HEART FAILURE

Predictors of Lack of Clinical Improvement at Mid-Term Follow-up With Cardiac Resynchronization Therapy

Ernesto Díaz-Infante, Antonio Berruezo, Lluís Mont, Paulo Osorio, Emilio García-Morán, Alba Marigliano, Marta Sitges, Manel Azqueta, Carles Paré, África Muxí, Pilar Paredes, Xavier Fosch, Salvador Ninot, Eulalia Roig, and Josep Brugada

Unidad de Arritmias, Instituto de Enfermedades Cardiovasculares, Hospital Clínico Universitario, Universidad de Barcelona, Barcelona, Spain.

Introduction. About 30% of all patients do not respond to cardiac resynchronization therapy for heart failure. The objective of the study was to analyze the variables that may predict the lack of response.

Patients and method. We analyzed the results in a series of 63 patients who received cardiac resynchronization with a biventricular device. Clinical and left ventricular function parameters were evaluated at the beginning of the study and at 6 months. Responders were defined as those who were alive, had not received a heart transplant, and who achieved more than a 10% increase in distance in the 6-minute walking test.

Results. Mean age was 68.3 (8) years, 51 patients (81%) were men, and NYHA functional class was III-IV in 79.4%. Mean left ventricular ejection fraction was 22.4% (6)%, QRS width was 177 (25) ms, and 77.8% were in sinus rhythm. Almost half (46%, n=29) had ischemic heart disease. At 6-month follow-up, 69.8% of the patients were responders. Ischemic heart disease, sustained monomorphic ventricular tachycardia and a degree of mitral regurgitation >II/IV before implantation were associated with lack of response. No association was found for any of the other baseline variables. Logistic regression analysis identified all three of the aforementioned variables as independent predictors of lack of response: ischemic heart disease OR=4.8, 95% CI, 1.2-18.3, *P*=.023; ventricular tachycardia OR=8.7, 95% CI, 1.8-41.3, *P*=.007; and mitral regurgitation OR=8.03, 95% CI, 1.7-37.1, *P*=.008.

Conclusion. The likelihood of responding to resynchronization therapy is lower in patients with ischemic heart disease, significant mitral regurgitation, or sustained monomorphic ventricular tachycardia.

SEE EDITORIAL ON PAGES **279-82**

Predictores de ausencia de mejoría clínica a medio plazo con la terapia de resincronización cardíaca

Introducción. Alrededor del 30% de los pacientes no responde al tratamiento de resincronización para la insuficiencia cardíaca. El objetivo del estudio ha sido analizar las variables que pueden ser predictoras de falta de respuesta.

Pacientes y método. Se analizaron los resultados de una serie de 63 pacientes a los que se implantó un dispositivo de resincronización biventricular. Se realizó una valoración clínica y de parámetros de función ventricular izquierda basal y a los 6 meses. Se consideró que habían mejorado los pacientes que estaban vivos sin trasplante cardíaco y habían aumentado más de un 10% la distancia caminada en el test de los 6 min.

Resultados. La edad media fue de 68,3 ± 8 años; 51 pacientes (81%) eran varones y la clase funcional de la NYHA era III-IV en el 79,4%. La fracción de eyección media fue 22,4 ± 6%, la duración del QRS, 177 ± 25 ms, y el 77,8% estaba en ritmo sinusal. Un 46% (n = 29) tenía cardiopatía isquémica. A los 6 meses, el 69,8% respondió al tratamiento. La ausencia de mejoría se asoció con cardiopatía isquémica, historia de taquicardia ventricular monomórfica sostenida e insuficiencia mitral de grado > II/IV previa al implante, pero no mostró relación con el resto de los parámetros basales analizados. En el análisis de regresión logística, las 3 variables fueron predictores independientes de la falta de mejoría (OR = 4,8; IC del 95%, 1,2-18,3; p = 0,023; OR = 8,7; IC del 95%, 1,8-41,3; p = 0,007; y OR = 8,03; IC del 95%, 1,7-37,1; p = 0,008, respectivamente).

Conclusión. La probabilidad de responder al tratamiento de resincronización es menor en pacientes con cardiopatía isquémica, insuficiencia mitral importante o historia de taquicardia ventricular monomórfica sostenida.

