Original Article

Prevalence of Left Ventricular Diastolic Asynchrony in Patient with Systolic Heart Failure

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Background: To study the occurrence of left ventricular (LV) diastolic asynchrony in patients with systolic heart failure (HF) and its relationship to diastolic function regardless of QRS duration.
Recent work has demonstrated that intraventricular asynchrony is a common finding in patients with systolic heart failure. Little attention has been paid to diastolic asynchrony in patients with systolic heart failure. We have therefore decided to determine the extent to which patients with systolic heart failure have evidence of diastolic asynchrony and whether or not diastolic asynchrony is correlated with diastolic dysfunction.
Patients and Methods: Tissue Doppler echocardiography was performed in 50 HF patients (LV EF=23 ± 8%). Diastolic and systolic asynchrony was determined by tissue synchronization imaging using a 6 basal, 6 mid-segmental model. Systolic and diastolic asynchrony were assessed by the maximal difference in time to peak systolic and early diastolic velocities between any two of 12 LV segments, and the standard deviation of time to peak systolic and early diastolic velocities of the 12 LV segments.
Results: The mean ± SD maximal difference in time to peak systolic velocity (controls: 17.2± 9.6 ms versus narrow QRS: 66.7 ± 38.0 ms versus wide QRS: 76.5± 34.6 ms, both P<0.05 versus controls) and in standard deviation of time to peak systolic velocity of 12 LV segments (controls: 15± 6.1 ms versus narrow QRS: 25.9± 15.3 ms versus wide QRS: 28.6±14.4ms, both P<0.05 versus controls) was prolonged in both the narrow and wide QRS groups compared with normal controls. Similarly, the maximal difference in time to peak diastolic velocity (controls: 39± 16.8 ms versus narrow QRS: 73.1± 58ms versus wide QRS: 108.5± 168 ms, both P<0.05 versus controls) and in standard deviation of time to peak early diastolic velocity of 12 LV segments (controls: 15.3±5.8ms versus narrow QRS: 25.1± .13.8ms versus wide QRS: 25.5± 14.9ms, both P<0.05 versus controls) was prolonged in both the narrow and wide QRS groups. The respective prevalence of systolic and diastolic asynchrony was 31.4% and 20%, in the narrow QRS group, and 40% and 28.6%, in the wide QRS group respectively. Stepwise multiple regression analysis showed that low ejection fraction and low mitral annular early diastolic velocity were independent predictors of both systolic and diastolic asynchrony. QRS complex duration was found to correlate only with diastolic asynchrony.
Conclusions: LV systolic and diastolic mechanical asynchrony is common in patients with HF regardless of QRS duration. Selection for cardiac resynchronization treatment should also be based on information about systolic and diastolic synchronicity.

Key words: Diastolic asynchrony, diastolic dysfunction, systolic heart failure.

Introduction

Recent work has demonstrated that intraventricular asynchrony is a common finding in patients with systolic heart failure. Little attention has been paid to diastolic

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asynchrony in patients with systolic heart failure.

Tissue Doppler imaging has been shown to be useful in quantifying regional myocardial motion and determining the severity of LV systolic asynchrony in patients with heart failure.[1-4] Quantitative determination of diastolic function is also clinically useful.[4-6] Therefore, the present study was conducted to assess whether or not LV diastolic asynchrony was present in patients with systolic heart failure and comparing it with systolic asynchrony regardless of QRS duration.

In addition, the potential predictors of severity of systolic and diastolic asynchrony were determined. Diastolic asynchrony may account for some CRT non-responders despite systolic resynchronization.

Patients and Methods

Fifty patients (54% men) with clinical symptoms and signs of heart failure and impaired systolic function by echocardiography (ejection fraction ≤ 35%, mean: 23 ±8%) were recruited. Of these, 20, 25 and 5 had coronary artery disease, dilated cardiomyopathy, and other etiologies (including hypertensive heart disease) respectively. Patients with coronary artery disease had either previous evidence of myocardial infarction diagnosed by standard criteria or angiographic indication of significant disease with or without previous coronary artery bypass graft surgery. Patients with atrial fibrillation prosthetic valve and significant valvular dysfunction were excluded from the study. As shown in Table 1, among the participating patients, QRS complexes were narrow (<120 ms; narrow QRS group) in 35 (70%) and prolonged (>120 ms; wide QRS group) in 15 (30%). The results were compared with those of 20 normal healthy volunteers (51% men). The volunteers had normal physical examination, electrocardiography and echocardiography findings, and did not have any history of cardiovascular or systemic disease.

