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CARDIOLOGY

Clinical research

Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration

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Aims The study aimed at evaluating the prevalence of interventricular and intraventricular contractile dyssynchrony in heart failure patients with either normal or prolonged QRS duration.
Methods and results Echocardiography and tissue Doppler imaging (TDI) were performed in 158 consecutive patients with advanced left ventricular dysfunction (LVEF $<35\%$); 61 patients had a normal QRS duration (Group 1), 21 patients had left bundle branch block with a QRS duration between 120 and 150 ms (Group 2) and 76 patients had a QRS duration $\geqslant$150 ms (Group 3). Interventricular dyssynchrony (defined by the presence of an interventricular mechanical delay greater than 40 ms) was found in 12.5%, 52.4% and 72% of patients in Group 1, 2 and 3, respectively ($p < 0.001$). Intraventricular dyssynchrony (defined by the presence of one or more differences greater than 50 ms among regional pre-ejection periods) was observed in 29.5%, 57.1% and 71% of patients in Group 1, 2 and 3, respectively ($p < 0.001$). No relationship was found between interventricular and intraventricular dyssynchrony.
Conclusions A substantial proportion of heart failure patients with a slightly prolonged QRS or even with normal conduction may exhibit ventricular dyssynchrony. Both standard echocardiography and TDI are necessary to describe the entire spectrum of mechanical abnormalities due to dyssynchrony.

Introduction

Cardiac resynchronization therapy can improve cardiac function and clinical status in patients with severe heart failure and left bundle branch block.[1–5] Since in initial studies patients with a wide QRS seemed to benefit the most from biventricular pacing, most of the patients enrolled in these trials had a QRS duration greater than 150 ms. More recently, it has been pointed out that even patients with slightly prolonged or normal QRS may exhibit dyssynchrony and are therefore potentially treatable by multisite pacing.[6] However, the mechanical abnormalities determined by the conduction disturbances in heart failure patients with either normal or slightly prolonged QRS duration have not been fully characterized. In fact the pathophysiology of abnormal electrical conduction is complex.[7,8] Ventricular

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[†] doi:10.1016/j.ehj.2004.03.002.

dyssynchrony may be observed at different levels: interventricular dyssynchrony refers to the delayed activation of one ventricle with respect to the other, whereas intraventricular dyssynchrony refers to the late activation of the lateral regions of the left ventricular chamber as compared to the interventricular septum. We still do not know whether there is a link between interventricular and intraventricular dyssynchrony, to what extent they are related to QRS morphology, to etiology of the disease or to the degree of left ventricular dysfunction. Focusing these issues is not only a matter of pathophysiological relevance but it is also important to solve the clinical problem of the identification of patients most likely to respond to cardiac resynchronization therapy.

We therefore designed a transversal observational study aimed at (1) defining the prevalence of interventricular and intraventricular dyssynchrony in heart failure patients with either normal or slightly prolonged QRS duration with respect to patients with wide QRS; (2) evaluating the relationship between interventricular and intraventricular dyssynchrony; (3) assessing whether or not dyssynchrony is related to QRS morphology or to the degree of left ventricular dysfunction. Standard echocardiography and tissue Doppler imaging (TDI) were used to provide a complete description of the mechanical abnormalities due to dyssynchrony.

Methods

Patients

The patients included in the study were selected among those referred to our department for heart failure diagnosis and management on the basis of the following inclusion criteria: (1) advanced systolic left ventricular dysfunction (left ventricular ejection fraction <35%); (2) etiology due to primary dilated cardiomyopathy (DCM), ischemic heart disease (IHD) or hypertension with normal coronary arteries. We excluded patients with: (1) non-sinus rhythm; (2) previous pacemaker implantation; (3) right bundle branch block and (4) valvular heart disease. Although we recognize that ventricular dyssynchrony may well be observed in the categories of patients excluded from the study, inclusion and exclusion criteria were selected in attempt to enrol a fairly homogeneous series of patients. A total number of 158 patients were included between March 2001 and July 2002: 120 were males and 38 females; mean age was 54.4 ± 12.3 years; etiology was DCM in 68%, IHD in 27% and hypertension in 5%; 71% was in NYHA class II and 29% in class III or IV. All patients underwent a standard 12-lead electrocardiogram and an ultrasound examination which included a specific evaluation of interventricular and intraventricular dyssynchrony. According to QRS duration, the patients were divided into three groups: 61 patients with a QRS duration <120 ms (Group 1), 21 patients with left bundle branch block and a QRS duration between 120 and 150 ms (Group 2) and 76 patients with a QRS duration = 150 ms (Group 3).

