Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 47, No. 11, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2005.11.087

Dynamic Ventricular Dyssynchrony

An Exercise-Echocardiography Study

Stephane Lafitte, MD, PHD,* Pierre Bordachar, MD,* Marianne Lafitte, MD,*
Stephane Garrigue, MD, PHD,* Sylvain Reuter, MD,* Patricia Reant, MD,* Karim Serri, MD,*
Valerie Lebouffos, MD,* Marianne Berrhouet, MD,* Pierre Jais, MD, PHD,* Michel Haissaguerre, MD,*
Jacques Clementy, MD,* Raymond Roudaut, MD,* Anthony N. DeMaria, MD†
Bordeaux, France; and San Diego, California.

OBJECTIVES We sought to assess the effects of exercise on ventricular dyssynchrony in patients with normal and depressed left ventricular (LV) function.

BACKGROUND Asynchronous myocardial contraction adversely influences ventricular function and is associated with a poor prognosis in heart failure. Exercise-induced changes in ventricular dyssynchrony may be an important determinant of dynamic changes in cardiac output and mitral regurgitation.

METHODS A total of 65 consecutive heart failure patients and 50 matched healthy control patients underwent exercise echocardiography. Conventional and tissue Doppler parameters were measured before and during symptom-limited exercise. Left ventricular dyssynchrony was defined as the standard deviation of 12 LV segmental electromechanical delays. Analysis of the control group allowed delimitation of normal cutoff values.

RESULTS In patients with normal left ventricular function, exercise did not modify the extent of LV asynchrony. In contrast, in heart failure patients, LV dyssynchrony increased by at least 20% in 34%, remained stable in 37%, and decreased by at least 20% in 29%. Moreover, 26% of heart failure patients had either exercise induction or normalization of ventricular dyssynchrony. A significant association was found between exercise-induced changes in dyssynchrony and the presence of ischemic cardiomyopathy ($p < 0.05$). Rest-exercise differences in ventricular dyssynchrony were correlated with changes in cardiac output and mitral regurgitation ($r = -0.63$ and 0.56, respectively).

CONCLUSIONS In heart failure patients, exercise can alter the magnitude of ventricular dyssynchrony. Some patients have a response to exertion with induction of ventricular dyssynchrony, whereas others show normalization. Changes in ventricular dyssynchrony during exercise correlate with alterations in cardiac output and mitral regurgitation. (J Am Coll Cardiol 2006;47: 2253–9) © 2006 by the American College of Cardiology Foundation

Echocardiography has provided evidence of the high prevalence of mechanical ventricular dyssynchrony in heart failure patients (1–2). Asynchronous myocardial contraction adversely influences ventricular function, increases the extent of mitral regurgitation, and is associated with a poor prognosis (3–5). Several ultrasound techniques, including conventional M-mode and Doppler recordings, tissue Doppler imaging, strain rate imaging, and three-dimensional echocardiography have been proposed to measure the level of interventricular (between the two ventricles) and left ventricular (LV) dyssynchrony (6–11). However, to date, all previous echocardiographic studies evaluating ventricular dyssynchrony were performed during rest conditions.

We hypothesized that: 1) exercise may dramatically change the presence and extent of ventricular dyssynchrony in a subset of heart failure patients, and 2) these dynamic changes in ventricular dyssynchrony may be associated with exercise-induced changes in hemodynamic parameters. Therefore, we conducted an exercise-echocardiographic study in normal patients and patients with depressed LV function to define the dynamic exercise-induced changes in ventricular dyssynchrony and to correlate these changes with those of cardiac output and mitral regurgitation.

METHODS

This prospective study involved 65 patients with compensated heart failure and 50 age- and gender-matched healthy volunteers with normal history, physical examination, electrocardiogram, echocardiography, and stress test. The mean age of heart failure patients was 67 ± 12 years. Inclusion criteria for heart failure patients were sinus rhythm and left ventricular systolic dysfunction with an ejection fraction <35%. Patients were in New York Heart Association functional class II (n = 19) or class III (n = 46). The origin of heart failure was ischemic in 33 patients and nonischemic in 32 patients. The etiology was considered ischemic if

From the *Cardiologic Hospital, Pessac and Bordeaux 2 University, Bordeaux, France; and the †Division of Cardiology, University of California at San Diego, San Diego, California. Dr. DeMaria is and has been a grantee and/or ad hoc consultant for virtually all echocardiography instrument companies. Drs. Lafitte and Bordachar participated equally in this study. Alan S. Pearlman, MD, served as guest editor for this paper.

