Cardiac Resynchronization Therapy Acutely Improves Diastolic Function

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Background: **Invasive studies have shown that cardiac resynchronization therapy (CRT) acutely improves left ventricular (LV) systolic performance and lowers filling pressures in a majority of patients with medically-refractory severe heart failure. Measurements included LV volume, ejection fraction, PWD early (E-wave) and atrial (A-wave) velocities, diastolic filling time (DFT), and DTI early diastolic mitral annular velocity (Em) at the lateral and septal annulus; PWD mitral E-wave/Em and E/FP were calculated to estimate LV filling pressures.**

Results: **Immediately after CRT, LV volumes decreased and LVEF increased significantly. PWD mitral E-wave velocity decreased and E-wave duration and DFT increased significantly; mitral E/FP ratio also decreased significantly, consistent with a decrease in LV filling pressure. Patients with a pre-CRT mitral E/A ratio >1 (n = 20), demonstrated improvements in LV diastolic filling and lower filling pressures whereas those with an E/A ratio ≤1 (n = 21) did not show significant changes in diastolic indices.**

Conclusions: **The acute effects of CRT include echocardiographic evidence of reduced LV volumes and increased LVEF with improved diastolic filling and lower filling pressures; LV relaxation is not significantly altered. The benefits in diastolic function are dependent on the PWD-determined LV filling characteristics prior to CRT.** (J Am Soc Echocardiogr 2005; 18:216-20.)

Cardiac resynchronization therapy (CRT) is an adjunctive treatment for patients with medically refractory heart failure, severe left ventricular (LV) systolic dysfunction, and an interventricular conduction delay. Prior invasive studies have shown that CRT acutely improves systolic performance (ie, cardiac output, peak +dP/dt, ejection fraction [EF]) and reduces pulmonary capillary wedge pressures but LV relaxation is unchanged.[1-8] The acute effects of CRT on measurements of LV function, determined by 2-dimensional (2D) and Doppler echocardiography including Doppler tissue imaging (DTI) and color M-mode flow propagation (FP) velocities, have not been well characterized.[9,10] This study was conducted to determine whether acute improvements in LV systolic function are accompanied by complimentary changes in echocardiographic measurements of LV diastolic function. The hypothesis was that immediately after CRT the reduction in LV volumes and improved systolic function results in improved LV diastolic function and lower filling pressures.

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METHODS

Patients scheduled to receive implantation of a CRT device were asked to participate in the study. Inclusion criteria were a history of stable, medically refractory heart failure symptoms despite optimized pharmacologic therapy for heart failure for at least 3 months; in sinus rhythm; QRS duration longer than 130 milliseconds; LV dilatation (2D echocardiographically determined LV diastolic diameter > 6.0 cm); and LV EF less than 35%. Exclusion criteria included prior atrioventricular sequential dual-chamber pacemaker, medically refractory atrial fibrillation, or symptomatic sinus node dysfunction. Clinical status (New York Heart Association [NYHA] classification) and quality-of-life score were determined using the Minnesota Living with Heart Failure Questionnaire. The PR interval and QRS duration were measured from the 12-lead electrocardiogram before CRT. The protocol was approved by the human studies committee.

CRT device implantation was performed by a transvenous approach with LV lead placement targeted to the midlateral wall, if an appropriate coronary sinus branch was present. Two-dimensional Doppler echocardiography was performed within 24 hours after implant, before