Electrocardiography

Standard 12-lead electrocardiograms were acquired at a paper speed of 25 mm/s and a scale of 10 mm/mV. The measurements of PR interval and QRS duration (recorded from the surface leads demonstrating the greatest values) and the assessment of QRS axis and morphology were performed by an experienced observer who was blinded to the echocardiographic characteristics of the patient. The typical ECG feature of left bundle branch block (LBBB) is a QRS duration $\geqslant 120$ ms, no q-wave but slurred, broad R waves in leads I, aVl and V6 and rS or QS deflections in lead V1. When a left axis deviation greater than 30° was present, associated with prominent S waves in leads II, III and V6, patients were classified as having "advanced left anterior hemiblock". A prolongation of the QRS which was not associated with the typical features of bundle branch blocks was considered as "aspecific intraventricular conduction delay".

Standard echocardiography

A complete M-mode, 2-D and Doppler evaluation was performed using a commercially available ultrasonographic equipment (System 5, Vingmed, GE). Left ventricular end-diastolic and end-systolic volumes and left ventricular ejection fraction were calculated using the area-length method. Mitral regurgitation was graded according to the jet area method. The right ventricular end-diastolic diameter was determined in the parasternal view. The systolic displacement of the lateral portion of the tricuspid annular plane was measured on the M-mode tracing under the 2D-echo guidance.

Assessment of interventricular dyssynchrony

The aortic pre-ejection time was measured from the beginning of QRS complex to the beginning of the aortic flow velocity curve recorded by pulsed-wave (PW) Doppler in apical 5-chamber view. The pulmonary pre-ejection time was measured from the beginning of QRS complex to the beginning of the pulmonary flow velocity curve recorded in the left parasternal view. The difference between the two values determined the interventricular mechanical delay (IVMD); an IVMD > 40 ms was considered as the cut-off value for interventricular dyssynchrony.