Manuscript received July 22, 2005; revised manuscript received November 10, 2005, accepted November 17, 2005.

JACC Vol. 47, No. 11, 2006
June 6, 2006:2253–9

Abbreviations and Acronyms

%DLC	= extent of myocardium showing delayed longitudinal contraction
LV	= left ventricular
SD-12	= standard deviation of time to peak systolic velocity of the 12 left ventricular segments
TO	= time to onset of segmental contraction
TO-6base	= maximal difference in time to onset of segmental contraction between any two of six basal left ventricular segments
TP	= time to peak systolic velocity
TP-6base	= maximal difference in time to peak systolic velocity between any two of six basal segments
TP-sep-lat	= difference between time to peak systolic velocity of septobasal and laterobasal segments
VTI	= velocity time integral

patients had either evidence of previous (>6 months) myocardial infarction or angiographic evidence of significant coronary artery disease (≥50% stenosis in one of the major epicardial coronary arteries that was considered to jeopardize sufficient myocardium to explain the observed depression of LV function).

Twenty-two patients manifested a narrow QRS complex (<120 ms) and 43 a wide QRS complex (≥120 ms). Each patient had to be able to perform a semisupine exercise echocardiographic test to the point of fatigue.

Exclusion criteria included a history of acute coronary syndrome or revascularization in the previous six months, technically inadequate echocardiogram, primary severe mitral regurgitation, permanent atrial fibrillation, and unstable ventricular rhythm.

All patients provided written informed consent for the study, which was approved by the institutional clinical research and ethics committee.

Exercise echocardiography. A symptom-limited graded bicycle exercise test was performed in the semisupine position on a tilting exercise table as previously described (12). After an initial workload of 20 W maintained for 3 min, the workload was increased every 2 min by 10 W. Echocardiographic images were collected at baseline and at the peak of exercise. Blood pressure and 12-lead electrocardiograms were recorded every minute.

Echocardiography. All echocardiographic examinations used a Vingmed-General Electric ultrasound system (System 7, Horten, Norway) equipped with a 2.5- to 5-MHz imaging probe and off-line cineloop analysis software. Recordings were obtained according to standard recommendations (13). All images were recorded digitally and analyzed off-line. Each parameter was measured on the average of three consecutive beats at rest and during exercise. Aortic and pulmonary pre-ejection delays were measured from aortic and pulmonary flow recordings with pulsed-wave Doppler and were defined as the time between the onset of the QRS and the onset of each respective ejection. Mitral regurgitation was quantified by the proximal isovelocity surface area method (14).

The tissue Doppler imaging color images were acquired from two-, three-, and four-chamber apical views to assess the longitudinal contraction of the left ventricle and were optimized for pulse repetition frequency, color saturation, sector size and depth (tissue Doppler frame rate 106.7 Hz, sample size for velocity 6 × 6 mm, segment length for strain 12 × 6 mm). Tracking of the region of interest was performed to maintain the sample volume in the region of interest throughout the cardiac cycle. The time to onset (TO) of segmental contraction was measured by placing the sample volume in the middle of 12 LV segments: basal and midsegmental portions of the inferoseptal, anterolateral, inferior, anterior, inferolateral, and anteroseptal walls. The TO was defined as the delay between the onset of the QRS and the onset of the first shortening wave during ejection. The time to peak (TP) systolic velocity was measured for the same 12 LV segments and was defined as the delay between the onset of the QRS and the peak of the shortening wave during ejection.

Dyssynchrony evaluation. Interventricular dyssynchrony was assessed as the difference between aortic and pulmonary pre-ejection delays (6). Several parameters of LV dyssynchrony were measured in this study (Fig. 1):

