Prognostic significance of left ventricular systolic dyssynchrony in patients with nonischemic dilated cardiomyopathy

İskemik olmayan dilate kardiyomiyopatili hastalarda sol ventrikül disenkroni parametrelerinin prognostik önemi

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Objectives: Left ventricular (LV) dyssynchrony parameters are still being investigated to guide and optimize treatment in heart failure. We investigated the prognostic importance of LV systolic dyssynchrony in nonischemic dilated cardiomyopathy (DCM) using tissue Doppler echocardiography.

Study design: The study included 62 patients (39 males, 23 females; mean age 40 years; range 9 to 77 years) with nonischemic DCM. All the patients were examined by electrocardiography, echocardiography including tissue Doppler imaging (TDI), and angiography. The patients were evaluated in two groups depending on the intraventricular delay (IVD) of ≤65 msec (group 1, 10 patients) and >65 msec (group 2, 52 patients). The primary endpoint was defined as overall mortality during a mean follow-up period of 1,253±177 days (range 943 to 1583 days).

Results: Group 2 patients had a significantly longer mean IVD (129±68 msec *vs.* 57.5±8.7 msec; p=0.013), higher rate of left bundle branch block (30.8% *vs.* 10%; p=0.05), longer QRS duration (145±29 msec *vs.* 129±23 msec; p=0.02), and higher mortality (55.8% *vs.* 10%; p<0.0001). Sudden cardiac death was seen in one patient in group 1, compared to 12 patients in group 2. All the remaining deaths (n=17) occurred in group 2. In ROC analysis, the cutoff level for IVD was 65 msec for predicting clinical endpoint (specificity 72%, sensitivity 46%). Kaplan-Meier survival analysis showed a significantly lower survival in group 2 (p=0.045). In multivariate analysis, admission IVD was the only significant independent predictor of mortality (p<0.001).

Conclusion: Our results showed that increased IVD was associated with increased risk for death in patients with nonischemic DCM, independent from the QRS width and LV ejection fraction. These patients might be considered earlier for cardiac resynchronization therapy.

Key words: Cardiomyopathy, dilated/mortality; echocardiography, Doppler; electrocardiography; heart conduction system; heart failure/complications; ventricular dysfunction, left/mortality.

Amaç: Kalp yetersizliği tedavisinde sol ventrikül disenkroni parametrelerinin önemi araştırılmakta olan bir konudur. Çalışmamızda iskemik olmayan dilate kardiyomiyopatili hastalarda doku Doppler yöntemi ile saptanan sol ventrikül sistolik disenkroni varlığının prognostik önemi araştırıldı.

Çalışma planı: Çalışmaya iskemik olmayan dilate kardiyomiyopatili 62 hasta (39 erkek, 23 kadın; ort. yaş 40; dağılım 9-77) alındı. Tüm hastalar elektrokardiyografi, doku Doppler görüntüleme de dahil ekokardiyografi ve anjiyografi ile değerlendirildi. İntraventriküler gecikme (İVG) süresine göre iki grup oluşturuldu: Grup 1'de İVG ≤65 msn olan 10 hasta, grup 2'de İVG >65 msn olan 52 hasta vardı. Primer sonlanım noktası tüm nedenlere bağlı mortalite olarak belirlendi. Hastalar ortalama 1,253±177 gün (dağılım 943-1583 gün) süreyle takip edildi.

Bulgular: Grup 2 hastalarında anlamlı derecede uzun ortalama İVG süresi (129±68 msn ve 57.5±8.7 msn; p=0.013), daha yüksek oranda sol dal bloku (%30.8 ve %10; p=0.05), daha uzun QRS (145±29 msn ve 129±23 msn; p=0.02) ve daha yüksek mortalite (%55.8 ve %10; p<0.0001) görüldü. Ani ölüm grup 1'de bir hastada, grup 2'de 12 hastada meydana geldi. Diğer ölümlerin tümü (n=17) grup 2 hastalarında görüldü. Klinik sonlanımı öngörmede ROC analiziyle hesaplanan İVG kesim değeri 65 msn bulundu (özgüllük %72, duyarlık %46). Kaplan-Meier analizinde sağkalım grup 2 hastalarında anlamlı derecede düşük bulundu (p=0.045). Çokdeğişkenli analiz, başvuru sırasındaki İVG'nin mortaliteyi öngörmede tek bağımsız etken olduğunu gösterdi (p<0.001).