Assessment of intraventricular dyssynchrony

Color tissue Doppler imaging was acquired in 2-D mode from the apical 4-chamber and 2-chamber views to assess myocardial regional function. Off-line analysis of the mean velocity profiles was performed at the level of the basal and medium segments of the interventricular septum and of the lateral, inferior and anterior walls. The regional pre-ejection period was measured for all segments from the beginning of QRS to the beginning of the positive component of the regional systolic velocity (S2) (defined by zero-crossing or, when this was not possible, as the beginning of the upstroke of the velocity curve after the isovolumic contraction phase) (Fig. 1). All the possible differences between the regional pre-ejection periods of the four basal segments and between the regional pre-ejection periods of the four medium segments were calculated. Intraventricular dyssynchrony was considered to be present if one or more absolute differences greater than 50 ms between two segments ("50 ms delta") were found either at basal or at medium level; the 50 ms threshold was chosen as it represents 1 standard deviation of the regional pre-ejection periods in the whole population enrolled in the study. In addition, the standard deviation of all regional pre-ejection periods was calculated in each patient as an index of global intraventricular dyssynchrony. A qualitative analysis of the regional systolic pattern was also performed, as previously described by Ansalone et al.[9] Patterns were identified according
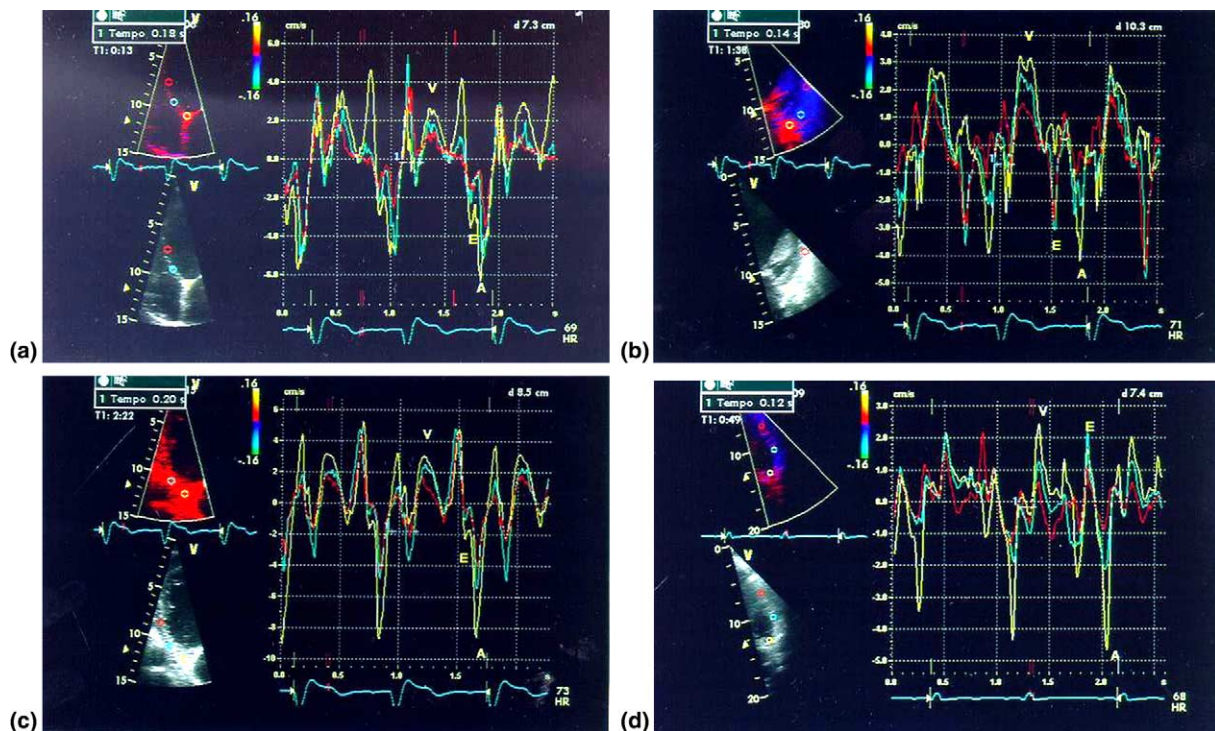
Fig. 1 Tissue Doppler imaging in apical views in a patient with dilated cardiomyopathy. Samples are positioned in the annulus (yellow) and in the basal (green) and medium (red) segments of each wall (left side of the pictures); the corresponding velocity profiles are displayed on the right side of the pictures, where solid lines indicate the prejection period measurements. (a) Prejection period in the basal segment of the interventricular septum. (b) Prejection period in the basal segment of the lateral wall. (c) Prejection period in the basal segment of the inferior wall. (d) Prejection period in the basal segment of the anterior wall. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

to the presence or absence of S2 positive or negative components: (pattern 1) (normal) defined by the presence of a single positive S2 wave; (pattern 2) defined by the presence of an early negative systolic component and a late positive systolic component; (pattern 3) defined by the presence of an early positive systolic component and a late negative systolic component; (pattern 4) defined by the presence of a single negative systolic movement. The interobserver and intraobserver variability was computed in 10 consecutive patients and it was found to be within acceptable limits for all tested variables (Lin correlation coefficient >80%).

Statistical analysis

The data are shown as mean values $\pm$SD for the continuous variables (or median and inter-quartile ranges (IQR) for skewed distributions) and as absolute or relative frequencies for categorical variables. Due to the small number of patients with hypertension, such patients were considered together with DCM patients for statistical analysis. Patients characteristics were compared by means of one way analysis of variance (overall comparison) and Scheffè test (post hoc pairwise comparisons) in case of continuous variables; the Fisher exact test was used to compare categorical variables. A general linear model was used to evaluate the association between intraventricular dyssynchrony and QRS groups, while controlling for patients baseline characteristics (age, ejection fraction, mitral regurgitation, left ventricular filling time); such characteristics were selected on clinical grounds. As pre-ejection times were measured for each patient in several segments at the basal and medium levels, Huber White robust

standard errors were computed to account for intra-patient correlation. No specific correlation structure was assumed in calculating robust standard errors. Differences between QRS groups were assessed while controlling for patients baseline characteristics. The Kruskall Wallis test was used for the overall comparison of the number of "50-ms delta" per patient in groups with different QRS duration. Spearman's co-efficient was calculated to evaluate correlations between QRS duration and standard deviation of pre-ejection periods or IVMD. The distribution of patients with intraventricular dys-synchrony in the presence or absence of interventricular dyssynchrony was compared by means of Fisher exact test; the Kappa statistic and its standard error (SE) were calculated to measure the agreement. Bonferroni correction was used for post hoc pairwise comparisons (unless otherwise specified). A 2-sided p value <0.05 was retained for statistical significance. The computations were made using Stata 7 (Stata Corp, College Station, TX).

