Effect of intraventricular dyssynchrony on diastolic function and exercise tolerance in patients with heart failure

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Aims Intraventricular dyssynchrony may contribute to the severity of heart failure [congestive heart failure (CHF)]. We assessed the correlates of intraventricular dyssynchrony and evaluated dyssynchrony as an independent predictive variable of exercise intolerance in CHF patients.

Methods and results Eighty-one CHF patients (66 ± 9 years) underwent cardiopulmonary exercise test. Left ventricular (LV) diastolic function was evaluated by transmitral patterns and tissue Doppler. Intraventricular dyssynchrony was calculated according to time intervals between the onset of QRS and the onset of systolic velocities of basal septum and lateral wall. We divided the patients based on the mean value (40 ms) of dyssynchrony. Patients with intraventricular dyssynchrony (>40 ms) showed higher New York Heart Association class (2.7 ± 0.6 vs. 2.2 ± 0.4, P < 0.001), higher brain natriuretic peptide (BNP) (415 ± 478 vs. 194 ± 205, P = 0.014), more frequent restrictive transmitral pattern (33 vs. 7%, P = 0.013), higher E/Ea (13 ± 7 vs. 10 ± 6, P = 0.016), lower mitral annulus peak systolic velocity (4.5 ± 1.1 vs. 5.5 ± 1.5 cm/s, P = 0.01), and peak oxygen consumption (13.8 ± 3.5 vs. 18.1 ± 3.9, P < 0.001), than patients without dyssynchrony (<40 ms). Predictors of exercise tolerance were intraventricular dyssynchrony (P = 0.035), log BNP (P = 0.003), and E/Ea (P = 0.004).

Conclusion Intraventricular dyssynchrony correlates with higher LV filling pressure and lower ejection fraction and it is an independent predictor of poor aerobic capacity; it may be helpful for functional evaluation of CHF patients.

Keywords
Heart failure; Intraventricular dyssynchrony; Exercise tolerance

Introduction

Left ventricular (LV) dyssynchrony is commonly present in heart failure [congestive heart failure (CHF)] patients, particularly in those with prolonged QRS complex duration.1 Electrical dyssynchrony leads to mechanical dyssynchrony and reduces ejection volume because blood moves around the LV from early- to late-activated segments, instead of contributing to ventricular ejection.2 The presence of intraventricular dyssynchrony in CHF patients has a much higher risk of worsening and a more severe prognosis than patients without dyssynchrony.3

The mechanical consequences of this electrical disorder are a decline in systolic performance, increase in LV wall stress, and increase in LV end-systolic volume.4 Furthermore, the presence of intraventricular dyssynchrony is an important determinant of diastolic dysfunction: in fact, it has been shown to shorten LV diastolic filling time,5 to directly impair diastolic function,6 and to cause diastolic as well as systolic dyssynchrony.5

Diastolic dysfunction influences signs and symptoms of CHF;7 it is a strong predictor of exercise tolerance8 and hence, intraventricular dyssynchrony may play a role in exercise tolerance.

Several echocardiographic techniques have been used to assess intraventricular dyssynchrony; however, tissue Doppler is the most extensively tested technique.9,10 Tissue Doppler measures the velocity of longitudinal cardiac motion and allows comparison of motion timing in relation to electrical activity (QRS complex) and it can provide accurate information on electromechanical coupling.11

The aims of our study were: (i) to assess the correlates of intra-LV dyssynchrony and (ii) to evaluate intra-LV...
dyssynchrony as an independent predictive variable of exercise intolerance in CHF patients.

**Methods**

**Patients population**

In a prospective, study design, from 2004 to 2007, 90 consecutive patients were prospectively enrolled from the division of cardiology and heart failure outpatient clinic of our institution. All patients showed an LV ejection fraction of < 45% at the echocardiography and had typical symptoms of CHF that were classified according to the New York Heart Association (NYHA) functional class. All patients were in sinus rhythm, and on optimal and maximally tolerated pharmacological therapy, according to the current guidelines. 

Forty-five patients (55%) had a history of hospital admission for acute CHF, definite as one or more hospitalization for acute cardiac decompensation. Exclusion criteria were (i) technically poor acoustic window precluding satisfactory imaging of LV [for two-dimensional (2D) echo], (ii) haemodynamic instability, (iii) documentation of life-threatening ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation), (iv) significant co-morbidity reducing life expectancy to < 1 year, (v) unwillingness to give informed consent, (vi) severe valvular disease, and (vii) previous cardiac resynchronization therapy.