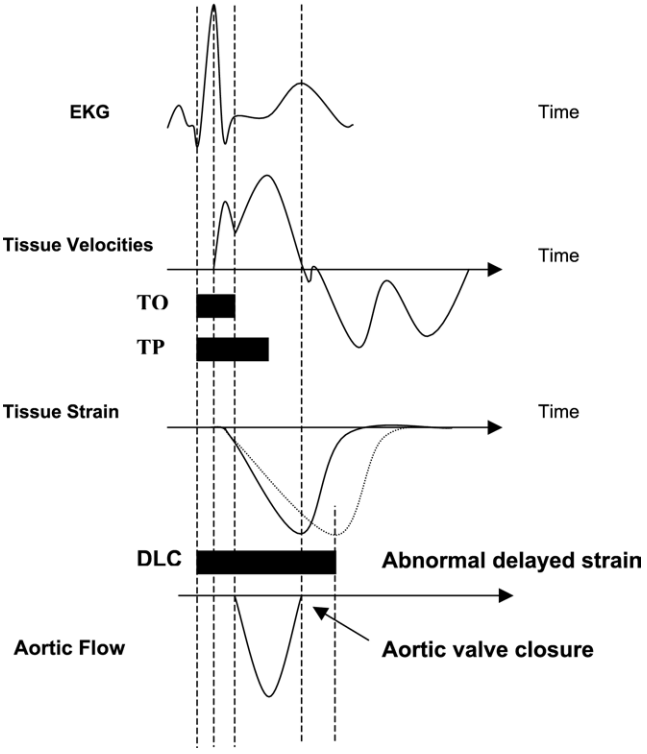

Figure 1. Three systolic phases analyzed for left ventricular dyssynchrony assessment. DLC = delayed longitudinal contraction; EKG = electrocardiogram; TO = time to onset of first shortening wave during ejection; TP = time to peak shortening wave during ejection.

Table 1. Rest and Exercise Interobserver and Intraobserver Variabilities

	Rest (%)		Exercise (%)	
	Intraobserver	Interobserver	Intraobserver	Interobserver
Inter-V dyssynchrony	4.1	5.2	4.9	6.2
TO-6base	8.5	8.9	9.8	10.1
TP-6base	7.9	8.3	9.8	9.4
TP-sep-lat	6.2	6.1	6.1	7.4
SD-12	8.9	10.4	8.1	11.9
%DLC	11.1	12.5	13.1	14.5

%DLC = extent of myocardium showing delayed longitudinal contraction; Inter-V = interventricular; LV = left ventricular; SD-12 = standard deviation of time to peak systolic velocity of the 12 left ventricular segments; TO-6base = maximal difference in time to onset of segmental contraction between any two of six basal left ventricular segments; TP-6base = maximal difference in time to peak systolic velocity between any two of six basal segments; TP-sep-lat = difference between time to peak systolic velocity of septobasal and laterobasal segments.

Maximal difference in TO between any two of six basal LV segments (TO-6base) (7).

Maximal difference in TP between any two of six basal segments (TP-6base) (7,8).

Standard deviation of TP of the 12 LV segments (SD-12) (8).

Difference between TP of septobasal and laterobasal segments (TP-sep-lat) (11). The parameters of dyssynchrony were normalized to RR interval [(dyssynchrony delay/RR interval) × 1,000] to compare the differences between rest and exercise.

The extent of myocardium showing delayed longitudinal contraction (%DLC) was calculated using strain and tracking analysis (9). The %DLC was defined as the percentage of the 12 studied LV segments that showed in-plane shortening after the aortic valve closure.

Statistical analysis. All data are presented as mean ± SD. Comparisons of echocardiographic parameters between rest and exercise and between control and heart failure patients were performed using repeated analysis of variance measures. Comparisons between nonparametric data were performed using Fisher exact tests. A value of $p < 0.05$ (two-sided) was considered significant.

Based on a Gaussian distribution, the normal cutoff value for the dyssynchrony parameter was determined as mean + 2 SD of the normal left ventricular function group. A heart failure patient was considered to present with abnormal dyssynchrony if the studied parameter was greater than the mean + 2 SD of the control group.

Dyssynchrony parameters were correlated with aortic velocity time integral (VTI) and mitral regurgitation by linear regression analysis. Reproducibility was assessed by calculation of interobserver and intraobserver variabilities in 20 consecutive heart failure patients and 15 consecutive control patients.

RESULTS

In all 65 patients, the protocol was successfully completed and technically adequate recordings were made for analysis. No patient experienced chest pain or manifested ST-segment depression during exercise.

Reproducibility. During exercise, intraobserver and interobserver variability was 5.2% and 6.1% for aortic VTI, and 7.8% and 8.3% for proximal isovelocity surface area.

The intraobserver and interobserver variabilities for measurement of ventricular dyssynchrony at rest and exercise are delineated in Table 1. They ranged from a low of 4.9% for interventricular dyssynchrony at rest to a high of 14.5% for %DLC with exertion.

Normal subjects. Normal subjects exercised for 16 ± 3.4 min and reached a mean workload of 95 ± 17 W. The changes from rest to exercise are summarized in Table 2.

