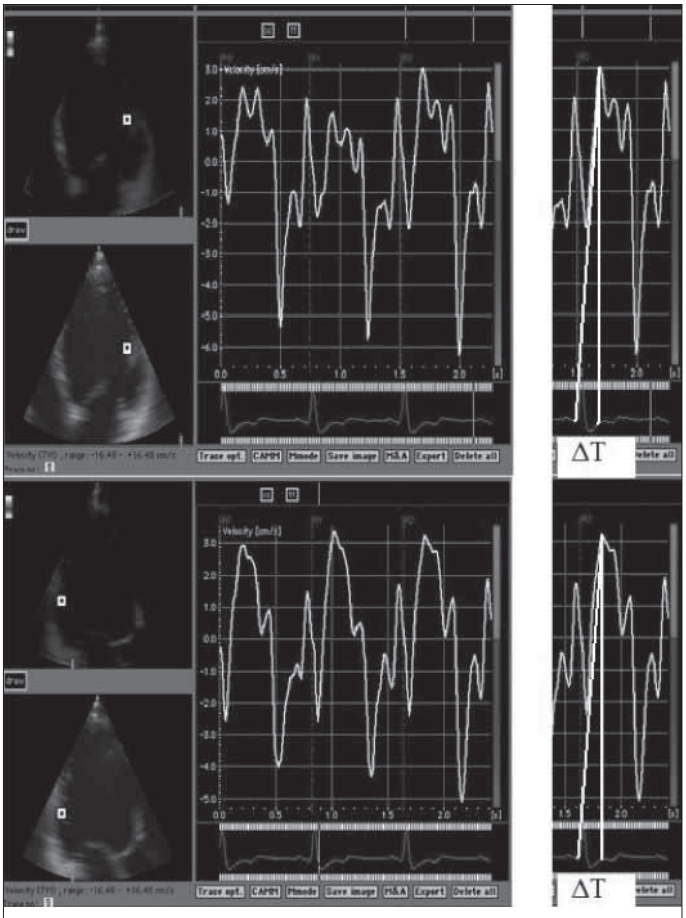
All patients were evaluated for their functional capacities. The 12-lead ECG's were obtained (0.5 to 150 Hz, 25 mm/sec, 10 mm/mV) and each patient had a recent coronary angiogram. Patients were subgrouped into two according to their QRS interval time (<120 msec, ≥120 msec).

Echocardiography

Standard echocardiographic evaluations with Doppler study were performed (System 5, Vingmed-General Electric, Norway). Left ventricle (LV) dimensions and ejection fraction were measured by modified biplane Simpson method according to the guidelines of the American Society of Echocardiography (16).

Doppler echocardiography was used for estimation of LV mitral early (E) and late (A) inflow velocities, their ratio (E/A), isovolumetric relaxation time and E-wave deceleration time and pulmonary artery pressure. 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 MR velocity spectrum (17).

Tissue Doppler imaging (TDI) was performed in the apical views (four chamber and long axis) for the long axis motion of the LV as previously described (18, 19). Two-dimensional echocardiography with tissue Doppler 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 (20). 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 recorded and the images were digitized and analyzed off-line by a computer (EchoPac 6.3, Vingmed-General Electric). Myocardial regional velocity curves were constructed from the digitized images (21). For detailed assessment of regional myocardial function, the sampling window was placed at the myocardial segment of interest. In the apical four-chamber view, both the basal septal and basal lateral segments and anterolateral papillary muscle, from the apical long axis view basal posterior segment and posteromedial papillary muscle were assessed. 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) velocities were quantified (Fig. 1) (22). For the assessment of septal-lateral systolic dyssynchrony (DYS Sep-Lat Sys) and papillary muscle systolic dyssynchrony (DYS Inter PAP Sys), the maximal difference in TS between basal septal and lateral segments and anterolateral and posteromedial papillary muscles were calculated. To assess global cardiac function, the myocardial sustained systolic (s), early diastolic (e) and late diastolic (a) velocities from the basal septal, basal lateral segments and tricuspid annulus were calculated. Significant systolic dyssynchrony was defined as a DYS Sep-Lat Sys of >60 msec and DYS Inter PAP Sys of >60 msec as defined previously (23, 24). The quantification of functional mitral regurgitation was performed using the proximal isovelocity surface area method as previously described (25). The effective regurgitant orifice



ΔT: Time from the onset of QRS to peak myocardial systolic velocity. (Ts)

Figure 1. Demonstration of measurement of dyssynchrony. 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) velocities were quantified

area (ERO, cm^2) and the regurgitant volume (Reg Vol, ml), were used as variables expressing the severity.