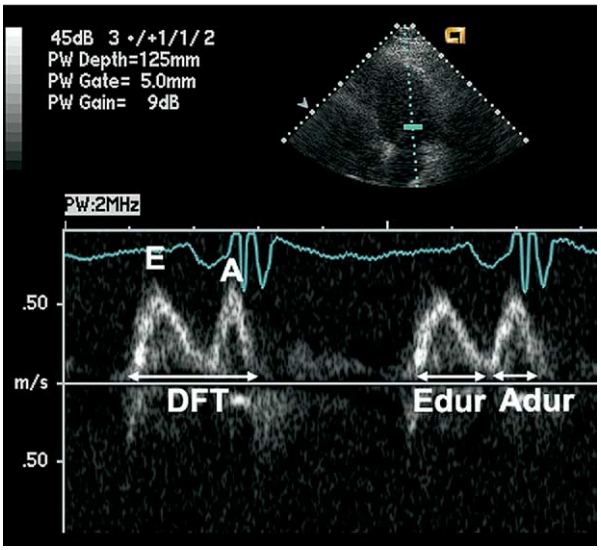

Figure 1 Pulsed wave Doppler mitral inflow velocity and measurements of left ventricular filling. *A*, Atrial filling velocity; *A dur*, atrial filling duration; *DFT*, diastolic filling time; *E*, early filling velocity; *E dur*, early filling duration.

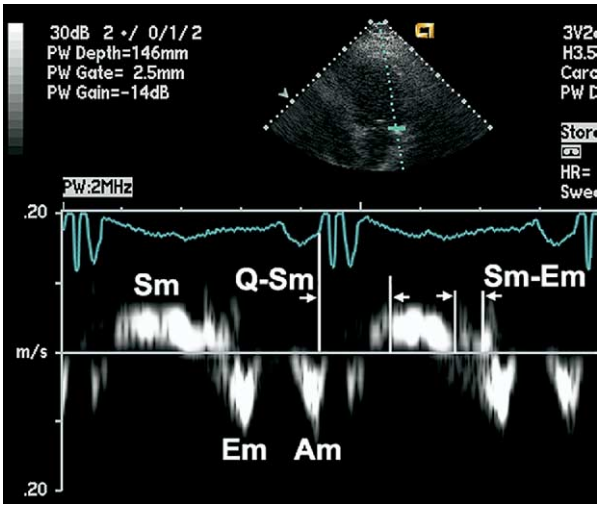

Figure 2 Doppler tissue imaging at lateral mitral annulus. Q wave to onset of systolic mitral annular velocity (*Sm*) represents electromechanical delay to onset of contraction. Time interval from end of Sm to onset of early diastolic mitral annular velocity (*Em*) is time from end of contraction to onset of relaxation. *Am*, Late diastolic mitral annular velocity at time of atrial contraction.

initiation of biventricular pacing. The CRT device was then programmed to atrial synchronous ventricular pacing mode and the atrioventricular delay (AVD) was programmed to 120 milliseconds or an AVD that was associated with the maximal increase in the continuous wave Doppler-derived aortic time velocity integral. After 10 minutes of biventricular pacing the echocardiogram was repeated.

Echocardiography

Two-dimensional quantitative measurements included LV volumes at end diastole and end systole from the apical 4- and 2-chamber views (method of disks) and calculation of the LV EF by the biplane method.[11] Pulsed-wave Doppler (PWD)-derived transmitral velocities were obtained at the mitral leaflet tips according to the American Society of Echocardiography guidelines.[12] Measurements (Figure 1) included the early diastolic (E) wave and atrial (A) wave velocities, the E/A ratio, the E wave and A wave duration, and the E wave deceleration time (DT). Diastolic filling time (DFT) was determined as the time interval from the onset of mitral valve opening to closure. Isovolumic relaxation time was measured from the closure of the aortic valve to opening of the mitral valve.

DTI was performed in the apical 4-chamber view by placement of a 3-mm sample volume at the lateral and septal mitral annulus. Measurements of the systolic (Sm), early diastolic (Em), and late diastolic (Am) velocities were obtained at each annular site (Figure 2). The time intervals from the Q wave to onset of Sm (Q-Sm) and from the end of Sm to onset of Em (Sm-Em) were determined. The ratio of PWD-derived mitral E wave velocity to Em (E/Em) was calculated to estimate LV filling pressure.[13,14] Color M-mode FP velocities were obtained in the apical 4-chamber view by positioning an M-mode cursor within the color flow profile of mitral inflow (Figure 3). The ratio of mitral E wave/FP velocity was calculated for an additional estimate of LV filling pressure.[15] All echocardiographic measurements were measured by an experienced echocardiographer and averaged over 3 to 5 consecutive cardiac cycles.