Table 2. Hemodynamic Parameters

	Control		Heart Failure Patients	
	Rest	Exercise	Rest	Exercise
Heart rate (beats/min)	75 ± 15	140 ± 29	69 ± 19	120 ± 15*
QRS duration (ms)	84 ± 5	86 ± 4	126 ± 15	125 ± 17
Systolic blood pressure (mm Hg)	122 ± 12	168 ± 20	110 ± 19	152 ± 22*
End-diastolic volume (ml)	88 ± 16	90 ± 14	199 ± 22	192 ± 18
End-systolic volume (ml)	32 ± 5	26 ± 7*	150 ± 26	144 ± 30
LV ejection fraction (%)	65 ± 4	73 ± 4*	24 ± 6	25 ± 9
Cardiac output (l/mn)	5.5 ± 1.9	9.4 ± 1.2*	2.1 ± 1.1	2.5 ± 1.6
LV filling time (ms)	479 ± 23	216 ± 19*	343 ± 31	242 ± 52*
Mitral deceleration time (ms)	199 ± 16	68 ± 11*	169 ± 25	138 ± 34*
Effective regurgitation orifice area (mm^2)	—	—	11 ± 4	21 ± 5

*$p < 0.05$ versus rest.
Abbreviations as in Table 1.

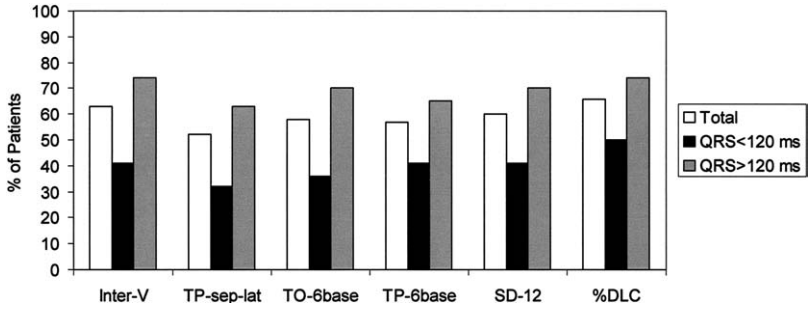

Figure 2. Percentage of heart failure patients with abnormal ventricular dyssynchrony at rest. %DLC = extent of myocardium showing delayed longitudinal contraction; Inter-V = interventricular dyssynchrony; SD-12 = standard deviation of TP of the 12 left ventricular segments; TO-6base = maximal difference in TO between any two of six basal left ventricular segments; TP-6base = maximal difference in TP between any two of six basal segments; TP-sep-lat = difference between TP of septobasal and laterobasal segments.

The dyssynchrony parameters (indexed to RR) did not significantly differ between rest and exercise in normal subjects: interventricular dyssynchrony (18 ± 8 ms vs. 15 ± 9 ms), TP-sep-lat (17 ± 9 ms vs. 18 ± 8 ms), TO-6base (23 ± 10 ms vs. 21 ± 9 ms), TP-6base (21 ± 12 ms vs. 22 ± 11 ms), SD-12 (16 ± 9 ms vs. 15 ± 9 ms) and %DLC (5 ± 2% vs. 6 ± 2%) (all p = NS).

Heart failure patients. The mean exercise duration and maximal workload in heart failure patients was less than in normal subjects (6.6 ± 1.3 min, 48 ± 7 W; $p < 0.01$). The changes from rest to exercise in heart rate, systolic blood pressure, electrocardiogram, and conventional echocardiographic parameters are summarized in Table 2.

Rest. All parameters of dyssynchrony were significantly higher in patients than in normal subjects: interventricular dyssynchrony (46 ± 16 ms vs. 18 ± 8 ms), TP-sep-lat (50 ± 21 ms vs. 17 ± 9 ms), TO-6base (63 ± 22 ms vs. 23 ± 10 ms), TP-6base (72 ± 34 ms vs. 21 ± 12 ms), SD-12 (51 ± 17 ms vs. 16 ± 9 ms), and %DLC (29 ± 15% vs. 5 ± 2%) (all $p < 0.01$). No significant difference in the mean value of any parameter of dyssynchrony was observed at rest between ischemic and nonischemic patients.

The percentage of patients showing abnormal dyssynchrony at rest is shown in Figure 2. Depending on the parameter measured, the percentage of patients showing abnormal dyssynchrony at rest ranged from 52% to 66% for the heart failure group as a whole, from 32% to 50% for the subgroup with QRS <120 ms, and from 63% to 74% for the subgroup with QRS >120 ms.

The simultaneous presence of an abnormal value for all six parameters of dyssynchrony (interventricular, %DLC, and four parameters of LV dyssynchrony) was observed in 24 patients (37%), 5 (23%) of whom had a narrow QRS and 19 (44%) had a wide QRS. In contrast, the presence of at least one of these parameters was observed in 56 patients (86%), 18 (82%) of whom had a narrow QRS and 38 (88%) a wide QRS. Five patients (8%) had only one parameter meeting criteria for abnormal dyssynchrony.