Coronary angiography was performed in all patients. All patients with ischaemic cardiomyopathy underwent dobutamine stress echocardiography to evaluate the presence of stress-induced ischaemia. No patients showed infarcted lateral wall. Nine patients were subsequently excluded: three patients with infarcted septum, two patients for poor echogenicity, and four patients for the presence of dobutamine stress-induced ischaemia. The remaining 81 patients, aged 66 ± 9 years (63 males), made up the final study population.

Teen age- and gender-matched healthy subjects, with no history of cardiovascular disease, normal clinical examination (including blood pressure), and surface electrocardiogram, volunteered to enrol in the study and were considered as a control group.

**Echocardiography**

Each patient underwent M-mode and 2D echocardiography, followed by colour flow imaging and pulsed- and continuous-wave Doppler ultrasound study. Echocardiograms were performed using a Hewlett-Packard ultrasonic scanner (Phillips 5500, Handover, MA, USA) equipped with 2.5 MHz transducer. M-mode echocardiograms were obtained from the 2D images under direct anatomic visualization.

Left atrial, LV end-diastolic, and end-systolic diameters were measured according to the guidelines of the American Society of Echocardiography. 

Left ventricular ejection fraction was evaluated with biplane transthoracic echocardiography by the modified Simpson rule using second harmonic imaging. 

Diastolic function was assessed by transmitral patterns and tissue Doppler. Pulsed mitral Doppler measurements were obtained with the transducer in the apical four-chamber view by positioning a 1–2 mm sample volume between the tips of the mitral valve leaflets in diastole, with the Doppler beam aligned perpendicular to the plane of the mitral annulus. 

We derived early peak filling velocity (E), late peak filling velocity (A), early to late filling ratio, and deceleration time of the mitral E-wave. Transmitral LV filling patterns were classified into: abnormal relaxation, pseudonormal, and restrictive. 

Mitrail regurgitation has been classified considering the recommendations from the American Society of Echocardiography, and grading in: mild, moderate, and severe. To quantify the severity of mitral regurgitation, we used the vena contracta, calculated as the narrowest portion of a jet that occurs at or just downstream from the orifice.

**Intraventricular dyssynchrony**

Tissue Doppler was performed in the pulsed-wave Doppler mode. Gain and filters were adjusted as need to eliminate background noise and to allow a clearer tissue signal. The tissue Doppler signals were recorded at a sweep speed of 100 mm/s. From the apical four-chamber view, a 5 mm sample volume was placed at the lateral and septal corners of the mitral annulus. The following measurements were made: peak systolic velocity (Sa), early (Ea) and late (Aa) diastolic velocities at the mitral annulus, and the ratio between early wave mitral flow and mitral annulus early diastolic velocity (E/Aa). 

Intraventricular dyssynchrony was calculated as the absolute septal–lateral delay, i.e. the difference in time intervals between the onset of QRS complex and the onset of mitral annulus systolic velocities of the basal septum and the basal lateral wall on ejection phase onset (Figure 1). Blinded intra- and inter-observer correlations for these parameters were assessed in 10 patients and reached 0.98 and 0.95, respectively. Measurements were made in three to five cardiac cycles and averaged. We divided the CHF patients into two groups, according to the mean value (40 ms) of the absolute septal–lateral delay: patients with intraventricular dyssynchrony (< 40 ms) and patients without intraventricular dyssynchrony (≥ 40 ms).

**Measurement of brain natriuretic peptide plasma levels**

In all patients, blood was sampled from the antecubital vein following 20 min of supine rest before exercise test. The peripheral venous blood was collected into a sampling tube containing EDTA as an anticoagulant. We used a rapid bedside test to determine brain natriuretic peptide (BNP) (Triage BNP, Biosite Diagnostics, San Diego, CA, USA). The triage BNP test is an immunofluorometric assay for quantitative determination of BNP in ethylenediaminetetraacetic acid-anticoagulated whole blood or plasma.