Statistical analysis

Statistical 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 unpaired t-test when normally distributed. Nonparametric tests were also used when abnormal distribution was found (Mann-Whitney U test). Categorical data between two or more groups were compared by the Pearson χ^2 test. The correlation of continuous variables was analyzed by Pearson and categorical variables by Spearman correlation analysis. Logistic regression analysis was performed to identify the independent predictors of functional mitral regurgitation >20 ml. A probability value of $p < 0.05$ was considered as significant.

Results

Study population included 27 females (29%) and 66 males (71%). Mean age was 40±15 years. The demographical, clinical, and echocardiographic characteristics of the patients are summarized in Table 1. Patients were evaluated according to the presence of systolic dyssynchrony: 37 patients (39%) had significant DYS Sep-Lat Sys and 25 patients (26%) had significant DYS Inter PAP Sys. Among patients with significant DYS Sep-Lat Sys, nine patients also had significant DYS Inter PAP Sys.

Patients having significant DYS Sep-Lat Sys had shorter E wave deceleration (p=0.003), and isovolumetric relaxation times (p=0.048), and lower TDI peak systolic velocities (p=0.001) than the patients without DYS Sep-Lat Sys. Rest of the clinical and echocardiographic parameters were similar between the two groups (Table 2). The group having significant papillary muscle dyssynchrony had higher number of females (p=0.05), decreased left ventricular systolic ejection fraction (p=0.05), dP/dt ratio p=0.05), and significantly higher Reg Vol (p=0.01), ERO (p=0.01),

Table 1. Demographic, clinical and echocardiographic characteristics of the study group

Gender, F/M	27/66
Age, years	40±15
NYHA, I-II / III-IV	64/29
LA, cm	4.8±0.8
LVESD, cm	6.2±0.8
LVEDD, cm	7.1±0.9
IVS, cm	1.00±0.24
PW, cm	1.0±0.25
LVEF, %	26±8
EPSS, cm	2.4±0.5
dP/dt, mmHg/msec	488±150
Reg Vol, ml	18.5±13.0
ERO, cm^2	0.15±0.12
E/A	2.1±1.1
EDT, msec	123±60
IVRT, msec	95±35
PAP, mmHg	51±15
RV TDI s, cm/sec	7.0±2.4
RV TDI e, cm/sec	5.7±2.6
RV TDI a, cm/sec	8.0±3.9
Sep TDI s, cm/sec	2.8±1.2
Sep TDI e, cm/sec	3.4±1.9
Sep TDI a, cm/sec	3.8±2.3

Data are presented as frequencies and Mean ± SD
dP/dT- delta pressure/delta time, EDT- E wave deceleration time, EPSS- E point septal separation, ERO- effective regurgitant orifice area, F- female, IVRT- isovolumic relaxation time, IVS- interventricular septum diameter, LA- left atrium diameter, LVEDD- left ventricular enddiastolic diameter, LVEF- left ventricular ejection fraction, LVESD- left ventricular end systolic diameter, M- male, NYHA- New York Heart Association, PAB- pulmonary artery systolic pressure, PW- posterior wall, Reg Vol- regurgitant volume, RV TDI a- tricuspid annulus TDI late diastolic velocity, RV TDI e- tricuspid annulus TDI early diastolic velocity, RV TDI s- tricuspid annulus TDI peak systolic velocity, Sep TDI a- basal septum TDI late diastolic velocity, Sep TDI e- basal septum TDI early diastolic velocity, Sep TDI s- basal septum TDI peak systolic velocity

Table 2. Characteristics of the patients with and without significant papillary muscle dyssynchrony