Exercise. Depending on the parameter measured, the percentage of patients showing abnormal dyssynchrony during exercise ranged from 55% to 69% for the whole heart failure group, from 32% to 45% for the patients with QRS <120 ms, and from 67% to 81% for the patients with QRS >120 ms (Fig. 3). Regarding rest assessment, no significant difference was observed during exercise in the mean value of any parameter of dyssynchrony between ischemic and nonischemic patients.

The mean value for the heart failure group did not change significantly from rest to exercise for any specific parameter of dyssynchrony. However, substantial changes were observed for each parameter in individual patients and consisted of both increases and decreases that offset each other in the mean value. Depending on the parameter, ventricular dyssynchrony increased by at least 20% in 28% to 40% of the patients, remained within 20% of rest in 35% to 43% of the patients, and decreased by at least 20% in 23% to 31% of the patients from rest to exercise (Figs. 4 and 5). The threshold of 20% was

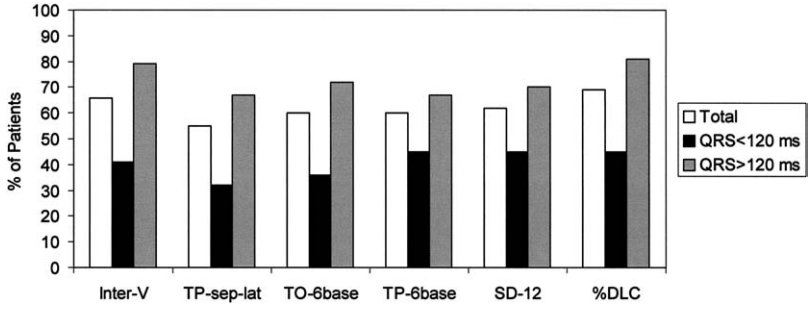

Figure 3. Percentage of heart failure patients with abnormal ventricular dyssynchrony during exercise. Abbreviations as in Figure 2.

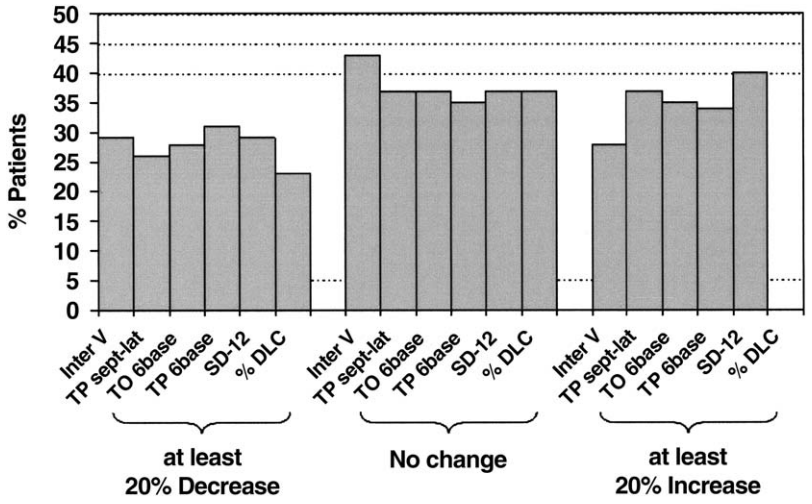

Figure 4. Percentage of patients with at least a 20% increase, at least a 20% decrease, or a stable value of dyssynchrony during exercise. Abbreviations as in Figure 2.

selected because it ensured more than 5% over the maximal variability of dyssynchrony measurement.

Depending on the applied parameter of dyssynchrony, we identified 20% to 26% of the patients with either significant dyssynchrony at rest that resolved during exercise or in whom significant dyssynchrony was absent at rest but appeared during exercise (Fig. 6). Of the patients who manifested a change of status from rest to exercise in at least one parameter of dyssynchrony, 80% presented with ischemic cardiomyopathy ($p < 0.05$). In 83% of the patients, the change in status from rest to exercise in one of the four parameters of LV dyssynchrony was attributable to prolongation of the electromechanical activation of a previously early-activated segment. In the other 17%, it was attributable to the shortening of the electromechanical activation of a previously late-activated segment.

All six parameters of dyssynchrony were abnormal during exertion in 27 patients (42%), 5 (23%) with narrow QRS and 22 (51%) with wide QRS. In contrast, at least one of these parameters was abnormal in 52 patients (80%), 16 (73%) with narrow QRS and 36 (84%) with wide QRS. Six patients (9%) had only one parameter meeting criteria for abnormal dyssynchrony during exercise.