Echocardiography

Standard echocardiography with Doppler studies was performed using a Vivid 7 digital ultrasound scanner (GE, Milwaukee, Wisconsin, USA) equipped with an ergonomically-designed M3S with a 3.5 MHz phase array matrix transducer. LV dimension and ejection fraction were measured according to the guidelines of the American Society of Echocardiography. [7] To determine ventricular asynchrony, spectral displays of 6 basal and 6 middle LV segments with pulsed wave tissue Doppler imaging (TDI) were obtained in the apical 4-, 3-, and 2-chamber views and stored digitally.[8] In brief, pulsed wave TDI was obtained by placing the sample volume in the middle of the each myocardial segment. Gain and filter settings were adjusted as needed to eliminate background noise and to allow for a clear spectral display. The measurements were performed with a sweep of 100 mm/s. Offline analysis of 3 end-expiratory beats were performed, and the results were averaged. For the measurement of timing, the beginning of the QRS complex was used as the reference point, where the time to peak systolic (TS) and early diastolic velocities (TE) was quantified.[3] For the assessment of synchronicity, the standard deviation of the time to peak systolic velocity (TS-SD) and the time to peak diastolic velocity (TE-SD) of all 12

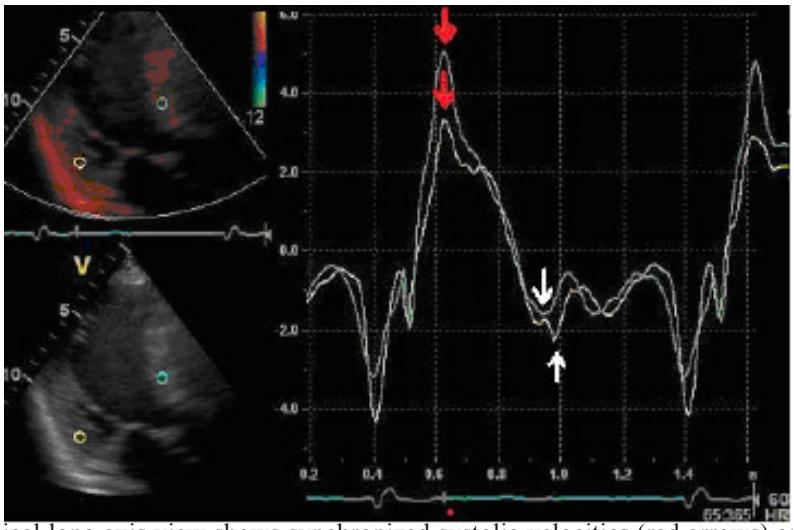

Figure 1: The apical long axis view shows synchronized systolic velocities (red arrows) and only mild delay of diastolic velocities (white arrows) of the basal posterior and the basal anteroseptal walls. The peak systolic and diastolic velocities are shown by the arrows.

LV segments (Fig. 1, 2) and the maximal difference in TS and TE between any two of the 12 LV segments were calculated. To assess global diastolic function, the mitral annular early diastolic (E_m) velocity from the basal septal segment was calculated.

Statistical analysis

Data were analyzed using a statistical software program (SPSS for Windows, version 11, SPSS Inc, Chicago, Illinois, USA). For comparison of parametric variables between the three groups, analysis of Co-variance was used to examine the effect of age and heart rate on the dependent variables, followed by one way analysis of variance. Linear regression analysis was performed to investigate the correlation between parametric variables. Categorical data between two or more groups were compared by the Pearson Chi-square test. Stepwise