Palabras clave: *Insuficiencia cardíaca. Marcapasos. Resincronización cardíaca.*

INTRODUCTION

About 30% of patients with heart failure have conduction disorders that cause asynchronous ventricular contraction. This negatively influences their prognosis.[1,2] Cardiac resynchronization is accepted as a complement to pharmacological treatment in persistent heart failure,[3] and randomized clinical trials have shown that it can improve functional capacity and quality of life.[4-7] Furthermore, the meta-analysis performed by Bradley et al[8] clearly shows that cardiac resynchronization therapy (CRT) improves survival in heart failure patients,[8] although about one third show no improvement.[5,6] This has been related to the location of the electrode and to certain echocardiographic variables,[9,10] but no clinical variables prior to implantation have been identified that might predict a failure to respond. The aim of this work was to prospectively analyze the variables that might predict such a lack of response to CRT.

PATIENTS AND METHODS

Patients

The patients selected for inclusion all suffered chronic heart failure, and all fell into New York Heart Association (NYHA) functional classes II-IV despite optimized pharmacological treatment (all had taken stable doses in the previous 2 months). All patients showed a left ventricular ejection fraction (LVEF) of ≤40%, a left ventricular end-diastolic diameter (LVEDD) of >55 mm, left bundle branch block with a QRS interval of ≥130 ms, and could only manage a distance of <500m in the 6-minute walking test. The study protocol was approved by our hospital's ethics committee, and all patients gave their signed consent to be included.

Methods

This study was a prospective, observational study in which patients were included in a consecutive fashion. Those that took part underwent a baseline examination that included determining their NYHA functional class, a 6-minute walking test,[11] The patients also completed a quality of life questionnaire (the Minnesota questionnaire for heart failure;[12] the greater the score, the worse the quality of life), echocardiogram (ventricular diameter, semiquantitative assessment[13] of the degree of mitral failure, and calculation of the ejection fraction using the Simpson biplanar method), and radioventriculography.

After this initial evaluation, all patients were implanted with a cardiac resynchronization device (either a Guidant ContakHF®, a Contak-Renewal,® or a Renewal II®; the last of these was used only when a defibrillator was indicated according to accepted criteria), placing one electrode in the right atrium (if the patient showed sinus rhythm), another at the apex of the right ventricle, and the specially designed Easy Track®, Guidant® electrode in a distal cardiac vein. The coronary sinus was catheterized using a guiding catheter.

All patients underwent a complete check-up at 6 months, although some required non-programmed examinations. Patients were deemed to have shown a positive CRT response on the basis of a composite clinical variable including no cardiac death or heart transplant and a >10% improvement in the distance covered in the 6-minute walking test. Although this test only correlates moderately well with peak oxygen consumption in patients with moderate or severe heart disease,[14] intrapatient reproducibility in the short term is very good.[15] Previous studies have shown that a minimum variation of 10% is required in order to confirm (99% confidence interval) a real effect of therapy.[14]

Programming the Resynchronization Devices

The resynchronization devices were programmed in DDD stimulation mode in patients with sinus rhythm and in VVIR in those with atrial fibrillation. Attempts were made to ensure a high percentage of biventricular stimulation in these latter patients, either with drugs or through the ablation of the atrioventricular node.

For patients with sinus rhythm, the AV interval was programmed for 140 ms, and the PV interval for 120 ms, in agreement with the results obtained in earlier studies with this kind of patient.[16-18] Biventricular stimulation was synchronous in all patients (VV interval=0).

Statistical Analysis

Qualitative variables are expressed as a number and percentage, whereas quantitative variables are expressed as means ± standard deviation (SD). Qualitative variables were compared using the χ^2 test, and the Student t test (for independent samples) used to compare quantitative variables. Improvement at follow-up was analyzed using the McNemar test (for qualitative variables) and the Student t test for paired data (quantitative variables). Multivariate analysis was performed using stepwise logistic regression. Significance was set at $P<.05$. All data were analyzed using SPSS v10.0 software.

RESULTS

Sixty eight patients were selected for the implantation of a biventricular stimulation device between January 2001 and January 2003. Attempts were made to locate the left ventricular stimulation electrode in the coronary venous system, but this was not possible in 5 patients (7.4%), and in another the possibility of left ventricular stimulation was lost due to diaphragm stimulation or an increase in the capture threshold. A left ventricular stimulating electrode was successfully implanted epicardially in 4 patients.