**Exercise test**

Nine of 81 CHF patients did not perform the cardiopulmonary exercise test: 3 patients for exercise-limiting diseases other than cardiac, 2 for peripheral vascular disease, 3 for relevant primary pulmonary disease, and 1 in NYHA functional class IV. The remaining 72 CHF patients (87%) underwent treadmill cardiopulmonary exercise test: 3 patients for exercise-limiting diseases other than cardiac, 2 for peripheral vascular disease, 3 for relevant primary pulmonary disease, and 1 in NYHA functional class IV. The remaining 72 CHF patients (87%) underwent treadmill cardiopulmonary exercise test:

![Figure 1](https://academic.oup.com/ehjcimaging/article-abstract/10/8/907/2396597/1)
exercise test (SensorMedics, Italy) according to the modified Bruce protocol, with expired gas measurement. Oxygen uptake, carbon dioxide production, and minute ventilation were measured using breath-by-breath gas analysis. A 12-lead electrocardiogram was continuously registered and blood pressure was recorded every minute by a cuff sphygmomanometer. Peak oxygen uptake was determined as the highest value in the terminal phase of exercise; the O₂ uptake at the anaerobic threshold was determined by the V-slope method.²⁶

Statistics

Data were expressed as mean ± SD for continuous variables and as numbers (per cent) for categorical variables. Logarithm base 10 transformation was performed on BNP (log BNP) values because of non-linear distribution. We divided CHF patients into two groups, according to the median value of septal–lateral delay: CHF patients with intraventricular dyssynchrony (>40 ms) and patients without intraventricular dyssynchrony (≤40 ms). The differences in continuous variables between CHF patients with and without intraventricular dyssynchrony were analysed by unpaired Student’s t-test, and in categorical variables by χ² test with Yates’ correction for continuity. Independent predictors of the exercise tolerance were assessed by multiple linear regression analysis.

A P-value of <0.05 was considered statistically significant. All statistical calculations were performed using SPSS for Windows, release 12.0 (Chicago, IL, USA).

Results

Patient characteristics

The clinical and echocardiographic characteristics of the patients and the controls are summarized in Table 1. The mean LV ejection fraction was 31 ± 8%. Three patients (4%) were in NYHA functional class I, 42 (52%) in NYHA class II, 35 (43%) in NYHA class III, and 1 (1%) in NYHA class IV. The cause of LV systolic dysfunction was ischaemic heart disease in 41 patients (51%). Forty-six patients (57%) had a left bundle branch block.

Intraventricular dyssynchrony and clinical and echocardiographic variables

We divided the patients population into two groups, according to the mean value of intraventricular dyssynchrony (40 ± 34 ms): 37 CHF patients with (>40 ms) and 44 without (<40 ms) intraventricular dyssynchrony. Congestive heart failure patients with intraventricular dyssynchrony, compared with patients without dyssynchrony, were more symptomatic, with higher incidence of NYHA functional class >2 (Table 2, P = 0.001), and with previous history of one or more hospital admissions for acute cardiac decompensation (Table 2, P = 0.001). The presence of ischaemic aetiology of CHF was similar in patients with and without intraventricular dyssynchrony.

Patients with intraventricular dyssynchrony showed a higher duration of QRS complex (Table 2, P = 0.004), higher BNP (Figure 2) and log BNP (Table 2, P = 0.04) levels, and larger LV end-diastolic diameter (Table 2, P = 0.032), compared with patients without intraventricular dyssynchrony.

Mitral regurgitation was mild in 40 patients (49%) and moderate in 41 (51%). No patients had a severe mitral regurgitation. Patients with intraventricular dyssynchrony had more severe mitral regurgitation with higher incidence of moderate mitral regurgitation (Table 2, P = 0.038).

Intraventricular dyssynchrony and systolic function

Intraventricular dyssynchrony was significantly related to global and regional systolic function. In fact, CHF patients with intraventricular dyssynchrony showed lower LV ejection fraction and lower mitral annulus peak systolic velocity (Figure 3), compared with patients without dyssynchrony.

Intraventricular dyssynchrony and diastolic function

Fifty-nine CHF patients (73%) showed an abnormal relaxation transmitial LV filling pattern, 5 (6%) a pseudonormal pattern, and 17 (21%) a restrictive transmitral pattern. Congestive heart failure patients with intraventricular dyssynchrony had higher incidence of restrictive transmitral pattern (Table 2, P = 0.013) and higher ratio between E-wave mitral flow and early diastolic velocity mitral annulus (E/Eₚ, Figure 4).