Results

Characteristics of the patients with or without conduction delay

Patients with LBBB were older than patients with normal QRS duration, had a greater functional impairment, a more advanced left ventricular systolic dysfunction, a higher degree of mitral regurgitation and a shorter left ventricular filling time (see Table 1).

Table 1 Clinical and echocardiographic characteristics of the patients according to QRS duration

	QRS < 120 ms (n = 61)	QRS ⩾ 120 < 150 ms (n = 21)	QRS ⩾ 150 ms (n = 764)	p (overall)
Age (years)	48 ± 13	58 ± 6	58 ± 11	<0.001
Gender (f/m)	11/50	7/14	20/56	0.32
NYHA class II/III—IV (%)	83/17	74/24	59/41	0.015
LVEF (%)	26.9 ± 6.4	26.7 ± 6.3	23.4 ± 6.4	0.004
LVEDV (ml)	254 ± 85	272 ± 82	346 ± 125	<0.001
Mitral regurgitation absent or mild/moderate (%)	80/20	48/52	47/53	0.001
LV filling time (% of RR)	44 ± 9	43 ± 11	39 ± 9	0.017

LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume and LV, left ventricular.

Interventricular dyssynchrony

The pulmonary pre-ejection period was similar in the three groups, whereas the aortic pre-ejection period was longer in Group 3 than in Group 1 and 2 patients (respectively, 169 ± 28 vs. 135 ± 29 vs. 122 ± 22, $p < 0.05$ all group comparisons); this determined a greater IVMD in patients with a QRS duration ⩾150 ms (respectively 59 ± 29 vs. 43 ± 30 vs. 18 ± 20 ms, $p < 0.05$ all group comparisons). Overall, a statistically significant correlation was found between IVMD and QRS duration, although in a context of wide scattering of the data ($r = 0.66$, $p < 0.001$) (Fig. 2). This correlation slightly improved if patients with pulmonary hypertension (transtricuspid pressure gradient >30 mm Hg) and/or right ventricular dysfunction (tricuspid annular plane systolic excursion <14 mm) were excluded from the analysis ($r = 0.70$). Etiology (IHD or DCM or hypertension) was not related to IVMD. A greater proportion of patients with interventricular dyssynchrony (IVMD > 40 ms) was observed in the groups with QRS duration ⩾150 ms or between 120 and 150 ms as compared to patients with normal QRS duration (respectively, 12.5% in Group 1, 52.4% in Group 2 and 72% in Group 3 (overall comparison: $p < 0.0001$; pairwise comparisons: $p < 0.001$ Group 2 and 3 vs. Group 1; $p = 0.24$ Group 2 vs. Group 3)). Patients with interventricular dyssynchrony had a lower left ventricular filling time than those without interventricular dyssynchrony (respectively, 39 ± 9% vs. 45 ± 8%, $p = 0.0001$). On the contrary, ejection fraction and left ventricular end-diastolic volume were similar in the two groups; the NYHA class was also similar (respectively, 65.1% NYHA class II and 34.9% NYHA class III or IV patients in the group with interventricular dyssynchrony vs. 74.7% NYHA class II and 25.4% NYHA class III or IV patients in the group without interventricular dyssynchrony).

Intraventricular dyssynchrony

As shown in Table 2, the regional pre-ejection periods were significantly different between QRS groups (overall comparison: $p < 0.0001$ while controlling for patients baseline characteristics; post hoc comparisons: $p < 0.001$ Group 3 vs. Group 1 and $p = 0.015$ Group 3 vs. Group 2). In Group 1 patients the most delayed segment was the medium anterior segment in 24.6% of cases. In
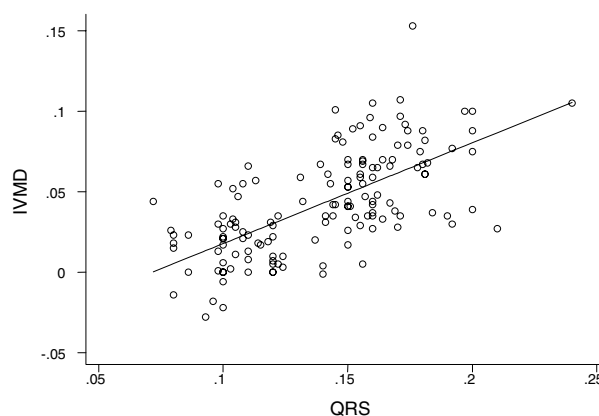

Fig. 2 Relationship between the interventricular mechanical delay (IVMD, ms) and QRS duration (QRS, ms) ($n = 158$ patients, $r = 0.66$, $p < 0.001$).