Correlation between exercise dyssynchrony and cardiac function. The results of linear regression analysis between aortic VTI and dyssynchrony parameters showed a significant inverse correlation between the exercise-rest changes in cardiac output and exercise-rest changes in TP-6base ($r = -0.65$, $p < 0.01$), changes in TO-6base ($r = -0.68$, $p < 0.01$), changes in SD-12 ($r = -0.63$, $p < 0.01$), and changes in TP-sep-lat ($r = -0.54$, $p < 0.05$). No significant correlation was observed with changes in %DLC or interventricular dyssynchrony.

Concerning the effects of exertion on mitral regurgitation, a correlation was observed between rest-exercise changes in effective regurgitant orifice area and rest-exercise changes in TP-6base, TO-6base, and SD-12 ($r = 0.59$, $r = 0.55$, $r = 0.56$, respectively; all $p < 0.05$). No significant

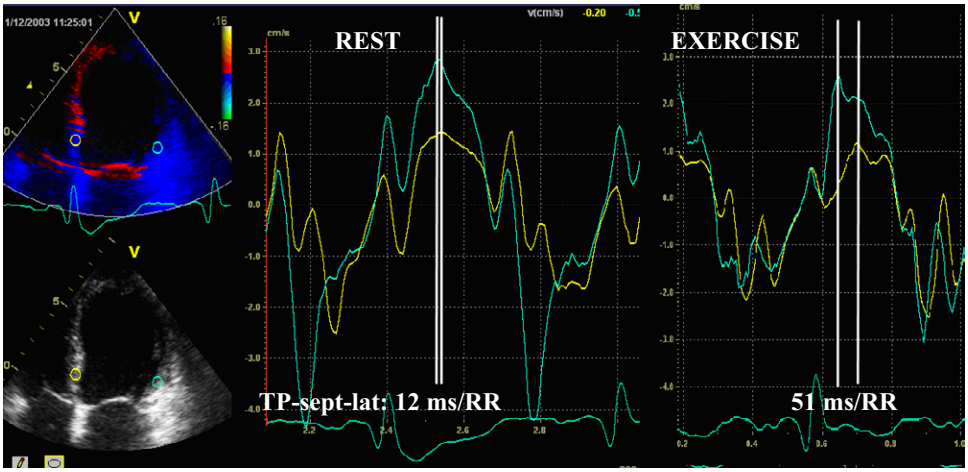

Figure 5. Example of one patient with a limited delay between septobasal and laterobasal segments peak of velocity at rest and major dyssynchrony during exercise. Abbreviation as in Figure 2.

JACC Vol. 47, No. 11, 2006
June 6, 2006:2253–9

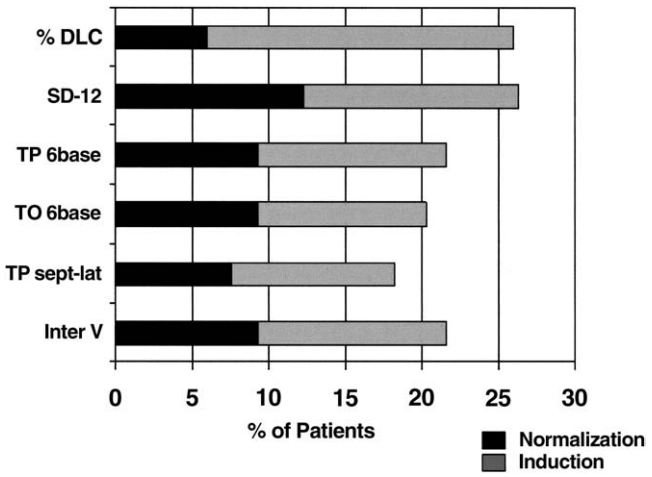

Figure 6. Percentage of patients with either exercise induction or normalization of ventricular dyssynchrony during exercise. Abbreviations as in Figure 2.

correlation was observed with Tp-sep-lat, %DLC, or interventricular dyssynchrony.

DISCUSSION

The current study, which evaluated the effects of exercise on multiple echocardiographic criteria of dyssynchrony, has yielded a number of important findings: 1) Ventricular dyssynchrony in patients with heart failure can be assessed during exercise. 2) In individual patients, we found significant variability in the prevalence and severity of dyssynchrony recorded at rest for individual echocardiographic criteria. 3) The extent of dyssynchrony was dynamic and changed between rest and exercise in a high proportion of patients. These dynamic changes varied substantially from patient to patient. In some patients, abnormal dyssynchrony was found at rest but not during exercise, whereas in others the reverse was observed. 4) Patients manifesting changes in exercise were more commonly observed to have ischemic cardiomyopathy. 5) Exercise-induced alterations in ventricular synchrony were associated with changes in stroke volume and the severity of mitral regurgitation.