Of the 64 patients who received CRT, 33 (51.7%) were given a pacemaker providing biventricular stimulation, and 31 (48.8%) received a defibrillator providing the same. One patient died of lung cancer 4 months after receiving the implant and was excluded from the analysis.

Tables 1 and 2 show the baseline characteristics of the 63 patients whose results were analyzed. Mean age was 68.3±8 years; 51 patients (81%) were male. Fifty patients (79.4%) fell into NYHA functional classes III or IV. The mean duration of the QRS interval was 177±25 ms and the mean LVEF recorded by echocardiography was 22.4±6%. Twenty nine patients (46%) had a history of ischemic heart disease (either coronary stenosis of >70% as demonstrated by coronary angiography, or at least one documented heart attack). Twenty one of these (72.4%) had suffered at least one heart attack (anterior localization in 16 patients [55.25%]).

Thirteen patients (20.6%) fell into NYHA functional class II at the time of inclusion. All had an LVEF of <30% and indication for a definitive pacemaker. A resynchronization device was implanted in each to prevent any clinical worsening of their condition that the inherent asynchrony of right ventricular stimulation might cause. Two additional patients had an LVEF of 35% and 40% but fell into NYHA functional class III despite optimized drug treatment.

Eighteen patients (28.6%) had experienced

TABLE 1. **Patients' Baseline Demographic Characteristics and Treatment Provided for Heart Failure Before Cardiac Resynchronization Therapy***

Baseline Characteristics (n=63)	
Age, years	68.3±8
Males, n (%)	51 (81)
NYHA functional class	
II	13 (20.6)
III	42 (66.7)
IV	8 (12.7)
Quality of life score	42.7±21.2
Distance covered in the 6-minute walking test, m	250±141
Heart disease, n (%)	
Non-ischemic	34 (54)
Ischemic	29 (46)
Type of resynchronization device, n (%)	
Pacemaker	32 (50.8)
Defibrillator	31 (49.2)
No clinical arrhythmia	7 (22.6)
Syncope with inducible VT/VF	3 (9.7)
SMVT	18 (58)
Ventricular fibrillation	3 (9.7)
Permanent atrial fibrillation, n (%)	14 (22.2)
PR, ms (n=49)	211±34
QRS, ms	177±25
Treatment, n (%)	
Digoxin	30 (47.6)
ACE inhibitor	55 (87.%)
Diuretics	62 (98.4)
Spironolactone	31 (49.2)
Beta-blockers	21 (33.3)
Amiodarone	24 (38.1)

*VF indicates ventricular fibrillation; ACE inhibitor, inhibitor of angiotensin converting enzyme; NYHA, New York Heart Association; VT, ventricular tachycardia; SMVT, sustained monomorphic ventricular tachycardia.

TABLE 2. **Baseline Echocardiographic Data and Systolic Function (as Determined by Nuclear Techniques)***

Baseline Characteristics (n=63)	
Echocardiographic measurements	
LVEF, %	22.4±6
LVEDD, mm	75.6±9
LVESD, mm	61±12
Degree of MR, n (%)	
0-I	39 (61.9)
II	13 (20.6)
III	10 (15.9)
IV	1 (1.6)
LVEF, % radioventriculography	22.2±10

*LVEDD indicates left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

clinically documented sustained monomorphic ventricular tachycardia (SMVT). Prior SMVT was not significantly associated with having suffered a

documented heart attack (23.5% in patients with no previous heart attack and 35.7% in those who had suffered one; P=.3), nor with age, functional class, the etiology of disease, or the dimensions or systolic function of the left ventricle.

Response at 6 Months Follow-up

Compared to baseline results, the group of 63 patients as a whole showed significant improvement at 6 months in terms of NYHA functional class, quality of life questionnaire score (41±20 compared to 30±18; P<.001), the distance covered in the 6-minute walking test (267±134 m compared to 398±150 m; P<.001), LVEDD (75±9 mm compared to 73±9 mm; P=.001), LVESD (61±12 mm compared to 57±9 mm; P=.007), LVEF (as determined by echocardiography) (23±6% compared to 28±9%; P<.001), and radioventriculography results (23±9% compared to 28±14%; P=.005).

With respect to the composite variable defined above for determining a positive response to CRT after 6 months, 44 patients (69.8%) showed satisfactory results (Table 3). During the follow-up period, no significant differences were seen between patients who responded positively and those who responded negatively with respect to the medication they used.