Group 2 and in Group 3 patients the most delayed segment was the medium lateral segment, in 28.6% and 27.6% of cases, respectively (Table 3). Intraventricular dyssynchrony (defined as at least one "50-ms delta") was present in 29.5% of Group 1 patients, in 57.1% of Group 2 patients and in 71.1% of Group 3 patients (overall comparison: $p < 0.0001$; pairwise comparisons: $p < 0.001$ Group 3 vs. Group 1, $p = 0.105$ Group 2 vs. Group 1, $p = 0.873$ Group 2 vs. Group 3). The median number of "50-ms delta" per patient (interquartile range) observed was: 0, (0—1) in Group 1 patients; 3, (0—6) in Group 2 patients and 3, (0—5.5) in Group 3 patients (overall comparison: $p = 0.0001$; pairwise comparisons: $p = 0.51$ Group 2 vs. Group 1, $p = 0.0001$ Group 3 vs. Group 1, $p = 1.000$ Group 2 vs. Group 3). No significant relationship was found between QRS duration and the standard deviation of regional pre-ejection periods ($r = 0.27$, $p = 0.064$). Etiology, type of intraventricular conduction delay, left ventricular ejection fraction and degree of mitral regurgitation were similar in patients with and without intraventricular dyssynchrony. On the contrary, the end-diastolic volume was greater and the left ventricular filling time was shorter in patients with intraventricular dyssynchrony (respectively, 325 ± 109 vs. 273 ± 114 ml, $p = 0.004$ and 39 ± 11% vs. 44 ± 11%, $p = 0.0008$). The NYHA class was similar (respectively, 68.4% NYHA class II and 31.6% NYHA class III or IV patients

Table 2 Regional pre-ejection periods

	QRS < 120 ms (n = 61)	QRS ⩾ 120 < 150 ms (n = 21)	QRS ⩾ 150 ms (n = 76)
Anterior, basal (ms)	122 ± 34	134 ± 50	144 ± 47
Anterior, medium (ms)	125 ± 38	143 ± 63	149 ± 59
Inferior, basal (ms)	123 ± 30	139 ± 34	179 ± 38
Inferior, medium (ms)	126 ± 31	140 ± 36	182 ± 41
Lateral, basal (ms)	133 ± 62	146 ± 53	167 ± 51
Lateral, medium (ms)	131 ± 45	147 ± 59	176 ± 51
Septum, basal (ms)	125 ± 54	125 ± 26	163 ± 38
Septum, medium (ms)	123 ± 27	134 ± 36	166 ± 39

Overall comparison of intraventricular conduction in the three QRS groups: $p < 0.0001$ (while controlling for baseline characteristics in a multivariate analysis). For post hoc pairwise comparisons see text.

Table 3 Most delayed segments

	QRS < 120 ms (n = 61)	QRS ⩾ 120 < 150 ms (n = 21)	QRS ⩾ 150 ms (n = 76)
Anterior, basal (%)	3.3	0	2.6
Anterior, medium (%)	24.6	23.8	7.9
Inferior, basal (%)	11.5	9.5	10.5
Inferior, medium (%)	16.4	4.8	14.5
Lateral, basal (%)	9.8	4.8	9.2
Lateral, medium (%)	13.1	28.6	27.6
Septum, basal (%)	9.8	4.8	7.9
Septum, medium (%)	11.5	23.8	19.7

Table 4 Regional contraction pattern by QRS duration

	QRS < 120 ms	QRS ⩾ 120 < 150 ms	QRS ⩾ 150 ms
Pattern 1 (%)	88.9	86.5	78.2
Pattern 2 (%)	1.0	3.2	4.1
Pattern 3 (%)	9.7	9.9	13.6
Pattern 4 (%)	0.4	0.4	4.1

$p < 0.001$ for overall comparison between QRS groups.
See Methods for the definitions of patterns.

in the group with intraventricular dyssynchrony vs. 74.2% NYHA class II and 25.8% NYHA class III or IV patients in the group without intraventricular dyssynchrony).