Feasibility. The evaluation of cardiac function during exercise has been shown to improve the understanding and management of several cardiac diseases (12). Nevertheless, in heart failure patients, the application of cardiac resynchronization has been primarily based on the evaluation of dyssynchrony at rest (15–19). Our results show that the assessment of ventricular dyssynchrony during exercise is feasible, with a level of reproducibility comparable with that at rest (Table 1). As expected, the more myocardial segments analyzed in deriving a given parameter, the lower is the reproducibility both for rest and exercise.

Evaluation of dyssynchrony at rest. Although it was not the purpose of this study to assess the ability of various echocardiographic parameters of dyssynchrony to predict the response to cardiac resynchronization, several observations are relevant in this regard.

The assessment of LV dyssynchrony has involved a multiparametric approach. Our results show for the first time the variability in dyssynchrony depending on the parameter studied. Only 37% of our patients showed dyssynchrony by all parameters, and 14% manifested none of these parameters. Thus, 49% of patients presented a combination of positive and negative criteria. The patients selected for cardiac resynchronization therapy would differ depending on whether the decision for therapy would be based on the interventricular dyssynchrony, the LV dyssynchrony, or the extent of myocardium showing delayed longitudinal contraction. More studies are needed to determine how to manage a patient in whom discordance between the parameters of dyssynchrony is observed. In the absence of data from a randomized controlled trial comparing rest variables, we believe that the best data predictive of a favorable response to cardiac resynchronization have been reported by Yu et al. (8). They reported that dyssynchrony, defined as the standard deviation of 12 electromechanical LV delays, best predicted the reverse remodeling after cardiac resynchronization. Although the evidence supporting this criterion is the strongest, our study shows that variability increases with the number of analyzed segments.

Rest-to-exercise dyssynchrony. In terms of the entire group of heart failure patients, there was no significant change in the mean degree of ventricular dyssynchrony between resting and exercise conditions. However, on closer inspection, three distinct groups of patients could be identified for each parameter: one with no difference between rest and exercise, one without dyssynchrony at rest but in which it was induced by exercise, and a third with dyssynchrony at rest that normalized on exercise. The percentage of patients who manifested such changes was similar for each individual echocardiographic parameter. As previously described (20), the mean value of the parameters of dyssynchrony at rest were not significantly different between ischemic and nonischemic patients. However, we observed that changes during exercise were more likely to occur in patients with ischemic cardiomyopathy. We hypothesized that this might be explained by the occurrence of subclinical ischemia leading to tardokinesis in some segments. Analysis showed that in most of the patients in whom dyssynchrony was normalized or induced with exercise, it was attributable to prolongation of electromechanical activation of a previous early-activated segment.

Clinical implications. The goal of this study was to describe the changes in dyssynchrony from rest to exercise in heart failure patients. We believe that the description of the effect of exercise on ventricular dyssynchrony improves the understanding of the physiology involved in dyssynchronous hearts. However, this was only the first step in determining whether exercise echocardiography would be of value in predicting the response to cardiac resynchronization. The changes in dyssynchrony observed during exercise were accompanied by changes in mitral regurgitation and stroke volume, suggesting hemodynamic significance. Based on

these observations, it is possible that therapeutic approaches such as cardiac resynchronization might improve exercise capacity in such patients. In contrast, patients in whom ventricular dyssynchrony disappears with exercise might not have an optimal response to biventricular pacing. A fixed pacemaker setting for interlead delay during biventricular pacing may not be physiological in the presence of dynamically changing synchrony. However, no data exist to establish whether cardiac resynchronization applied based on exercise dyssynchrony would yield superior results to that based on evaluation at rest. We believe our data establish the importance of performing a trial to answer these questions.

Study limitations. The echocardiographic measurements were performed at rest and during maximal symptom-limited exercise. It is uncertain what effects would be produced by a lesser degree of exertion. This study included New York Heart Association functional class II patients and excluded class IV patients. It also included patients with a narrow QRS. Only 62% of the patients included met the usual criteria for cardiac resynchronization (New York Heart Association functional class III or IV, QRS >120 ms). However, it has recently been shown that some patients with a narrow QRS may benefit from cardiac resynchronization (21). Our study confirms that a significant proportion of these patients present with mechanical ventricular dyssynchrony, the target of the therapy. Moreover, although the sample size did not enable comparison of the response to exercise of those with narrow to wide QRS complexes, induction and normalization seemed similar between the two subgroups.