Parameters	Significant DYS Inter PAP Sys (n=25)	Nonsignificant DYS Inter PAP Sys (n=68)	p*
Gender, F\M	11/14	16/52	0.05
Age, years	40±12	39±16	0.771
NYHA, I-II / III-IV	17/8	47/21	0.918
LA, cm	4.9±0.7	4.7±0.9	0.377
LVEDD, cm	7.1±0.9	7.1±0.9	0.709
LVESD, cm	6.3±0.7	6.2±0.8	0.725
IVS, cm	1.00±0.24	1.00±0.24	0.165
PW, cm	0.95±0.20	0.99±0.30	0.867
LVEF, %	23.7±7.0	26.6±8.0	0.05
EPSS, cm	2.4±0.5	2.4±0.6	0.425
dP/dt, mmHg/msec	443±158	505±144	0.05
Reg Vol, ml	24±13	16±12	0.012
ERO, cm^2	0.19±0.01	0.14±0.01	0.011
Mitral E vel., m/sec	0.9±0.2	0.8±0.2	0.264
Mitral A vel., m/sec	0.4±0.1	0.5±0.2	0.008
E/A	2.5±0.9	2.0±1.1	0.032
EDT, msec	105±39	129±65	0.256
IVRT, msec	99±30	95±36	0.443
PAP, mmHg	52±13	50±16	0.708
RV TDI s, cm/sec	6.4±2.0	7.3±2.5	0.07
Sep TDI s, cm/sec	2.3±0.9	3.0±1.2	0.007
Sep TDI e, cm/sec	3.0±1.5	3.5±1.9	0.355
Sep TDI a, cm/sec	3.9±1.5	4.1±2.4	0.049
DYS Inter PAP Sys, msec	98±55	21±13	<0.0001

Data are presented as frequencies and Mean ± SD

*unpaired t-test and Pearson $\chi 2$ test

dP/dT- delta pressure/delta time, EDT- E wave deceleration time, EPSS- E point septal separation, ERO- effective regurgitant orifice area, F- female, IVRT- isovolumic relaxation time, IVS- interventricular septum diameter, LA- left atrium diameter, LVEDD- left ventricular enddiastolic diameter, LVEF- left ventricular ejection fraction, LVESD- left ventricular end systolic diameter, M- male, NYHA- New York Heart Association, PAB- pulmonary artery systolic pressure, PW- posterior wall, Reg Vol- regurgitant volume, RV TDI a- tricuspid annulus TDI late diastolic velocity, RV TDI e- tricuspid annulus TDI early diastolic velocity, RV TDI s- tricuspid annulus TDI peak systolic velocity, Sep TDI a- basal septum TDI late diastolic velocity, Sep TDI e- basal septum TDI early diastolic velocity, Sep TDI s- basal septum TDI peak systolic velocity

and E/A ratio (p=0.03) than the patients without papillary muscle dyssynchrony. Their basal septum systolic (p=0.007), and late diastolic velocity (p=0.049) values were also significantly lower than in the patients without dyssynchrony.

Fifty-five patients who had QRS intervals less than 120 msec were evaluated for the prevalence of septum, lateral and papillary muscle dyssynchrony and its association with functional MR. Fifteen patients (27%) had significant DYS Inter PAP Sys, and 26 (47%) had significant DYS Sep-Lat Sys. Patients having significant DYS Inter PAP Sys had less basal septum TDI peak systolic velocities (p=0.038) and greater Reg Vol (p=0.03) (Figure 2) and ERO areas (p=0.03) than the patients without DYS Inter PAP Sys (Table 3). In addition, the patients with DYS Sep-Lat Sys had significantly higher E/A ratio (p=0.049), lower E wave deceleration time (p=0.001), and isovolumetric relaxation time (p=0.02), tricuspid annulus TDI peak systolic velocities (p=0.001) than the patients without DYS Sep-Lat Sys. Rest of the clinical and echocardiographic parameters were similar (Table 4).

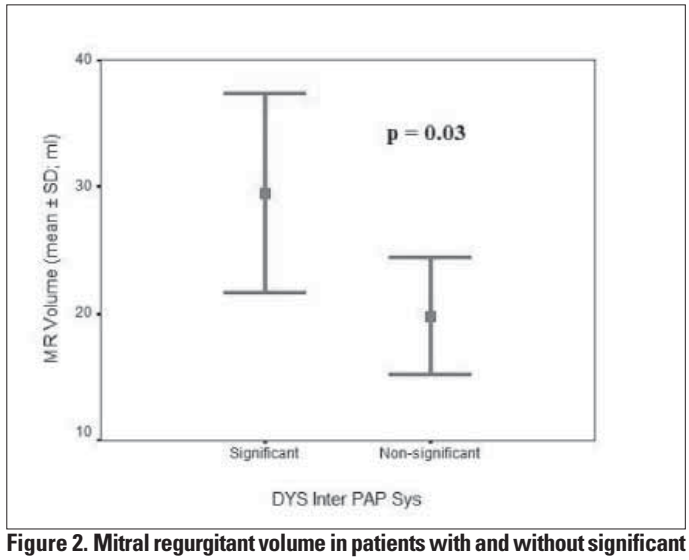


Figure 2. Mitral regurgitant volume in patients with and without significant papillary dyssynchrony