Regional contraction patterns

A slightly greater percentage of abnormal regional contraction patterns were observed in Group 3 than in Group 1 or 2 patients; however, even in Group 3 patients more than 75% of segments were defined as having a "normal" contraction pattern (Table 4). Dyskinetic patterns were definitely more frequent in patients with ischemic heart disease than in patients with primary dilated cardiomyopathy or hypertension ($p < 0.001$) (Table 5).

Correlation between inter and intra-ventricular dyssynchrony

Among patients with intraventricular dyssynchrony (defined by "at least one" 50-ms delta), 64% also had interventricular dyssynchrony (defined as IVMD > 40 ms); among patients without intraventricular dys-synchrony, 28% had interventricular dyssynchrony ($p < 0.0001$). The agreement between the 2 types of dyssynchrony was therefore poor ($\kappa = 0.37$, SE 0.08).

Discussion

The study demonstrates that in heart failure patients with LBBB, inter and intraventricular dyssynchrony are common, regardless of QRS duration. Furthermore, there is a substantial proportion of heart failure patients with normal QRS duration who may also exhibit dyssynchrony. To

Table 5 Regional contraction pattern by etiology of disease

	Ischemic etiology	Non-ischemic etiology
Pattern 1 (%)	74.1	84.7
Pattern 2 (%)	5.2	2.7
Pattern 3 (%)	13.9	11.3
Pattern 4 (%)	6.8	1.3

$p < 0.001$ for overall comparison between groups.
See Methods for the definitions of patterns.

provide a complete description of the mechanical abnormalities due to dyssynchrony both standard echocardiography and TDI should be used, since no relationship seems to link inter and intraventricular dyssynchrony.

Pathophysiology of abnormal electrical conduction

Different types of infranodal conduction abnormality may determine the classical left bundle branch block pattern on the surface electrocardiogram: from focal proximal lesions (even longitudinal dissociation with asynchronous conduction) in the bundle of His to inhomogeneous spread of excitation wavefronts across the scarred tissue of the dilated ventricle.[10–15] The activation of left ventricular endocardium might be different in such conditions but the left ventricular conduction system is not easily accessible by electrophysiological study and endocardial catheter mapping has rarely been performed.[16] Scarce information has also been obtained on the mechanical correlates of these electrical abnormalities, although the paradoxical motion of the interventricular septum in left bundle branch block has first been described in 1973.[17–19] The reason is that only recent technology, such as tagged magnetic resonance imaging or tissue Doppler imaging, has allowed a precise evaluation of the sequence and timing of regional left ventricular contraction in heart failure patients.[20–25] The present study is the first one in which standard echocardiography and tissue Doppler imaging have both been used to obtain a complete picture of the mechanical abnormalities in a large series of consecutive patients with left ventricular dysfunction, with or without left bundle branch block. Patients with slightly prolonged or normal QRS were focused since even such patients may exhibit dyssynchrony and might therefore be considered as candidates to multisite pacing.

Interventricular dyssynchrony

The interventricular delay was significantly related to QRS duration, although a wide scattering of the data around the identity line was observed. The data are consistent with those obtained in a smaller series of DCM patients, although the correlation coefficient was substantially higher in the previous report than in our population.[26] We hypothesized that a prolonged right ventricular pre-ejection period (as in the case of right ventricular dysfunction or of pulmonary hypertension) could reduce the difference between aortic and pulmonary pre-ejection periods and therefore impair the correlation between interventricular dyssynchrony and QRS duration. However, the correlation only slightly improved by excluding the patients with right ventricular dysfunction and/or pulmonary hypertension. Clearly, the site of the left bundle branch block (e.g., in the proximal or distal part of the conduction system) might be an important determinant of the degree of interventricular dyssynchrony. Interventricular dyssynchrony was not related to etiology. As expected, a greater prevalence of interventricular dyssynchrony

(IVMD > 40 ms) was observed in patients with LBBB than in patients with normal QRS duration; importantly, it turned out that this prevalence did not differ between the group with a QRS duration greater than 150 ms and the group with a QRS duration between 120 and 150 ms. In addition, a small percentage of patients with normal QRS duration also showed interventricular dyssynchrony.