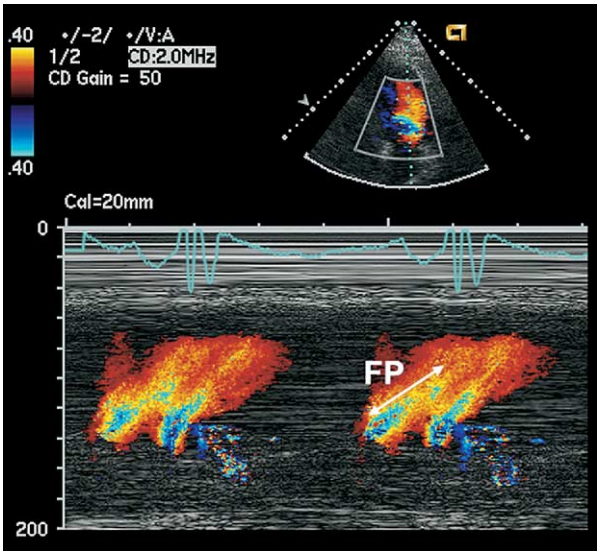

Figure 3 Color mode flow propagation (*FP*) velocity and measurement of slope of color inflow.

Statistical Analysis

Continuous variables are expressed as mean ± 1 SD. Comparisons of the echocardiographic variables of patients before and after CRT were performed using the appropriate Student *t* test (SPSS, Version 11.0, SPSS Inc, Chicago, Ill). Statistical significance was determined as a *P* value of <.05.

RESULTS

The study population included 41 patients (age 58 ± 11 years, 65% men) with primarily nonischemic LV systolic dysfunction (71%). Pharmacologic therapy included angiotensin-converting enzyme inhibitors (100%), β-blockers (91%), digoxin (71%), loop diuretics (88%), and potassium-sparing agents (62%). The NYHA classification score (3.1 ± 0.5) and Minnesota Living with Heart Failure scores (73 ± 17) were indicative of significant functional impairment before CRT. The 12-lead electrocardiographic QRS duration was 180 ± 20 milliseconds and PR interval was 200 ± 20 milliseconds. The LV pacing lead was placed in a midlateral or posterior-lateral vein in the majority of patients (84%) and the programmed AVD interval was 119 ± 25 milliseconds.

Heart rate was unchanged after CRT (75 ± 12 vs 74 ± 12, $P = .71$).

As shown in Table 1, LV end-diastolic and end-systolic volumes decreased, and LV EF increased significantly after CRT (all $P < .001$). PWD transmitral E wave velocity decreased significantly ($P = .009$); E wave duration and DFT increased significantly ($P = .003$ and .001, respectively) and DT showed a trend to increase ($P = .08$). PWD-derived A wave indices, E/A ratio, and isovolumic relaxation time were unchanged.

The DTI-derived Q-Sm time intervals at the lateral and septal annulus decreased significantly after CRT ($P = .003$ and $< .001$, respectively); Sm-Em time interval at the septal annulus decreased significantly ($P = .004$). DTI-derived Em, Am velocities, and the mitral E wave/DTI-derived Em ratio were unchanged. The mitral E wave/color M-mode FP velocity ratio decreased significantly ($P = .02$) without significant changes in FP velocity.

Acute Effects and the Pre-CRT Mitral E/A Ratio

To determine whether improvements in diastolic function were related to the LV filling pattern before CRT, patients were grouped according to the baseline PWD-derived mitral E/A ratio to ≤ 1 (n = 21) or >1 (n = 20). There were no significant differences between the groups in age, NYHA classification, heart failure score, heart rate, QRS duration, LV pacing site, or programmed AVD. An ischemic cause of heart failure was more often present in those with a mitral E/A > 1.