The patients who responded positively to CRT showed a significant improvement in their functional class, quality of life score (13±17 points), 6-minute walking test results (170±125 m) and LVEF (6±8%), and showed significant reductions in their LVEDD (3±5 mm) and LVESD (5±8 mm).

Nineteen patients (30.2%) experienced no clinical improvement in terms of the composite CRT response variable. Of these, 4 (6.3%) died of heart disease and 3 (4.8%) required a transplant during the 6 month follow-up period. Of the 12 remaining, no significant changes were seen in functional class, quality of life questionnaire score, LVEF, LVEDD, or LVESD (Table 3).

Predictors of Response to Treatment

The results were examined to determine which baseline clinical, electrocardiographic or echocardiographic variables were associated with CRT response (Table 4).

A lack of improvement in the mid term was associated with ischemic heart disease, the existence of clinically documented SMVT prior to implantation, and moderate (at least) mitral regurgitation (grades II-IV [scale=0-IV]). No other variables were associated with a lack of response.

These 3 predictors were included in regression analysis and showed independent predictive power of an absence of improvement: SMVT (OR=8.7; 95% CI, 1.8-41.3; P=.007), moderate (at least) mitral regurgitation (OR=8.03; 95% CI, 1.7-37.1; P=.008), and ischemic heart disease (OR=4.8; 95% CI, 1.2-18.3; P=.023).

If the patients who died or who received a transplant are excluded, and a subanalysis performed using only the data of those who covered >110% their original distance in the 6-minute walking test at 6 months (n=56), only 2 variables appear as predictors of an absence of improvement: prior SMVT (OR=8.8; 95% CI, 1.7-45.8; P=.009) and ischemic heart disease (OR=9.6; 95% CI, 1.6-59.5; P=.015).

TABLE 3. **Change in Patient Variables**

Variables	No Improvement (n=12)			Improvement (n=44)		
	Baseline	6 Months	*P*	Baseline	6 Months	*P*
NYHA functional class, n (%)						
I	0	0	.5	0	15 (34.1)	<.001
II	3 (25)	4 (33.3)	.5	9 (20.5)	22 (50)	<.001
III	6 (50)	6 (50)	.5	32 (72.7)	7 (15.9) <	.001
IV	3 (25)	2 (16.7)	.5	3 (6.8)	0	<.001
Quality of life score	36±19	38±14	.8	42±20	29±18	<.001
Distance covered in the 6-minute walking test, m	251±189	208±180	.04	264±125	434±118	<.001
Echocardiogram						
LVEF, %	24±5	25±6	.8	23±6	29±9	<.001
LVEDD, mm	75±9	74±8	.4	75±9	73±9	.002
LVESD, mm	59±12	58±9	.95	62±12	57±10	.002
Radioventriculography						
LVEF, %	16±7	18±9	.2	24±9	29±12	.007

*LVEDD indicates left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

TABLE 4. **Baseline Data With Respect to Composite Clinical Variable**

Variables	No Improvement (n=19)	Improvement (n=44)	P
Age, years	68.3±6	68±8	.99
Masculine sex, n (%)	16 (84.2)	35 (79.5)	.67
Ischemic heart disease, n (%)	13 (68.4)	16 (36.4)	.019
Atrial fibrillation, n (%)	5 (26.3)	9 (20.5)	.61
PR, ms	221±34	207±34	.2
QRS, ms	180±27	176±24	.6
Defibrillator	11 (57.9)	20 (45.5)	.4
Clinical SMVT prior to implantation, n (%)	10 (52.6)	8 (18.6)	.007
NYHA functional class			
II	4 (21.1)	9 (20.5)	
III	10 (52.6)	32 (72.7)	
IV	5 (26.3)	3 (6.8)	.1
Quality of life score	41.5±20	42±20	.5
Distance covered in the 6-minute walking test, m	215±175	264±125	.3
Echocardiogram			
LVEF, %	22.4±6	23±6	.97
LVEDD, mm	78±10	75±9	.18
LVESD, mm	62±13	62±12	.5
MR≥II/IV, n (%)	11 (57.9)	13 (29.5)	.033
Radioventriculography			
LVEF, %	24.8±14	24±9	.4

*LVEDD indicates left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; MR, mitral regurgitation; SMVT, sustained monomorphic ventricular tachycardia.