Sonuç: İskemik olmayan dilate kardiyomiyopatili hastalarda artmış İVG süresi, ejeksiyon fraksiyonu ve QRS genişliğinden bağımsız olarak, daha yüksek ölüm riski ile ilişkilidir. Bu hastaların erken kardiyak resenkronizasyon tedavisi için değerlendirilmesi uygun olabilir.

Anahtar sözcükler: Kardiyomiyopati, dilate/mortalite; ekokardiyografi, Doppler; elektrokardiyografi; kalp iletim sistemi; kalp yetersizliği/komplikasyon; ventrikül disfonksiyonu, sol/mortalite.

Received: January 17, 2009 *Accepted:* March 27, 2009

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Heart failure is an important public health problem and its prevalence is on the incline.[1-3] There is a complex sequence of electrical and mechanical events in the systolic phase of the myocardial cycle. Widening of the QRS complex on the surface electrocardiogram suggests a slowdown of the electrical input propagation through the myocardium. This finding is associated with increased mortality and morbidity in patients with heart failure.[4-6] The sequence of electrical activation and mechanical function determines ventricular systole, and in turn, clinical endpoints. Electromechanical dyssynchrony impairs cardiac contraction and coordination of relaxation, and also influences major cardiac events independent from ejection fraction (EF) and QRS duration (QRSd).[7,8]

In this study, we investigated the impact of left ventricular (LV) systolic dyssynchrony on long-term mortality in patients with nonischemic dilated cardiomyopathy (DCM).

PATIENTS AND METHODS

Patient selection. The study included 62 consecutive patients (39 males, 23 females; mean age 40 years; range 9 to 77 years) who were admitted to our hospital with heart failure-related symptoms and were diagnosed as having nonischemic DCM. None of the patients had prior cardiac resynchronization therapy. Twelve-lead electrocardiograms were obtained and all patients underwent echocardiographic evaluation including tissue Doppler imaging (TDI) and cardiac catheterization. Functional capacity of the patients was assessed according to the New York Heart Association (NYHA) classification. Patients with hypertension, significant coronary artery disease, echocardiographic evidence for organic valvular disease, congenital heart disease, and atrial fibrillation were excluded.

The patients were divided into two groups depending on the intraventricular delay (IVD); hence, group 1 consisted of 10 patients with an IVD of ≤65 msec, and group 2 consisted of 52 patients with an IVD of >65 msec. Written informed consent was obtained from all participants and the study was approved by the local ethics committee.

Electrocardiographic examination. Standard 12-lead electrocardiograms were obtained at a paper speed of 25 mm/sec and a scale of 10 mm/mV. The measurement of QRSd (recorded from the surface leads demonstrating the greatest values) was performed by an experienced observer who was blinded to the echocardiographic characteristics of the patients.

Echocardiographic examination. Standard echocardiographic examination was performed by a Vingmed Vivid System 5 (General Electric, Norway) device using a 2.5 MHz transducer. Two-dimensional echocardiographic examination was performed from the standard parasternal long- and short-axis, and apical two-, three-, and four-chamber views. Left ventricular systolic and diastolic diameters and LV ejection fraction (by biplane Simpson's method) were measured by two-dimensional and M-mode echocardiography. Tissue Doppler imaging was performed in 2.5-3.5 MHz frequencies and by second harmonic imaging, from the apical two-, three-, and four-chamber views. Images were recorded digitally (EchoPac 6.3, Vingmed-General Electric). For the evaluation of regional myocardial functions, the sample volume was placed at the basal and mid segments of the six myocardial regions (septum, lateral, anterior, inferior, anterior septum, and posterior). Simultaneous electrocardiographic recordings were obtained throughout TDI. The peak systolic velocities of the 12 LV segments were measured. Ts (segmenter time) was measured for each segment as the duration from the initiation of electrocardiographic QRS to the peak systolic velocity. The difference between the highest and lowest Ts values of the 12 LV segments was calculated as IVD.