Conclusions. In heart failure patients, exercise can alter the magnitude of ventricular dyssynchrony. Some patients have a response to exertion with induction of ventricular dyssynchrony, whereas others show normalization. Changes in ventricular dyssynchrony during exercise correlate with changes in cardiac output and mitral regurgitation. These data suggest the need for a prospective study to determine whether the response of ventricular dyssynchrony to exertion may help select candidates for cardiac resynchronization therapy.

Reprint requests and correspondence: Dr. Anthony N. DeMaria, University of California San Diego, Division of Cardiology, 200 West Arbor Drive, San Diego, California 92103-9000. E-mail: ademaria@ucsd.edu.

REFERENCES

1. Yu CM, 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.
2. Ghio S, Lin H, Zhang Q, et al. Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration. Eur Heart J 2004;25:571–8.
3. Xiao HB, Lee CH, Gibson DG. Effect of left bundle branch block on diastolic function in dilated cardiomyopathy. Br Heart J 1991;66: 443–7.
4. Breithardt OA, Sinha AM, Schwammenthal E, et al. Acute effect of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. J Am Coll Cardiol 2003;41:765–70.
5. Bader H, Garrigue S, Lafitte S, et al. Intra-left ventricular electromechanical asynchrony. A new independent predictor of severe cardiac events in heart failure patients. J Am Coll Cardiol 2004;43:248–56.
6. Cazeau S, Bordachar P, Jauvert G, et al. Echocardiographic modeling of cardiac dyssynchrony before and during multisite stimulation: a prospective study. Pacing Clin Electrophysiol 2003;26:137–43.
7. Bordachar P, Lafitte S, Reuter S, et al. Echocardiographic parameters of ventricular dyssynchrony validation in patients with heart failure using sequential biventricular pacing. J Am Coll Cardiol 2004;44: 2157–65.
8. Yu CM, Fung JW, Zhang Q, et al. Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. Circulation 2004;110:66–73.
9. Sogaard P, Egeblad H, Pedersen AK, et al. Sequential versus simultaneous biventricular resynchronization for severe heart failure: evaluation by tissue Doppler imaging. Circulation 2002;106:2078–84.
10. Bax JJ, Ansalone G, Breithardt OA, et al. Echocardiographic evaluation of cardiac resynchronization therapy: ready for routine clinical use? A critical appraisal. J Am Coll Cardiol 2004;44:1–9.
11. Bax JJ, Molhoek SG, van Erven L, et al. Usefulness of myocardial tissue Doppler echocardiography to evaluate left ventricular dyssynchrony before and after biventricular pacing in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2003;91:94–7.
12. Lancellotti P, Troisfontaines P, Toussaint AC, et al. Prognostic importance of exercise-induced changes in mitral regurgitation in patients with chronic ischemic left ventricular dysfunction. Circulation 2003;108:1713–7.
13. Gottdiener JS, Bednarz J, Devereux R, et al., American Society of Echocardiography. American Society of Echocardiography recommendations for use of echocardiography in clinical trials. J Am Soc Echocardiogr 2004;17:1086–119.
14. Bargiggia GS, Tronconi N, Sahn DJ, et al. A new method for quantification of mitral regurgitation based on color flow Doppler imaging of flow convergence proximal to regurgitant orifice. Circulation 1991;84:1481–9.
15. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–80.
16. Gras D, Leclercq C, Tang AS, et al. Cardiac resynchronization therapy in advanced heart failure; the multicenter InSync clinical study. Eur J Heart Fail 2002;4:311–20.
17. Kass DA. Predicting cardiac resynchronization response by QRS duration: the long and short of it. J Am Coll Cardiol 2003;320: 2125–7.
18. Leclercq C, Kass DA. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. J Am Coll Cardiol 2002;234:194–201.
19. Auricchio A, Stellbrink C, Butter C, et al. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. J Am Coll Cardiol 2003;42:2109–16.
20. Van de Veire N, De Sutter J, Van Camp G, et al. Global and regional parameters of dyssynchrony in ischemic and nonischemic cardiomyopathy. Am J Cardiol 2005;95:421–3.
21. Achilli A, Sassara M, Ficili L, et al. Long-term effectiveness of cardiac resynchronization therapy in patients with refractory heart failure and "narrow" QRS. J Am Coll Cardiol 2003;42:2117–24.