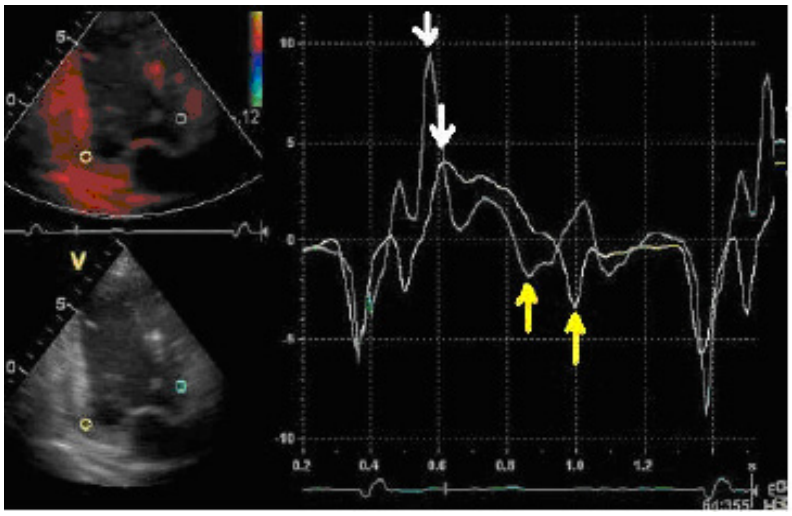

Figure 2. The apical two chamber view shows only mild (30 ms) systolic and significant (130 ms) diastolic delay of basal inferior segment over the basal anterior segment The peak systolic (white arrows) and diastolic (yellow arrows) velocities are shown by the arrows

Table 1. Comparison of clinical and echocardiographic data between heart failure patients with narrow and wide QRS complexes and normal controls

	Narrow QRS (n=15)	Wide QRS (n=35)	P value
Age (years)	52.5±18.7	59.5±14.2	NS
Male/ Female (%)	53/47 %	54/46%	NS
QRS duration (ms)	90 ±10	135±20	<0.05
Causes of heart failure (%)			
Coronary artery disease	6(30%)	14(70%)	
Dilated cardiomyopathy	8(32%)	17(68%)	
Hypertension	6(30%)	14(70%)	

EF: ejection fraction, Peak E wave: peak early diastolic wave velocity, E_m: mitral annular velocity. Data are mean ± SD

multiple regression analysis was performed to assess potential independent covariates on systolic and diastolic asynchrony. The results are expressed as mean ±SD. P value less than 0.05 was considered to be significant.

Results

There were no differences in age (control: 52±8.2 versus narrow QRS: 52.5±18.7 versus wide QRS: 59.5±14.2 years) and sex (53% versus 54% versus 55% male) between normal controls and the patients' groups. Table 1 shows the baseline clinical characteristics of the narrow and wide QRS groups. The age, gender, and etiology of heart failure were not different between the two groups. In the wide QRS group, 70% had a left bundle branch block pattern, 23% had a right bundle branch block pattern, and 7% had intraventricular conduction delay. The mean LV ejection fraction was significantly lower in the patients' groups than in controls (control: 64±5 versus narrow QRS: 23.3±8 versus wide QRS: 22.9±8.9 %, both P<0.05 versus normal).

Systolic asynchrony

The systolic synchronicity was impaired in patients with heart failure. The maximal difference

Table 2. Comparison of systolic and diastolic asynchrony indices between heart failure patients with narrow and wide QRS complexes and normal controls.

	1. Controls (n=20)	2. Narrow QRS (n=15)	3. Wide QRS (n=35)	P value (1 versus 2)	P value (1 versus 3)	P value (2 versus 3)
TS-diff (msec)	17.2 ± 9.6	66.7±38.0	76.5±34.6	<0.05	<0.05	NS
TS-SD (msec)	15 ± 6.1	25.9±15.3	28.6±14.4	<0.05	<0.05	NS
TE-diff (msec)	49 ± 16.8	73.1±58	108.5±168	<0.05	<0.05	NS
TE-SD (msec)	15.3 ± 5.8	25.1±13.8	25.5±14.9	<0.05	<0.05	NS
Septal-lateral delay(S) (msec)	9± 8	45.1±34	49.6±35.3	<0.05	<0.05	NS
Septal-lateral delay (E) (msec)	11±10	25.7±22	25.3±21	<0.05	<0.05	NS

Data are mean ±SD. TS-diff: maximal difference in time to peak myocardial systolic velocity among all 12 left ventricular segments; TS-SD: standard deviation of the time to peak myocardial systolic velocity of all 12 left ventricular segments, TE-diff: maximal difference in time to peak myocardial early diastolic velocity among all 12 left ventricular segments; TE-SD: standard deviation of the time to peak myocardial early diastolic velocity of all 12 left ventricular segments, Septal-lateral delay(S) : difference in time to peak myocardial systolic velocity between basal septum and lateral segments, Septal-lateral delay(E) : difference in time to peak myocardial early diastolic velocity between basal septum and lateral segments.

in TS was prolonged in the narrow QRS group compared with normal subjects (control: 17.2 ± 9.6 versus narrow QRS: 66.7±38.0 msec, P<0.05) and was the longest (76.5±34.6 msec) in the wide QRS group (Table 2).