Table 1 Two-dimensional-pulsed/Doppler tissue imaging and color M-mode measurements (n = 41)

Variable	Pre-CRT	Post-CRT
LV end-diastolic volume, mL	225 ± 89	213 ± 85†
LV end-systolic volume, mL	171 ± 76	151 ± 72†
LV ejection fraction, %	25 ± 6	31 ± 8†
E wave velocity, cm/s	83 ± 33	78 ± 29*
E wave duration, ms	177 ± 50	202 ± 60*
A wave velocity, cm/s	65 ± 25	65 ± 27
A wave duration, ms	135 ± 36	140 ± 31
E/A ratio	1.6 ± 1.1	1.5 ± 1.1
Diastolic filling time, ms	354 ± 93	397 ± 112*
Deceleration time, ms	177 ± 44	189 ± 49
Isovolumic relaxation time, ms	107 ± 35	110 ± 29
Em lateral, cm/s	9.6 ± 2.6	9.0 ± 2.9
Am lateral, cm/s	8.5 ± 2.2	8.7 ± 2.8
Q-Sm lateral, ms	212 ± 40	190 ± 48*
Sm-Em lateral, ms	130 ± 45	124 ± 41
Mitral E/Em lateral	8.9 ± 4.0	9.2 ± 4.0
Em septal, cm/s	5.9 ± 1.4	5.9 ± 1.8
Am septal, cm/s	7.4 ± 2.5	7.5 ± 2.3
Q-Sm septal, ms	197 ± 43	168 ± 33†
Sm-Em septal, ms	173 ± 44	148 ± 47*
Mitral E/Em septal	14.9 ± 7.1	14.2 ± 6.8
Flow propagation, cm/s	37 ± 9	38 ± 8
Mitral E/FP	2.3 ± 0.8	2.1 ± 0.6‡

Variables expressed as mean ± SD.
Am, DTI late diastolic mitral annular velocity; CRT, cardiac resynchronization therapy; E/A, pulsed wave Doppler early/late filling velocity ratio; Em, DTI early diastolic mitral annular velocity; FP, flow propagation; LV, left ventricular; Q, electrocardiographic onset of ventricular depolarization.
*$P < .01$.
†$P < .001$.
‡$P < .05$ vs Pre-CRT.

As shown in Table 2, the pre-CRT LV volumes and LV EF were similar between groups. Immediately after CRT, LV volumes decreased and LV EF increased significantly in both groups. All of the pre-CRT PWD-derived indices, except E wave duration and DFT, differed significantly (all $P < .05$) between groups. In addition, the mitral E/Em, E/FP, and FP velocities were significantly higher (all $P < .01$) in patients with mitral E/A > 1. Immediately after CRT, patients with an E/A ratio ≤ 1 demonstrated no significant changes in PWD-derived indices of diastolic function. In contrast, patients with a mitral E/A ratio > 1 demonstrated significant decreases in E wave velocity ($P < .001$), increases in E wave duration and DFT (both $P < .01$), and DT ($P < .05$) immediately after CRT.

DTI and FP velocities were not significantly different between groups before CRT. Immediately after CRT, patients with a mitral E/A ratio ≤ 1 demonstrated significant decreases in the Q-Sm and Sm-Em time intervals at the septal annulus ($P < .001$ and .03, respectively). Patients with an E/A ratio > 1 also

Table 2 Two-dimensional pulsed-wave/Doppler tissue imaging and color M-mode measurements by pulsed-wave Doppler mitral E/A ratio prior to resynchronization therapy