Table 3. Characteristics of the patients having narrow QRS intervals with and without significant papillary muscle dyssynchrony

Parameters	DYS Inter PAP Sys (n=55)						
	(+) n=15			(-) n=40			
	Mean	Median	Min-Max	Mean	Median	Min-Max	p*
Gender, F\M	5/10			8/32			0.310
NYHA, I-II / III-IV	12/3			29/11			0.570
Age, years	40±11	35	28-64	37±17	35	19-77	0.316
LA, cm	4.9±0.8	5.14	2.86-5.90	4.7±0.9	4.94	2.30-6.23	0.630
LVEDD, cm	7.1±0.9	7.04	5.70-9.35	6.9±0.9	7.11	5.38-8.85	0.777
LVESD, cm	6.2±0.8	6.14	4.80-8.06	6±0.8	5.89	4.38-7.48	0.411
IVS, cm	1.0±0.3	0.94	0.68-1.75	1.0±0.2	1.04	0.64-1.90	0.188
PW, cm	1.0±0.2	0.99	0.55-1.50	1±0.2	0.90	0.62-1.80	0.490
LVEF, %	24±7	24	12-39	28±7	27	10-40	0.094
EPSS, cm	2.4±0.4	2.60	1.79-2.87	2.2±0.5	2.42	1.11-3.26	0.086
dP/dt , mmHg/msec	457±159	427	300-800	527±149	525	300-900	0.109
Reg Vol, ml	29.5±14.0	29.4	11.4-57	19.8±13.0	18.5	2.4-64.0	0.030
ERO, cm^2	0.23±0.06	0.230	0.11-0.42	0.16±0.02	0.135	0.02-0.58	0.030
E/A	2.7±1.0	2.96	0.98-4.4	2.1±1.1	2.01	0.52-5.00	0.118
EDT, msec	118±35	115	68-173	135±67	116	53-184	0.790
IVRT, msec	93±31	95	47-138	92±33	92	44-176	0.747
PAP , mmHg	52±13	52	33-80	49±15	45	25-85	0.443
RV TDI s, cm/sec	6.5±1.4	6.05	4.26-8.83	7.4±2.7	6.84	2.13-14.7	0.199
Sep TDI s, cm/sec	2.5±0.7	2.59	1.18-3.95	3.2±1.3	3.19	0.66-6.15	0.038
Sep TDI e, cm/sec	3.1±1.6	3.15	0.60-6.64	3.8±2.2	3.17	0.72-10	0.369
Sep TDI a, cm/sec	3.1±1.4	3.01	1.05-5.40	3.7±1.9	3.88	0.13-8.86	0.363
DYS Inter PAP Sys	90±21	87	63-129	19±13	22	0-49	<0.0001
DYS Sep-Lat Sys	47±34	39	0-126	67±60	62.5	2-289	0.273

Data are presented as frequencies, Mean ± SD and Median (Min-Max) values

*unpaired t-test, Mann-Whitney U test and Pearson χ^2 test

dP/dT- delta pressure/delta time, EDT- E wave deceleration time, EPSS- E point septal separation, ERO- effective regurgitant orifice area, F- female, IVRT- isovolumic relaxation time, IVS- interventricular septum diameter, LA- left atrium diameter, LVEDD- left ventricular enddiastolic diameter, LVEF- left ventricular ejection fraction, LVESD- left ventricular end systolic diameter, M- male, NYHA- New York Heart Association, PAB- pulmonary artery systolic pressure, PW- posterior wall, Reg Vol- regurgitant volume, RV TDI a- tricuspid annulus TDI late diastolic velocity, RV TDI e- tricuspid annulus TDI early diastolic velocity, RV TDI s- tricuspid annulus TDI peak systolic velocity, Sep TDI a- basal septum TDI late diastolic velocity, Sep TDI e- basal septum TDI early diastolic velocity, Sep TDI s- basal septum TDI peak systolic velocity