DISCUSSION

This study reports the prospective results for our first 63 patients treated with CRT, and they agree with those of earlier studies with respect to the number of patients who responded to resynchronization therapy (69.8%) for heart failure with intraventricular conduction disorders.[5,6]

The main novelty of this work is that it identifies pre-implantation clinical and echocardiographic variables that help identify patients with less chance of clinically benefiting from resynchronization therapy. Improvement was defined in terms of a composite variable that takes into account those patients who are lost to follow-up through cardiac death or heart transplant (these patients experience a change in their clinical status far more important than a change in functional class, quality of life or tolerance to exercise). The available literature does not include death or heart transplant as a lack of response to CRT, variables that studies on the response to pharmacological treatment for heart failure have included.[19] Variation in quality of life scores (which include psychosocial elements) is here understood to be more subjective and likely to be greater: it was therefore not included in the composite variable. Ischemic heart disease, the existence of documented SMVT at some point prior to implantation, and at least moderate mitral regurgitation were found to be independent predictors of a lack of response to CRT therapy.

Among those patients who improved clinically in terms of the composite variable at 6 months, the degree of improvement was greater than that reported in earlier studies comparing the effects of resynchronization and placebo therapy, and similar to that obtained with drugs widely prescribed in the treatment of heart failure. This may be because the groups of patients who truly improved were not analyzed independently in these other studies. Furthermore, as in the subanalysis of the MIRACLE[20] and MUSTIC[21] trials, it is here shown that CRT leads to inverse remodeling (the LVEDD and LVESD of the left ventricle become smaller and its systolic function increases). The data for the present patients show that this remodeling is significant in patients who improve from a clinical point of view. This suggests that, to a large degree, the improvement provided by resynchronization therapy could be due to the induction of inverse remodeling in the mid term. The subanalyses of the MIRACLE and MUSTIC trials mentioned above show that ischemic patients experience an improvement in their LVEF and a reduction in their LVEDD and LVESD with CRT at 6-9 months, although significantly less than that experienced by non-ischemic patients.

The patients who did not respond to CRT showed a notable worsening in the distance they covered in the 6-minute walking test, in functional class, in their quality of life questionnaire scores, in LVEDD and LVESD, and in left ventricular systolic function.

Together, these results validate the composite clinical variable used to define those patients who improve with CRT.

The study performed by Reuter et al[22] is one of the few in which patients have been classified on the basis of their CRT response (as determined by the same composite clinical variable); the results of this work also identify ischemic heart disease as a predictor of a lack of response. This might be due to akinetic or dyskinetic areas—areas of fibrosis with no viable myocytes—that are impossible to resynchronize despite stimulation at the point of greatest electrical delay.

The present results are also supported by those of Gasparini et al.[23] These authors show that in patients with ischemic heart disease, CRT does lead to an improvement, but not so great as that achieved in non-ischemic patients.

Unlike the present study, which showed mitral regurgitation (at least moderate) to be a significant predictor of a lack of improvement, Reuter et al[22] found no such association.

It may be that clinical SMVT predicted a failure to improve with CRT in the present patients since they had a greater probability of dying because of arrhythmia. However, all of them had a defibrillator, and when those who died or received a transplant were removed from the analysis, SMVT continued to be a predictor of a failure to improve.

Limitations

The main limitation of this work is the reduced sample size; this is why the confidence intervals for the relationships between the predictors and the likelihood of a lack of response are so wide. Similarly, this reduced sample size diminishes the statistical power to identify other possible predictors of a lack of response. However, this approximation in the identification of variables that might negatively influence the response to CRT—a laborious and costly form of treatment—is important. Further studies with larger samples should minimize these limitations.

The aim of this work was to identify predictors of a lack of response that can be easily recorded by the clinician, not the identification of special echocardiographic predictors. The echocardiographic measurements made were therefore not directed towards the evaluation of intraventricular or interventricular asynchrony, but focused on LVEDD and LVESD, left ventricular systolic function, and the degree of mitral regurgitation. These were then correlated with the clinical course of the patients. Since the goal was to analyze the influence of different variables on the response to CRT before implantation of the resynchronization device, factors such as the effect of the position of the left ventricular electrode

were not analyzed.