Intraventricular dyssynchrony and exercise tolerance

Seventy (86%) of the 81 CHF patients performed cardiopulmonary exercise testing limited by symptoms (either shortness of breath or fatigue). During exercise, we found that systolic blood pressure (from 123 ± 21 to 151 ± 24 mmHg, P < 0.001) and heart rate (from 78 ± 12 to 122 ± 16 mmHg, P < 0.001) increased significantly. Mean peak oxygen consumption value was 15 ± 4 mL/kg/min. Patients with intraventricular dyssynchrony had lower exercise tolerance, compared with patients without intraventricular dyssynchrony (Figure 5).

At multiple linear regression analysis, including age, LV ejection fraction, LV end-diastolic diameter and volume, log BNP, E/Eₚ, and intraventricular dyssynchrony, independent predictors of exercise tolerance were: intraventricular dyssynchrony (OR = 0.218, 95% CI = 0.053–0.901, P = 0.035), log BNP (OR = 0.054, 95% CI = 0.008–0.359, P = 0.003), and E/Eₚ (OR = 0.822, 95% CI = 0.719–0.940, P = 0.004).

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Table 1: Clinical and echocardiographic characteristics of the heart failure patients and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>HF patients (81)</th>
<th>Controls (10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 ± 9</td>
<td>59 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>63 (78)</td>
<td>8 (80)</td>
<td>NS</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>48 ± 6</td>
<td>36 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>63 ± 6</td>
<td>49 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>52 ± 6</td>
<td>30 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-diastolic volume (mL)</td>
<td>145 ± 38</td>
<td>87 ± 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-systolic volume (mL)</td>
<td>100 ± 34</td>
<td>31 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>31 ± 8</td>
<td>64 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>16 ± 6</td>
<td>24 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraventricular dyssynchrony</td>
<td>40 ± 34</td>
<td>7 ± 5</td>
<td>0.001</td>
</tr>
</tbody>
</table>
This study demonstrates that CHF patients with intraventricular dyssynchrony were more symptomatic, showed higher BNP levels, impaired systolic and diastolic function, and lower exercise tolerance.

Widening of the QRS complex on the surface electrocardiogram usually indicates an impaired (or slowed) propagation of the electrical input, a finding frequently associated with increased morbidity and mortality in CHF patients. Moreover, half of the CHF patients without complete bundle branch block have major intraventricular...
electromechanical dyssynchrony and recent data have demonstrated that mechanical dyssynchrony is not necessarily related to electrical dyssynchrony.\textsuperscript{28}

Echocardiography is the most widely used tool to assess mechanical dyssynchrony, and tissue Doppler has been found to be the most useful among different echocardiographic modalities.\textsuperscript{9–11} Identifying CHF patients with intraventricular dyssynchrony may also be helpful for the therapeutic strategy. Investigators have established that ventricular stimulation of both the right ventricle and LV (biventricular pacing) can improve the mechanics of the failing heart with discoordinate contraction, enhancement of clinical symptoms, increased exercise capacity, and cessation or reversal of chronic chamber remodelling.\textsuperscript{9,10,20–23,29}

The PROSPECT study\textsuperscript{30} demonstrated that no single echocardiographic measure of dyssynchrony may be recommended to improve patient selection for cardiac resynchronization therapy beyond current guidelines; moreover, we showed as the evaluation of simple parameters of intraventricular dyssynchrony may be helpful for the clinical and functional evaluation of patients with chronic heart failure. Bader \textit{et al.}\textsuperscript{3} demonstrated that independent of the LV ejection fraction and QRS width, CHF patients with intraventricular dyssynchrony have a much higher risk of worsening and a more severe prognosis than patients without asynchrony. In this study, to the standard evaluation of regional systolic function and diastolic function ($E/E_a$) by means of pulsed tissue Doppler, we added an additional parameter (intraventricular dyssynchrony) useful in the functional evaluation of the CHF patients, it is significantly related to clinical conditions, global and regional systolic function, diastolic function, and exercise tolerance.