Among 55 patients with narrow QRS intervals, 8 patients (14%) had no functional MR, 9 patients (16.5%) had less 10 ml (mild, mean DYS Inter PAP Sys: 19±16 msn), 15 patients (27%) had 10-20 ml (mild-moderate, mean DYS Inter PAP Sys: 36±23 msn), 18 patients (33%) had 20-40 ml (moderate-severe, mean DYS Inter PAP Sys: 40±29 msn), and 5 patients (9%) had 40 ml or more (severe, mean DYS Inter PAP Sys: 70±38 msn) functional MR. These four subgroups of patients were investigated for the difference in DYS Inter PAP Sys. The most significant difference was obtained by the comparison of the mild and severe functional MR subgroups (DYS Inter PAP Sys: 19±16 vs 70±38; p=0.028).

Furthermore, the study patients were subdivided into 2 groups according to the severity of functional MR which was measured based on regurgitant volume Thirty-one patients (56%) had MR Vol<20 ml (Group 1) and twenty-four patients (44%) had MR Vol>20 ml (Group 2). Functional MR was correlated with ERO (r=0.917, p<0.0001), NYHA functional class (r=0.293, p=0.045), left atrial diameter (r=0.415, p=0.004), E point septal separation (r=0.303, p=0.038), dP/dt (r=-0.358, p=0.02), and DYS Inter PAP Sys (r=0.321, p=0.028). Group 2 included more patients with NYHA Class III-IV (p=0.015), with larger left atrial (p=0.001), left ventricular end-systolic (p=0.03) and end-diastolic diameters (p=0.03), and with a higher E/A ratio (p=0.007) than Group 1. However, E wave deceleration (p=0.042), isovolumic relaxation (p=0.024), and pulmonary acceleration time (p=0.017) were shorter than Group 1. Among 31 patients in Group 1, 5 patients (16%) had significant DYS Inter PAP Sys, and among 24 patients in Group 2, 10 patients (42%) had significant DYS Inter PAP Sys (p=0.035). The rest of the clinical and echocardiographic variables was similar between the two groups (Table 5).

Logistic regression analysis was performed in patients with narrow QRS interval. Mitral regurgitant volume >20 ml was determined as the dependent variable and the left atrial diameter, NYHA functional

Table 4. Characteristics of the patients having narrow QRS intervals with and without significant septum-lateral wall dyssynchrony

Parameters	DYS Sep-Lat Sys (n=55)						
	(+) n=26			(-) n=29			
	Mean	Median	Mix-Max	Mean	Median	Min-Max	p
Gender, F\M	6/20			7/22			0.926
Age, years	40±16	38.5	14-77	35±14	32	19-64	0.269
NYHA, I-II / III-IV	21/5			20/9			0.316
LA, cm	4.7±0.7	4.90	3.52-5.90	4.8±1.0	5.14	2.30-6.23	0.376
LVEDD, cm	7.0±0.8	7.16	5.38-8.85	6.9±0.9	7.04	5.44-9.38	0.794
LVESD, cm	6.0±0.7	5.93	4.38-7.48	6.1±0.9	6.23	4.48-8.06	0.631
IVS, cm	1.1±0.26	1.1	0.78-1.75	1.0±0.26	0.94	0.64-1.90	0.076
PW, cm	1.0±0.25	0.99	0.66-1.50	0.90±0.24	0.90	0.55-1.80	0.058
LVEF, %	28±7	26	16-40	25±7	27	10-38	0.344
EPSS, cm	2.3±0.4	2.34	145.00-3.26	2.3±0.5	2.44	1.11-3.18	0.815
dP/dt , mmHg/msec	475±143	458	300-800	558±156	533	400-900	0.070
Reg Vol , ml	21±15	17	2.98-64.00	23±13	23	2.4-57.00	0.227
ERO cm^2	0.17±0.02	0.130	0.02-0.58	0.20±0.02	0.199	0.02-0.42	0.134
E/A	2.6±1.2	2.61	0.98-5.0	1.9±1.1	1.64	0.52-4.90	0.049
EDT, msec	101±28	101	53-173	164±71	160	75-184	0.001
IVRT, msec	82±27	78	44-138	103±35	100	50-176	0.027
PAP, mmHg	52±14	48.5	30-85	47±15	45	25-75	0.285
RV TDI s, cm/sec	6.0±1.9	6.03	2.13-10.93	8.5±2.5	8.67	4.54-14.73	0.001
Sep TDI s, cm/sec	3.3±1.3	3.07	0.00-6.15	2.8±1.1	2.94	0.66-4.96	0.102
Sep TDI e, cm/sec	3.7±2.1	3.4	0.72-10.00	3.5±2.0	2.96	0.60-8.66	0.420
Sep TDI a, cm/sec	3.9±1.9	4.15	0.63-8.86	3.2±1.7	3.41	0.13-6.47	0.155
DYS Inter PAP Sys	33±30	27.5	0-109	43±39	25	1-129	0.637
DYS Sep-Lat Sys	103±52	84.5	62-289	24±18	21	0-59	<0.0001