Similarly, the TS-SD was significantly prolonged in the narrow QRS group (control: 15 ± 6.1 versus narrow QRS: 25.9±15.3 msec, P<0.05); though it was further increased in the wide QRS group (28.6±14.4 msec). When a maximal difference of time to peak systolic velocity (TS-diff) of>100 ms and a TS-SD of>33 ms were used to define significant systolic asynchrony, this was not found in the control group but was present in 31.4% of patients in the narrow QRS group and in 40% of patients in the wide QRS group (P<0.05). In addition, systolic asynchrony was more prevalent in patients with wide than in those with narrow QRS complexes by both TS-diff and TS-SD.

Diastolic asynchrony

Diastolic asynchrony was also evident in patients with heart failure. The maximal difference in time to peak early diastolic velocity (TE-diff) was prolonged in the narrow QRS group (control: 49±16.8 versus narrow QRS: 73.1±58 msec, P<0.05) and was longest (108.5±168 msec) in the wide QRS group. In addition, TE-SD was significantly longer in the narrow QRS group than in the normal subjects (control: 15.3±5.8 versus narrow QRS: 25.1±13.8 msec,_P<0.05) and was further prolonged (25.5±14.9 msec) in the wide QRS group (Table 3). Overall, 26% of patients had prolonged TE-SD as an evidence of diastolic asynchrony. When a maximal difference of TE of>100 ms was used to define significant diastolic asynchrony, it was not found in the normal controls but was present in 20% of patients in the narrow QRS group and in 28.6% of patients in the wide QRS group. In addition, in patients with narrow QRS complexes, the prevalence of merely abnormal TS-SD was 31.4%, of merely abnormal TE-SD was 20%, which was different from those with wide QRS

Table 3. Comparison of time to peak myocardial early diastolic velocity (TE) between heart failure patients with narrow and wide QRS complexes and normal controls

Segment	1. Controls (n=20)	2. Narrow QRS (n=15)	3. Wide QRS (n=35)	P value (1 versus 2)	P value (1 versus 3)	P value (2 versus 3)
Basal septal	486±46	466±101	493±72	NS	NS	NS
Basal anteroseptal	495±45	469±80	492±75	NS	NS	NS
Basal anterior	484±43	462±122	480±74	NS	NS	NS
Basal lateral	485±49	447±112	484±75	NS	NS	NS
Basal posterior	482±42	466±109	487±77	NS	NS	NS
Basal inferior	481±44	462±129	486±79	NS	NS	NS
Mid-septal	486±46	466±102	494±70	NS	NS	NS
Mid-anteroseptal	495±46	469±80	493±74	NS	NS	NS
Mid-anterior	484±43	462±122	478±77	NS	NS	NS
Mid-lateral	484±49	447±112	486±80	NS	NS	NS
Mid-posterior	482±43	467±108	489±78	NS	NS	NS
Mid-inferior	481±43	462±129	484±86	NS	NS	NS

Data are mean ±SD.

complexes with a respective prevalence of 40% and 28.6%. Table 3 shows the regional TE in individual LV segments.

Relative incidence of diastolic and systolic asynchrony in HF patients

There were isolated diastolic asynchrony in 26%, isolated systolic asynchrony in 34%, coexisting diastolic and systolic asynchrony in 35.3% of HF patients. Therefore overall systolic or diastolic asynchrony was present in 60% of HF patients.

There was no correlation between positive diastolic and systolic asynchrony but there was significant correlation between negative systolic and diastolic asynchrony (negative P=75%)

Diastolic asynchrony was associated with diastolic dysfunction but it not related to the severity of diastolic dysfunction.

Predictors of systolic and diastolic asynchrony

Clinical and echocardiographic predictors of systolic asynchrony were sought in the present study. Using univariate analysis, no significant relation was found between TS-diff or TS-SD and the duration of the QRS complex. However, low LV ejection fraction and E_m velocity significantly correlated with more severe systolic asynchrony (P<0.001). For diastolic asynchrony, univariate analysis showed that all the tested parameters significantly correlated with diastolic asynchrony. However, the stepwise multiple regression model found that only a low E_m (P<0.001) and prolonged QRS complex duration (P<0.001) were independent predictors of diastolic asynchrony.

We found that the less LV ejection fraction, the more probability of diastolic asynchrony and systolic asynchrony (both *r*=0.9, P<0.01), and the less E_m velocity, the more probability of diastolic and systolic asynchrony (P<0.01 and P=0.02 respectively).