Intraventricular dyssynchrony

Ansalone et al. used tissue Doppler imaging to study 31 heart failure patients implanted with a biventricular pacemaker and found that in about one third of cases the lateral wall was the most delayed segment before implantation.[24] Similar results were observed in the present series even though a different TDI approach was used to define dyssynchrony: the lateral wall showed the most delayed movement only in about one third of patients with QRS duration above 120 ms. These data indicate that in heart failure patients with LBBB the sequence of left ventricular activation and wall motion may differ from patient to patient and in about two third of cases the most delayed segment is not the lateral wall. The prevalence of intraventricular dyssynchrony was similar in the group with a QRS duration greater than 150 ms and the group with a QRS duration between 120 and 150 ms. Interestingly, there was a substantial proportion of patients with normal QRS duration who also showed dyssynchrony, although no clinical characteristic or echocardiographic parameter differentiated such patients from those with normal QRS duration and no dyssynchrony.

Regional contraction patterns

Dyskinetic patterns were significantly more frequent in patients with ischemic heart disease than in patients with dilated cardiomyopathy. Therefore, care must be taken when considering an abnormal regional contraction pattern as an index of dyssynchrony in heart failure patients. In addition, it is true that a higher percentage of abnormal regional patterns was observed in patients with QRS duration ⩾150 ms than in patients with normal conduction; however, even in patients with QRS duration ⩾150 ms, the great majority of segments could be defined as having a "normal" displacement pattern, which limits the clinical value of the analysis of patterns.

Limitations

The study does not explain how mechanical dyssynchrony is linked to the electrical abnormality; to solve this issue an electrophysiological study mapping the endocardial activation in the left ventricle would be required. Although ethical considerations preclude a large scale correlation study between tissue Doppler imaging and endocardial mapping, this would be extremely important since in electrophysiological studies the latest site of activation in patients with LBBB is located in the lateral-

posterior left ventricle whereas TDI studies, including the present one, demonstrate that in a substantial percentage of cases the septum or the anterior wall are the most delayed sites. We defined intraventricular dyssynchrony on the basis of differences in regional pre-ejection periods, although in previous studies dyssynchrony was defined on the basis of differences in the time from QRS to the peak systolic velocity.[27,28] We preferred the former index to the latter which is the sum of the pre-ejection period plus a variable and unpredictable part of the ejection time (from beginning to peak velocity). However, theoretical considerations do not help to identify which index of intraventricular dyssynchrony is the most useful either in the identification of responders to cardiac resynchronization therapy or in the identification of the optimal site for pacing; a prospective trial is necessary to solve this issue. In fact, as recent studies have shown, even simplified indexes of intraventricular dyssynchrony may be of potential clinical usefulness.[29,30] The present study does not include data on strain, a new tissue Doppler modality which can be used to determine whether myocardial velocities detected by tissue Doppler imaging represent true contraction or are merely passive.[31] We acknowledge that this is a limitation for the interpretation of regional systolic displacements, particularly in patients with ischemic heart disease. TDI results should be used with caution as far as the identification of the optimal site for pacing is concerned.

Conclusions

A substantial proportion of heart failure patients with slightly prolonged QRS or even with normal conduction may exhibit ventricular dyssynchrony and may be considered as potential candidates to multisite pacing. The present study emphasizes the necessity of a combined approach with standard echocardiography and tissue Doppler imaging to characterize the spectrum of mechanical abnormalities due to ventricular dyssynchrony, since no relationship links inter and intraventricular dyssynchrony and it is still to be clarified which index of ventricular dyssynchrony is better related to functional improvement in patients treated with biventricular pacing.

References

1. Blanc JJ, Etienne Y, Gilard M et al. Evaluation of different ventricular pacing sites in patients with severe heart failure: results of an acute hemodynamic study. *Circulation* 1997;**96**:3273–7.

2. Leclercq C, Cazeau S, Le Breton H et al. Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure. *J Am Coll Cardiol* 1998;**32**:1825–31.

3. Auricchio A, Stellbrink C, Block M et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. *Circulation* 1999;**99**:2993–3001.

4. Cazeau S, Leclerq C, Lavergne T et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;**344**:837–80.

5. Abraham WT, Fisher WG, Smith AL et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–53.

6. Yu C-M, Lin H, Zhang Q et al. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. *Heart* 2003; **89**:54–60.

7. Leclercq C, Kass DA. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. *J Am Coll Cardiol* 2002;**39**:194–201.

8. Breithardt G, Khun H, Hammel D et al. Cardiac resynchronization therapy into the next decade: from the past to morbidity/mortality trials. *Eur Heart J Suppl* 2002;**4**(Suppl D):D102–10.