**Intraventricular dyssynchrony and diastolic function**

Left ventricular diastolic function is physiologically coupled to LV systolic performance and it is an important determinant of symptoms and outcome in patients with LV systolic dysfunction.\textsuperscript{31}

Several investigators have shown that induced asynchrony impairs isovolumic relaxation in either ventricular or atrioventricular pacing.\textsuperscript{32,33} In accordance to these studies, we showed that intraventricular dyssynchrony influences diastolic dysfunction. In fact, we found higher incidence of restrictive transmitral pattern and higher $E/E_a$ in patients with intraventricular dyssynchrony (Table 2, Figure 4).

**Intraventricular dyssynchrony and systolic function**

Previous studies demonstrated that intraventricular dyssynchrony reduced systolic function, with an increase in end-systolic volume and wall stress, and delayed relaxation.\textsuperscript{34} Particularly, early contraction occurs when pressure is low and does not lead to ejection, whereas late contraction occurs at higher level of wall stress and results in paradoxical stretch of early-contracting segments. Accordingly, in this study, the presence of intraventricular dyssynchrony was related to impaired global and regional systolic function, with lower ejection fraction and peak systolic velocity of mitral annulus (Table 2, Figure 3).

**Intraventricular dyssynchrony and mitral regurgitation**

In our study, 51% of the patients showed a moderate degree of mitral regurgitation, with higher incidence in patients with intraventricular dyssynchrony. In agreement with our results, previous papers demonstrated that asynchronous myocardial contraction adversely influenced ventricular function and increased the extent of mitral regurgitation.\textsuperscript{35} Conversely, producing a more efficient LV contraction, cardiac resynchronization therapy may increase transmural force closure and thereby reduce the severity of functional mitral regurgitation at rest and during dynamic exercise in patients with LV dilatation and asynchrony.\textsuperscript{36}

**Intraventricular dyssynchrony and brain natriuretic peptide levels**

In this study, we found that BNP was higher in CHF patients with intraventricular dyssynchrony. Hence, BNP and intraventricular dyssynchrony are both expression of the severity
of heart failure. Moreover, the relationship between intraventricular dyssynchrony and BNP levels may be explained through the correlation between intraventricular dyssynchrony and diastolic function (Figure 2). In fact, in a previous study, we demonstrated that BNP levels reflect the presence of diastolic dysfunction and were directly related to LV filling pressure.3,4

Intraventricular dyssynchrony and exercise tolerance

In our study, intraventricular dyssynchrony influences exercise tolerance (Figure 5). In patients with LV systolic dysfunction, maximal exercise cardiac output is primarily dependent on LV diastolic filling properties because of impaired myocardial contractility.37,38 In fact, elevated LV filling pressure, assessed with E/Ea, was the strongest predictor of reduced exercise tolerance.8,39 According to these data, we have shown greater intraventricular dyssynchrony in CHF patients with elevated LF filling pressure: this may explain the role of intraventricular dyssynchrony in the impairment of exercise tolerance. In fact, independent predictors of exercise tolerance were intraventricular dyssynchrony, diastolic function (E/Ea), and severity of CHF (BNP levels), confirming the central role of intraventricular dyssynchrony in this context.

Study limitations

This study is an observational analysis of CHF patients. Sample size is relatively small, and larger studies could be important to further confirm our findings. A heterogeneous CHF patient population was recruited, even though this would better reflect the clinical usefulness of intraventricular dyssynchrony in a ‘real-world’ setting of chronic heart failure patients.

Speckle tracking strain analysis is a recent method which allows the assessment of myocardial deformation in 2D. However, 2D strain was not available at the time of study design in our institution.

We used pulsed tissue Doppler because of excellent temporal resolution for measuring intraventricular mechanical dyssynchrony, and its availability in the majority of cardiological ultrasound systems. The advantage of pulsed-wave tissue Doppler imaging is that it does not require high-end equipment, specific software, or offline analysis, but its disadvantage is that it requires sampling of multiple regions from different cardiac cycles. However, the aim of our study is to assess the functional parameters and not to predict the response to cardiac resynchronization therapy.

Conclusion

Intra-LV dyssynchrony correlates with higher LV filling pressure and lower LV ejection fraction and it is an independent predictor of poor aerobic capacity in CHF patients. Thus, the analysis of intra-LV dyssynchrony may be helpful for the clinical and functional evaluation of patients with chronic heart failure.

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Conflict of interest: none declared.

References