Discussion

The present study illustrates the changes in systolic and diastolic synchronicity in patients with HF. Irrespective of QRS duration; patients with HF could develop mechanical asynchrony in both systole and diastole. Isolated diastolic asynchrony in 26%, isolated systolic asynchrony in 34%, coexisting diastolic and systolic asynchrony were observed in 35.3% of HF patients. Although the condition was more prevalent in the wide QRS group, it was not uncommon in patients with narrow QRS complexes. It appeared that diastolic and systolic asynchrony may occur as a result of myocardial disease rather than electromechanical delay. Among various clinical and echocardiographic predictors of asynchrony, it was observed that poor systolic function and less E_m velocity predicted both systolic and diastolic asynchrony, while wide QRS duration only predicted diastolic asynchrony.

Systolic asynchrony in patients with HF

Systolic asynchrony is characteristic of patients with HF who have a wide QRS complex, which signifies electromechanical delay.[3,4,9] Despite improving knowledge of systolic synchronicity in HF patients with wide QRS complexes, it remains unclear whether cardiac diseases may result in systolic asynchrony even in patients with narrow QRS complexes. This study illustrates that systolic asynchrony

is a common feature in these patients. Two criteria (TS-diff of>100 ms and TS-SD of>33 ms) consistently found that significant systolic asynchrony occurred in 31.4% of patients with narrow QRS complexes. Intriguingly, both univariate and multivariate analyses found that the degree of LV asynchrony did not correlate with the duration of QRS complexes. Therefore, electrocardiography is not a good measure of mechanical asynchrony.[5,6] Predictors of systolic asynchrony were also sought in the present study.

QRS complex duration was not found to be correlated with systolic asynchrony. A low mean EF and E_m velocity were independent predictors of systolic asynchrony.

Therefore, it appeared that more severe systolic dysfunction and LV dilatation were associated with more severe systolic asynchrony, irrespective of QRS complex duration.

Diastolic asynchrony in patients with HF

Similar to systolic asynchrony, diastolic asynchrony also occurred in 20% of patients with HF and narrow QRS complexes, and in about 28.6 % of those with wide QRS complexes.

Diastolic asynchrony has been described in patients with coronary heart disease, and preserved LV function by radionuclide ventriculography[7,10] and recently in patients with LV hypertrophy and HF by tissue Doppler imaging.[6,11] We observed that diastolic asynchrony occurred as commonly as systolic asynchrony in patients with HF. The other predictor of diastolic asynchrony is diastolic dysfunction, as illustrated by the negative correlation with mean E_m velocity. The latter parameter has been reported to be a good index of global diastolic function, which decreased as diastolic dysfunction worsened.[8] Interestingly, coexistence of systolic and diastolic asynchrony is more common in patients with wide than with narrow QRS complexes (30% versus 13%, P=0.02), and the correlation between the two conditions is only modest (Table 5).

Clinical implication

LV systolic and diastolic asynchrony resulted in ineffective contraction and relaxation. As cardiac output is dependent not only on systolic emptying but also on diastolic filling, systolic and diastolic asynchrony may cause additive hemodynamic compromise in the failing heart. Cardiac resynchronization has proved to be effective in improving symptoms and systolic function and in reducing LV size in patients with wide QRS complexes,[9,12-15] as a result of improved LV systolic synchronicity.[9,12,13] However, accurate selection of those who will

Table 4. Comparison of the frequency of systolic, diastolic , and combined systolic and diastolic asynchrony in patients with narrow and wide QRS complexes

	Narrow QRS (n=15)	Wide QRS (n=35)	Total (n=50)	P value
Systolic asynchrony	31.4%	40%	34%	0.6
Diastolic asynchrony	20%	28.6%	26%	0.9
Combined systolic and diastolic asynchrony	13%	30%	35.3%	0.02

respond to the treatment is vital and will help ensure that the treatment is cost-effective. This has not been satisfactorily achieved on the basis of the current guidelines, where QRS complex duration is the only surrogate determinant of cardiac asynchrony.[14,16-18]

In patients with wide QRS complexes, systolic asynchrony assessed by magnetic resonance[4] or tissue Doppler imaging[12,13] was superior to QRS complex duration in predicting acute hemodynamic, clinical, or echocardiographic responses.

Our study showed that LV systolic and diastolic asynchrony are common in patients with systolic HF irrespective of QRS duration. In HF patients, diastolic asynchrony may be present in the absence of systolic asynchrony. Selection for cardiac resynchronization treatment should also be based on information about systolic and diastolic synchronicity.

Conflicts of Interest no declare.

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