	E/A ≤ 1.0 (n = 21)		E/A > 1.0 (n = 20)	
Variable	**Pre-CRT**	**Post-CRT**	**Pre-CRT**	**Post-CRT**
End-diastolic volume, mL	205 ± 93	195 ± 90‡	245 ± 82	230 ± 77‡
End-systolic volume, mL	155 ± 81	139 ± 75†	188 ± 69	164 ± 67†
LV ejection fraction, %	26 ± 5	31 ± 7†	24 ± 6	30 ± 9†
E wave velocity, cm/s	60 ± 24	60 ± 20	106 ± 23	96 ± 24†
E wave duration, ms	165 ± 56	186 ± 64	190 ± 42	219 ± 52*
A wave velocity, cm/s	79 ± 19	78 ± 23	50 ± 21	51 ± 24
A wave duration, ms	148 ± 28	149 ± 23	122 ± 40	131 ± 37
E/A ratio	0.8 ± 0.2	0.8 ± 0.2	2.4 ± 0.9	2.3 ± 1.1
Deceleration time, ms	194 ± 46	202 ± 54	158 ± 33	176 ± 42‡
Diastolic filling time, ms	343 ± 80	379 ± 115	365 ± 105	417 ± 109*
IVRT, ms	127 ± 29	126 ± 26	88 ± 29	94 ± 24
Em lateral, cm/s	8.9 ± 2.5	8.9 ± 3.0	10.3 ± 2.6	9.1 ± 2.8
Am lateral, cm/s	9.8 ± 1.9	10.0 ± 2.7	7.1 ± 1.6	7.3 ± 2.2
Q-Sm lateral, ms	206 ± 46	195 ± 55	218 ± 33	184 ± 44*
Sm-Em lateral, ms	141 ± 52	139 ± 47	118 ± 34	110 ± 29
E/Em lateral	6.8 ± 2.5	7.1 ± 2.6	11.1 ± 4.2	11.5 ± 3.9
Em septal, cm/s	6.2 ± 1.6	5.8 ± 1.6	5.6 ± 1.2	6.2 ± 2.0
Am septal, cm/s	8.6 ± 1.9	8.5 ± 2.0	6.1 ± 2.5	6.5 ± 2.2
Q-Sm septal, ms	207 ± 43	173 ± 32†	185 ± 40	163 ± 33*
Sm-Em septal, ms	183 ± 36	162 ± 42‡	163 ± 51	135 ± 49‡
E/Em septal	10.0 ± 4.5	10.6 ± 3.8	20.1 ± 5.5	17.5 ± 7.4‡
Flow propagation, cm/s	33 ± 10	34 ± 7	42 ± 6	43 ± 7
E/Flow propagation	1.9 ± 0.8	1.8 ± 0.5	2.6 ± 0.6	2.3 ± 0.6*

Variables expressed as mean ± SD.
CRT, Cardiac resynchronization therapy; *LV,* left ventricular; *IVRT,* isovolumic relaxation time.
*$P < .01$.
†$P < .001$.
‡$P < .05$ vs Pre-CRT.

demonstrated significant decreases in both DTI-derived Q-Sm lateral and Q-Sm septal time intervals ($P = .002$ and .01, respectively); Sm-Em relaxation time at the septal annulus also decreased ($P = .05$). Neither the DTI nor FP velocities changed significantly after CRT in either group. However, both the mitral E wave/Em septal and E/FP ratio decreased significantly in the patients with a pre-CRT mitral E/A > 1 ($P = .03$ and .01, respectively).

DISCUSSION

This investigation revealed that CRT acutely decreases LV volumes and improves LV EF, decreases the left atrial-LV pressure gradient (ie, mitral E wave velocity), and increases LV DFT, primarily during early diastole (ie, E wave duration). However, there are no significant changes in noninvasive indices of LV relaxation (ie, PWD-derived isovolumic relaxation time). These results suggest the acute improvements in LV diastolic filling after CRT are caused by decreases in LV volumes.

Importantly, the results of this study demonstrate that acute effects of CRT on LV diastolic function appear to differ with regard to LV filling characteristics before CRT. Significant changes in PWD-derived measurements of LV diastolic function after CRT were only observed for patients with a mitral E/A ratio > 1.0. This group demonstrated significant decreases in E wave velocity and improvement in indices of diastolic filling (ie, E wave duration, DFT, and DT). These patients likely had elevated filling pressures as evidenced by a pseudonormalized or restrictive LV filling pattern.[16] Conversely, patients with a pre-CRT mitral E/A ≤ 1.0 did not have changes in PWD-derived measurements of LV diastolic function. It could be postulated that these patients have relatively optimal LV filling characteristics and normal filling pressures. Therefore, CRT may not provide demonstrable benefits in diastolic function by conventional 2D Doppler echocardiographic measurements despite significant reduction in LV volumes and improvements in LV EF.