Angiographic examination. All patients with nonischemic DCM underwent coronary angiography. Patients who had epicardial coronary artery stenosis greater than 50% were excluded.

Medical treatment. Patients received classical treatment for heart failure including ACE inhibitors, beta-blockers, diuretics, and digoxin.

Clinical follow-up and endpoint. The mean follow-up period was 1,253±177 days (range 943 to 1583 days). The primary endpoint was defined as overall mortality. Death occurring within the first 24 hours following admission was defined as sudden cardiac death. Otherwise, it was considered to be due to progressive heart failure.

Statistical analysis. All statistical analysis were performed using the SPSS (for Windows, version 13.0) software package. Continuous variables were expressed as mean ± standand deviation (SD). Comparisons were made using the Student t-test, Mann-Whitney U-test, Fisher's exact test, or chi-square test, as appropriate. Spearman's correlation coefficient was used to test associations between IVD and echocardiographic and clinical parameters. Univariate and multivariate Cox regression analyses (with backwards elimina-

Table 1. Demographic, clinical, and echocardiographic characteristics of the patients

	Group 1 (n=10, IVD ≤65 msec)			Group 2 (n=52, IVD >65 msec)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			35.2±11.3			42.0±16.6	N S
Sex (Females)	1	10.0		22	42.3		**<0.001**
NYHA functional class			1.8±0.8			2.1±0.9	N S
Electrocardiography							
Left bundle brunch block	1	10.0		16	30.8		**0.05**
QRS duration (m/sec)			129±23			145±29	**0.02**
Echocardiography							
Left ventricular							
End-systolic diameter (cm)			6.1±0.8			6.2±0.8	N S
End-diastolic diameter (cm)			7.0±0.7			7.0±0.9	N S
Ejection fraction (%)			24.5±7.3			24.0±7.9	N S
Mitral inflow							
E-wave deceleration time (msec)			108.5±74.9			118±58.4	N.S
E/A			2.2±0.9			2.1±1.1	N.S
Restrictive pattern	8	80.0		42	80.8		N.S
Left atrium diameter (cm)			4.9±0.9			4.7±0.8	N S
Mitral regurgitation (severe)	3	30.0		14	26.9		N S
Intraventricular delay (sec)			57.5±8.7			129.0±68.0	**0.013**
Mortality	1	10.0		29	55.8		**<0.001**
Sudden death	1	10.0		12	23.1		
Progressive heart failure	–			17	32.7		

IVD: Intraventricular delay; NYHA: New York Heart Association; NS: Not significant.

tion model) were used to evaluate the prognostic value of variables. Receiver-operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff point for IVD values with respect to prognosis. Survival curve for IVD value was derived using the Kaplan-Meier method. For all analyses, a *p* value of less than 0.05 was considered statistically significant.

RESULTS

The clinical and echocardiographic characteristics of the patients are summarized in Table 1. Medications of the patients are listed in Table 2. The two patient groups were similar with respect to age, LV EF, systolic and diastolic dimensions, diastolic function parameters, left atrium diameter, number of patients with severe mitral regurgitation, and NYHA class. There were more female patients in group 2 (10% *vs*. 42.3%; p<0.001). Group 2 patients had a significantly longer mean IVD (129±68 msec *vs*. 57.5±8.7 msec; p=0.013), higher rate of left bundle branch block (30.8% *vs*. 10%; p=0.05), longer QRSd (145±29 msec *vs*. 129±23 msec ; p=0.02), and higher mortality (55.8% *vs*. 10%; p<0.0001) than patients in group 1 (Table 1).