9. Ansalone G, Giannantoni P, Ricci R et al. Doppler myocardial imaging in patients with heart failure receiving pacing treatment. *Am Heart J* 2001;**142**:881–96.

10. Narula OS, Javier RP, Samet P et al. Significance of His and left bundle recordings from the left heart in man. *Circulation* 1970;**42**:385–96.

11. Rosen KM, Rahimtoola SH, Sinno MZ et al. Bundle branch and ventricular activation in man: a study using catheter recordings of left and right bundle branch potentials. *Circulation* 1971;**43**:193–203.

12. Watt Jr TB, Pruitt RD. Focal lesions in the canine bundle of His. Their effect on ventricular excitation. *Circ Res* 1972;**31**:531–45.

13. Cannom DS, Goldreyer BN, Damato AN. Atrioventricular conduction system in left bundle branch block with normal QRS axis. *Circulation* 1972;**46**:129–37.

14. Seipel L, Breithardt G, Kuhn H. Left bundle branch block in patients with and without cardiomyopathy. In: Kaltenbach M, Loogen F, Olsen EGJ, editors. Cardiomyopathy and myocardial biopsy. Berlin, Heidelberg: Springer; 1978. p. 237–50.

15. Josephson ME. Intraventricular conduction disturbances. In: Josephson ME, editor. Clinical cardiac electrophysiology: techniques and interpretations. Malvern, PA: Lea & Febiger; 1993. p. 117–49.

16. Vassallo JA, Cassidy DM, Marchlinski FE et al. Endocardial activation of left bundle branch block. *Circulation* 1984;**69**:914–23.

17. Mc Donald IG. Echocardiographic demonstration of abnormal motion of the interventricular septum in left bundle branch block. *Circulation* 1973;**48**:272–80.

18. Rosenbush SW, Ruggie N, Turner DA et al. Sequence and timing of left ventricular wall motion in bundle branch block. Assessment by radionuclide cineangiography. *Circulation* 1982;**66**:1113–9.

19. Grines CL, Bashore TM, Boudoulas H et al. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. *Circulation* 1989;**79**:845–53.

20. Wyman BT, Hunter WC, Prinzen F et al. Mapping propagation of mechanical activation in the paced heart with MRI tagging. *Am J Physiol Heart Circ Physiol* 1999;**276**:H881–91.

21. Prinzen FW, Hunter WC, Wyman BT et al. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. *J Am Coll Cardiol* 1999;**33**:1735–42.

22. Wyman BT, Hunter WC, Prinzen FW et al. Effects of single- and biventricular pacing on temporal and spatial dynamics of ventricular contraction. *Am J Physiol Heart Circ Physiol* 2002;**282**:H372–9.

23. Nelson GS, Curry CW, Wyman BT et al. Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. *Circulation* 2000;**101**:2703–9.

24. Ansalone G, Giannantoni P, Ricci R et al. Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing. *J Am Coll Cardiol* 2002;**39**:489–99.

25. Sogaard P, Egeblad H, Kim W et al. Tissue Doppler imaging predicts improved systolic performance and reverse left ventricular remodeling during long-term cardiac resynchronization therapy. *J Am Coll Cardiol* 2002;**40**:723–30.

26. Rouleau F, Merheb M, Geffroy S et al. Echocardiographic assessment of the interventricular delay of activation and correlation to the QRS width in dilated cardiomyopathy. *PACE* 2001;**24**:1500–6.

27. Yu CM, Chau E, Sanderson JE et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002; **105**:438–45.

28. Bax JJ, Malhoek SG, Marwick TH et al. Usefulness of myocardial tissue Doppler echocardiography to evaluate left ventricular dyssynchrony

before and after biventricular pacing in patients with idiopatic dilated cardiomyopathy. *Am J Cardiol* 2003;**91**:94—7.

29. Pitzalis MV, Iacoviello M, Romito R et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. *JACC* 2002;**40**:1615—22.

30. Cazeau S, Bordacher P, Jauvert A et al. Echocardiographic modeling of cardiac dyssynchrony before and during multisite stimulation. *PACE* 2003;**26**:1—7.

31. Hatle L, Sutherland GR. Regional myocardial function, a new approach. *Eur Heart J* 2000;**21**:1337—57.