Data are presented as frequencies, Mean ± SD and Median (Min-Max) values

*unpaired t-test, Mann-Whitney U test and Pearson χ^2 test

dP/dT- delta pressure/delta time, EDT- E wave deceleration time, EPSS- E point septal separation, ERO- effective regurgitant orifice area, F- female, IVRT- isovolumic relaxation time, IVS- interventricular septum diameter, LA- left atrium diameter, LVEDD- left ventricular enddiastolic diameter, LVEF- left ventricular ejection fraction, LVESD- left ventricular endsystolic diameter, M- male, NYHA- New York Heart Association, PAB- pulmonary artery systolic pressure, PW- posterior wall, Reg Vol- regurgitant volume, RV TDI a- tricuspid annulus TDI late diastolic velocity, RV TDI e- tricuspid annulus TDI early diastolic velocity, RV TDI s- tricuspid annulus TDI peak systolic velocity, Sep TDI a- basal septum TDI late diastolic velocity, Sep TDI e- basal septum TDI early diastolic velocity, Sep TDI s- basal septum TDI peak systolic velocity

class, E point septal separation, dP/dt, and DYS Inter PAP Sys were included as the independent parameters in the model. The logistic regression analysis revealed that the patients with NYHA functional Class III-IV had 6.4 times (OR=6.4, 95% CI: 1.1-37.1, p=0.038) and these with significant DYS Inter PAP Sys had 9.5 times (OR:9.5, 95% CI: 1.17-75.78, p=0.034) increased risk of developing functional MR > 20 ml.

Discussion

In our study, we found out that papillary muscle dyssynchrony is a relatively common in patients with DCM with narrow QRS intervals. In addition, papillary muscle dyssynchrony was associated with greater mitral regurgitant volume and increased severity of MR.

Functional MR is a common finding among the heart failure patients in general, and it effects prognosis (26-27). Therefore, several treatment modalities aim to reduce MR. Surgical management of functional MR decreases mitral annular size, however MR may persist or relapse following the surgery (28-29). Interestingly, CRT has been demonstrated to improve functional MR in the acute and chronic period (6-8, 11, 12). This finding has been attributed to the improved coordination of the papillary muscular contractions following the CRT (8, 11, 12). On the other hand, patients with minimal papillary muscle dyssynchrony were reported to have no improvement in their functional MR after CRT (12). Previous studies demonstrated that the patients with QRS intervals less than 120 ms may also have intraventricular dyssynchrony, and benefit from CRT (13-15, 23, 30). Soyama et al. demonstrated that intraventricular dyssynchrony has a role in the development of MR in patients with DCM (9). However, in their study group 39% of patients had left bundle branch block and 28% of the patients had atrial fibrillation. This study underlined the need for further studies in dilated cardiomyopathy patients with sinus rhythm and narrow QRS.

Table 5. Characteristics of the narrow QRS patients with MR Vol below and above 20 ml

Parameters	MR Volume <20 ml (n= 31)	MR Volume >20 ml (n=24)	p*
Gender, F\M	10/21	3/21	0.087
Age, years	40±18	35±11	0.396
NYHA, I-II / III-IV	27/4	14/10	0.015
LA, cm	4.4±0.9	5.2±0.6	0.001
LVEDD, cm	6.8±0.9	7.3±0.7	0.032
LVESD, cm	5.9±0.9	6.3±0.6	0.030
LVEF, %	27.7±8.0	26.1±7.0	0.586
EPSS, cm	2.2±0.6	2.4±0.3	0.250
dP/dt, mmHg/msec	536±140	485±164	0.157
Reg Vol, ml	11.6±5.5	32.9±11.8	<0.0001
ERO, cm^2	0.90±0.05	0.27±0.09	<0.0001
Mitral E/A	1.97±1.30	2.72±0.80	0.007
EDT, msec	148±71	107±32	0.042
IVRT, msec	100±32	81±30	0.024
PAT, msec	102±31	82±24	0.017
PAP, mmHg	46±15	54±13	0.120
RV TDI s, cm/sec	7.6±2.8	6.7±1.9	0.177
Sep TDI s, cm/sec	3.2±1.3	2.8±1.2	0.335
Sep TDI e, cm/sec	3.5±2.3	3.8±1.8	0.314
Sep TDI a, cm/sec	3.9±1.9	2.9±1.5	0.065
DYS Inter PAP Sys, Yes/No	5/26	10/14	0.035