The large number of patients with ventricular arrhythmias in our sample could be a selection bias; for many patients, the indication of CRT was based on the recommendations of the arrhythmia department. However, the percentage of patients that did not respond is similar to that seen in other studies.

CONCLUSIONS

Resynchronization therapy for moderate-severe heart failure with a wide QRS complex caused by left bundle branch block leads to an improvement in nearly 70% of patients. The remaining 30%, however, do not improve or their condition worsens. Those who do respond do so clearly and show substantial clinical improvement. Ischemic heart disease, clinically documented prior SMVT, and at least moderate mitral regurgitation are pre-implantation factors that predict a negative response to CRT. This should be borne in mind before embarking on such therapy.

REFERENCES

1. Farwell D, Patel NR, May A, Ralph S, Sulke AN. How many people with heart failure are appropriate for biventricular resynchronization? Eur Heart J 2000;21:1246-50.
2. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation 1997;95:2660-7.
3. García-Bolao I, Macías A, Alegría E, Berenguel A, Gavira JJ, Azcárate P, et al. Tratamiento de la insuficiencia cardíaca avanzada mediante estimulación biventricular. Experiencia inicial en una serie de 22 casos consecutivos. Rev Esp Cardiol 2003;56:245-52.
4. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, et al. Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873-80.
5. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. N Engl J Med 2002;346:1845-53.
6. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, et al. Pacing Therapies in Congestive Heart Failure (PATH-CHF) Study Group. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 2002;39:2026-33.
7. Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 2002;40:111-8.
8. Bradley DJ, Bradley EA, Baughman KL, Berger RD, Calkins H, Goodman SN, et al. Cardiac resynchronization and death from progressive heart failure. A meta-analysis of randomized controlled trials. JAMA 2003;289:730-40.

9. Alonso C, Leclercq C, Victor F, Mansour H, de Place C, Pavin D, et al. Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure. Am J Cardiol 1999;84:1417-21.
10. Sogaard P, Egeblad H, Kim WY, Jensen HK, Pedersen AK, Kristensen BO, et al. Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. J Am Coll Cardiol 2002;40:723-30.
11. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985;132:919-23.
12. Rector RS, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure. II. Content, reliability, and validity of a new measure: the Minnesota Living with Heart Failure Questionnaire. Heart Fail 1987;3:198-209.
13. Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG, et al. Color Doppler assessment of mitral regurgitation with orthogonal planes. Circulation 1987;75:175-83.
14. Zugck C, Kruger C, Durr S, Gerber SH, Haunstetter A, Hornig K, et al. Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? Eur Heart J 2000;21:540-9.
15. Opasich C, Pinna GD, Mazza A, Febo O, Riccardi PG, Capomolla S, et al. Six-minute walking performance in patients with moderate-to-severe heart failure; is it a useful indicator in clinical practice? Eur Heart J 2001;22:488-96.
16. Delurgio D, Leon A, Abraham W, Kocovic D, Messenger J, Hayes DL. Echo-guided AV optimization for cardiac resynchronization does not change over time [abstract]. Pacing Clin Electrophisiol 2001;24:651.
17. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, 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.
18. Sogaard P, Egeblad H, Pedersen AK, Kim WY, Kristensen B, Hansen PS, et al. Sequential versus simultaneous biventricular resynchronization for severe heart failure. Circulation 2002;106: 2078-84.
19. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe heart failure: Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429-35.
20. St. John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, et al. Effect of cardiac resynchronization on left ventricular size and function in chronic heart failure. Circulation 2003;107:1985-90.
21. Duncan A, Wait D, Gibson D, Daubert JC. Left ventricular remodeling and hemodynamic effects of multisite biventricular pacing in patients with left ventricular systolic dysfunction and activation disturbances in sinus rhythm: sub-study of the MUSTIC (Multisite Stimulation in Cardiomyopathies) trial. Eur Heart J 2003;24:430-41.
22. Reuter S, Garrigue S, Barold SS, Jais P, Hocini M, Haissaguerre M, et al. Comparison of characteristics in responders versus nonresponders with biventricular pacing for drug-resistant congestive heart failure. Am J Cardiol 2002;89:346-50.
23. Gasparini M, Mantica M, Galimberti P, Genovese L, Pini D, Faletra F, et al. Is the outcome of cardiac resynchronization therapy related to the underlying etiology? PACE 2003;26:175-80.