The value of IVD in predicting clinical endpoints was evaluated by ROC analysis. The cutoff level for IVD was calculated as 65 msec for clinical endpoints (specificity 72%, sensitivity 46%). Kaplan-Meier survival analysis was performed to evaluate life expectancy of patients having higher and lower IVD cutoff values. Group 2 patients had a significantly lower survival (chi-square=4.01; p=0.045; Fig. 1). Overall, 30 patients died during the follow-up period. Sudden cardiac death was seen in one patient in group 1, compared to 12 patients in group 2. All the remaining deaths (n=17) occurred in group 2 and were due to the progression of heart failure. In univariate analysis of clinical and echocardiographic variables, NYHA class, left ventricular EF, IVD, mitral inflow E-wave deceleration time, E/A ratio, EDT, restrictive diastolic

Table 2. Medications used in the patient groups

	Group 1		Group 2		
	n	%	n	%	*p*
Beta-blockers	9	90.0	42	80.8	N S
Angiotensin converting enzyme inhibitors	10	100.0	47	90.4	N S
Angiotensin receptor blockers	–		2	3.9	N S
Diuretics	10	100.0	47	90.4	N S
Aspirin	10	100.0	49	94.2	N S
Coumadin	–		1	1.9	N S
Digoxin	1	10.0	9	17.3	N S
Nitrates	1	10.0	7	13.5	N S

Group 1: IVD ≤65 msec; Group 2: IVD >65 msec; NS: Not significant.

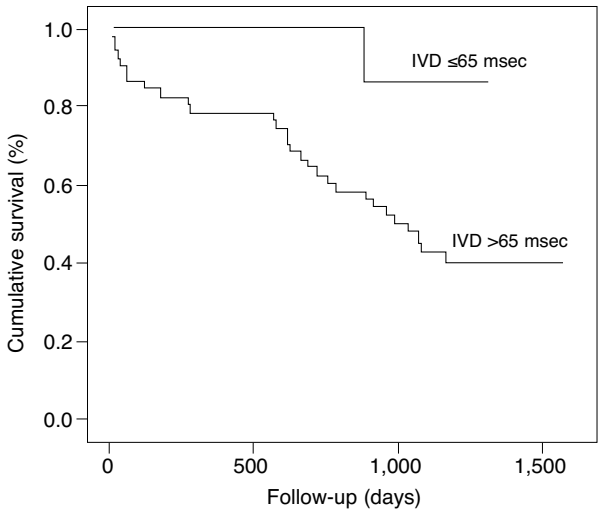

Figure 1. Kaplan-Meier survival analysis.

pattern, and left ventricular end-systolic diameter were associated with the occurrence of the primary endpoint. Multivariate analysis identified admission IVD as the only significant independent predictor of the primary endpoint: hazard ratio for IVD ≤65 msec was 0.003 (95% CI 0.001-0.005; p<0.001).

DISCUSSION

This study demonstrates the prognostic importance of intraventricular dyssynchrony assessed by tissue Doppler echocardiography in nonischemic DCM. The results of our study have several important implications. First, we demonstrated that DCM patients with IVD >65 msec had a significantly higher risk for death than those with IVD ≤65 msec, being independent from the LV EF and QRS width. Second, we demonstrated that there was no association between mortality and QRS duration or presence of left bundle branch block.

Our results support the findings of two recent studies which demonstrated the presence of IVD >65 msec as an independent risk factor for mortality.[8,9] Different from the previous studies, we used a noninvasive technique and studied a highly specific subgroup of patients with nonischemic DCM. Furthermore, our follow-up duration was quite long. In addition, we demonstrated that QRS prolongation did not correlate with the IVD value. This observation raises important questions regarding the potential mechanisms of mechanical ventricular dyssynchrony in patients without complete bundle branch block. Animal studies of heart failure have shown decreased ventricular conduction secondary to interstitial fibrosis and impaired intra- and intercellular calcium handling.[10,11] Our results support this finding since intra-LV dyssynchrony independently influenced the mortality risk of DCM patients. Therefore, we suggest that admission IVD be measured and recorded in each heart failure patient. Echocardiographic TDI appears to be an optimal modality since it is noninvasive, reproducible, and may be used to identify patients with a dismal prognosis.