Data are presented as frequencies, Mean ± SD and Median (Min-Max) values
*unpaired t-test, Mann-Whitney U test and Pearson χ^2 test
dP/dT- delta pressure/delta time, EDT- E wave deceleration time, EPSS- E point septal separation, ERO- effective regurgitant orifice area, F- female, IVRT- isovolumic relaxation time, IVS- interventricular septum diameter, LA- left atrium diameter, LVEDD- left ventricular enddiastolic diameter, LVEF- left ventricular ejection fraction, LVESD- left ventricular endsystolic diameter, M- male, NYHA- New York Heart Association, PAB- pulmonary artery systolic pressure, PW- posterior wall, Reg Vol- regurgitant volume, RV TDI a- tricuspid annulus TDI late diastolic velocity, RV TDI e- tricuspid annulus TDI early diastolic velocity, RV TDI s- tricuspid annulus TDI peak systolic velocity, Sep TDI a- basal septum TDI late diastolic velocity, Sep TDI e- basal septum TDI early diastolic velocity, Sep TDI s- basal septum TDI peak systolic velocity

Our study revealed that functional MR is frequently present in DCM patients who have narrow QRS and sinus rhythm and this is associated with papillary muscle dyssynchrony. Eighty five percent of narrow QRS patients had functional MR in our study. In addition, 27% had significant DYS Inter PAP Sys and these patients also had significantly greater degree of functional MR compared to the patients without significant dyssynchrony. We found out a positive correlation between the severity of functional MR and DYS Inter PAP Sys. This information suggests that the papillary muscle dyssynchrony is one of the important causes of functional MR in this group of patients. The patients with functional MR Volume>20 ml had more significant DYS Inter PAP Sys. In addition, the logistic regression analysis revealed that the presence of significant DYS Inter PAP Sys is an independent predictor of functional MR. These findings provides further evidence for the association of papillary muscle dyssynchrony and functional MR. On the other hand, 47% of patients with narrow QRS intervals had significant DYS Sep-Lat Sys. This group of patients may also benefit from CRT. Treatment of MR in patients with DCM with severe functional MR seems to be very crucial (31, 32).

Since the surgical treatment of MR is associated with high perioperative morbidity and mortality, treating functional MR with alternative methods such as CRT seem reasonable. (33). Overall, CRT improves mortality in selected heart failure population. In addition, Achilli et al. reported the improvement of the functional MR in 14 narrow QRS patients who initially have intraventricular dyssynchrony following the CRT (30). It may be useful to search intraventricular and papillary muscle dyssynchrony in patients with non-ischemic DCM and narrow QRS intervals since they may benefit from CRT.

Study limitations

We do not have a comparison group such as the patients with intraventricular or papillary muscle dyssynchrony who did not receive CRT secondary to their QRS duration or functional class. This is the major limitation of our study since we do not have a follow-up data. However, our clinical practice is based on current guideline recommendations. Therefore, such investigation is almost impossible to perform. In addition, myocardial velocity measurements with color-coded TDI method reflect active contractions as well as passive myocardial movements. Hence, re-analysis of our hypothesis with more specific methods such as myocardial strain and strain rate might be more reliable. The cut-off value (60 msec) for the detection of papillary muscle dyssynchrony may also be inappropriate after considering the localization of papillary muscles in the remodeled myocardium. Finally, studies with larger number of patients and novel echocardiographic modalities will be useful to determine the appropriate cut-off values for papillary muscle dyssynchrony.

Conclusion

Papillary muscle dyssynchrony is correlated with functional MR in non-ischemic DCM patients with sinus rhythm. This finding persists in patients with narrow (<120 msec) QRS intervals. Appropriate interpretation of papillary muscle dyssynchrony may change the treatment and outcome in these patients. Papillary muscle dyssynchrony may help predict patients who will benefit from CRT.

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