The use of DTI and color M-mode FP velocities to assess LV diastolic function, combined with 2D and PWD-derived transmitral flow indices, provided additional insight regarding the acute effects of CRT on systolic and diastolic function. DTI measurements of the time to onset of contrac-

tion (Q-Sm) at the lateral and septal annulus improved after CRT, as previously reported by others.[10] There were no significant changes in LV relaxation when determined by DTI Em or FP velocities. The Sm-Em time interval at the septal annulus decreased immediately after CRT and suggests the timing of onset of septal relaxation improves, regardless of LV filling characteristics. These findings differ from a recent study and may be a result of the difference in methods of acquisition of DTI velocities.[10] The current study also used the E/Em septal and E/FP velocity ratios to confirm that LV filling pressures decrease in patients with pseudonormalized or restrictive filling, but were unchanged in patients with an E/A ratio $\leq$ 1.

Limitations

Invasive measurements of LV systolic and diastolic function were not performed in this study and, therefore, echocardiographic measurements are used as surrogates of invasive determinants of LV diastolic function. However, the results are consistent with prior invasive studies that have shown CRT acutely increases LV systolic performance and decreases filling pressure, without changes in LV relaxation.[1-8] The study design was limited to determine the acute effects of CRT on echocardiographic measurements of LV diastolic function. Whether the findings in this investigation can be used to determine long-term response after CRT and clinical outcomes requires further study.

Conclusions

The acute effects of CRT can be characterized by echocardiographic evidence of reduction in LV volumes and increased LV EF. Improvements in diastolic filling and lower filling pressures are observed and LV relaxation is unchanged, although the timing of ventricular septal relaxation shortens. The acute effects of CRT on LV diastolic function are also dependent on the PWD-determined filling characteristics before device implant.

REFERENCES

1. Cazeau S, Ritter P, Lazarus A, Gras D, Backdach H, Mundler O, et al. Multisite pacing for end stage heart failure: early experience. Pacing Clin Electrophysiol 1996;19:1748-57.
2. Blanc J, Etienne Y, Gilard M, Mansourati J, Munier S, Boschat J, 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.
3. Leclercq C, Cazeau S, Le Breton H, Ritter P, Mabo P, Gras D, et al. Acute hemodynamic effects of biventricular pacing in patients with end-stage heart failure. J Am Coll Cardiol 1998; 32:1825-31.
4. Kass DA, Chen C, Curry C, Talbot M, Berger R, Fetics B, et al. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. Circulation 1999;99:1567-73.
5. 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.
6. Kerwin WF, Botvinick EH, O'Connell JW, Merrick SH, DeMarco T, Chatterjee K, et al. Ventricular contraction abnormalities in dilated cardiomyopathy: effect of biventricular pacing. J Am Coll Cardiol 2000;35:1221-7.
7. Nelson GS, Berger RD, Fetics BJ, Talbot M, Hare JM, Kass DA, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle branch block. Circulation 2000;102:3053-9.
8. Perego GB, Chainca R, Facchini M, Frattola A, Balla E, Zucchi S, et al. Simultaneous vs sequential biventricular pacing in dilated cardiomyopathy: an acute hemodynamic study. Eur J Heart Fail 2003;5:305-13.
9. Breithardt OA, Stellbrink C, Franke A, Balta O, Diem BH, Bakker P, et al. Acute effects of cardiac resynchronization therapy on left ventricular Doppler indices in patients with congestive heart failure. Am Heart J 2002;143:34-44.
10. Yu CM, Lin H, Fung WH, Zhang Q, Kong SL, Sanderson JL. Comparison of acute changes in left ventricular volume, systolic and diastolic functions, and intraventricular synchronicity after biventricular and right ventricular pacing for heart failure. Am Heart J 2003;145:G1-7.
11. Schiller NB, Shah PM, Crawford M, De Maria A, Devereux R, Feigenbaum H, et al. Recommendations for quantification of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358-67.
12. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler quantification task force of the nomenclature and standards committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002;15:167-84.
13. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a non-invasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527-33.
14. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a simultaneous Doppler-catheterization study. Circulation 2000;102:1788-94.
15. Garcia MJ, Ares MA, Asher C, Rodriguez L, Vandervoort P, Thomas JD. An index of early left ventricular filling that combined with pulsed Doppler peak E velocity may estimate capillary wedge pressure. J Am Coll Cardiol 1997;29: 448-54.
16. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic application for the study of diastolic function. J Am Coll Cardiol 1998;32:865-75.