Identifying DCM patients with intra-LV dyssynchrony may also be helpful for the treatment strategy. Currently, despite optimal individualized treatment for heart failure, there is no specific drug that precludes or even mitigates electromechanical ventricular dyssynchrony. Therefore, the presence of IVD >65 msec (independent of the QRS width) may be used to select patients for cardiac resynchronization therapy, which has been shown to reduce the degree of LV mechanical dyssynchrony.[12-16]

On the other hand, the prognostic significance of dyssynchrony seems to be more important than the treatment of dyssynchrony with CRT. We evaluated dyssynchrony in a similar way to that of the Rethin-Q trial.[17] However, the results of the Rethin-Q trial did not favor TDI indexes in selecting candidates for CRT. Moreover, the PROSPECT study reported a high variability of the difference between septal and lateral delays as well as of the difference between the time-to-peak of systolic velocities measured at 12 LV myocardial segments.[18] Also the reproducibility of all the TDI indexes was very low. Although the results were negative, we used similar tissue velocity indexes for stratifying mortality since those trials were the two main studies on this subject. In fact, the role of echocardiography in predicting heart failure patients after CRT has been previously published. Bax et al.[19] used tissue Doppler parameters as the predictor criteria. Our study involved a lower number of patients but a more particular group (DCM), whereas Bax et al.[19] included patients (n=85) with ischemic cardiomyopathy. Two parameters used in both studies were similar and were based on TDI. Bax et al.[19] used only two segments; however, we used 12-segment analysis in our study. This is not a major difference in terms of analyzing dyssynchrony, but has a high impact in terms of reproducibility.[18] All TDI parameters reported in the literature including the peak velocities were associated with a low yield level and a high rate of variability. Thus, one could argue that the impact of our results might be based on a relatively nonreliable parameter. Similarly, the choice of the dyssynchrony parameter is also questionable. In order to increase

reproducibility, we used a combined parameter (TDI peak velocity from 12 segments as Yu et al.[12] and maximum-minimum delay as Bax et al.[19]).

Previously, Cho et al.[20] demonstrated that left ventricular dyssynchrony was an independent predictor of all-cause mortality in patients with reduced EF, and that ischemic etiology was not associated with mortality. We investigated this association in nonischemic DCM patients. Interestingly, IVD predicted all-cause mortality independently of LV EF and QRS width in our study. This study merits attention since there is no conclusive evidence in the literature on the prognostic significance of dyssynchrony.

Limitations. *(i)* The major limitation of our study is its sample size. Influences of severe mitral regurgitation, left bundle branch block, and QRS duration on survival could have been better assessed with a larger group of patients. There is an obvious possibility that the results may not be justified in much larger patient groups. Nonetheless, in the given sample, it appears that the data do support our conclusions. Therefore, further studies in a similar design and with a higher number of subjects especially in group 1 are necessary. Even though multivariate analysis has limitations in the presence of small sample size, it was shown in our study that the QRS duration was not associated with prognosis, which was contrary to some literature reports on larger series of patients.[6] There was also a wide difference between the number of patients in group 1 and 2 (10 *vs*. 52). The finding that, albeit not equally distributed, most of the demographic, clinical, and echocardiographic features did not reach a statistically significance level might somewhat have been influenced by the small number of patients in group 1.

(ii) Considering relatively low NYHA classes in both groups (class 1.8 to 2.1), a lower mortality rate could have been expected in group 2 rather than a rate of 55.8%. Such a high mortality rate is uncommon in class I-II patients. On the other hand, it was surprising that the presence of a restrictive pattern, which is an uncommon finding in class I-II patients and may be associated with increased mortality, was quite common in both groups (80% vs. 80.8%). This finding needs to be validated in larger patient groups.

(iii) The pulsed-wave TDI echocardiographic technique did not permit us to differentiate passive from active LV wall motion. To determine the exact initiation moment of regional contraction, strain or strain rate derived from tissue Doppler echocardiography could be more beneficial. This could be particularly important in patients with ischemic heart failure and segmentary wall motion abnormalities. However, none of the study patients in our study had ischemic heart failure.

(iv) As proposed in the PROSPECT study, the single parametric approach should be given up and replaced by a multiparametric strategy integrating different levels and types of dyssynchrony.[18]

(v) Finally, we did not calculate the statistical number of patients required for this study. Again, according to the PROSPECT study, dyssynchrony studies should at least include 100 patients from two to three centers.

In conclusion, nonischemic DCM patients with increased IVD have a significantly higher risk for death. This finding is independent from the QRS width and LV EF. These patients might be screened for cardiac resynchronization therapy.

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