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Clinical and Procedural Characteristics of Acute Hemodynamic Responders Undergoing Triple-Site Ventricular Pacing for Advanced Heart Failure

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Abstract

The advantages of triple-site ventricular pacing (Tri-V) compared to conventional bi-ventricular site pacing (Bi-V)-have been reported. We sought to identify the predictors of acute hemodynamic Tri-V responders. Acute hemodynamic studies were performed in 32 patients with advanced heart failure during a Tri-V implantation. After the right ventricular (RV) and left ventricular (LV) leads were implanted for a conventional Bi-V system, an additional pacing lead was implanted in the RV outflow tract for Tri-V. The left ventricular $+dP/dt_{Max}$ and tau were measured during AAI, Bi-V and Tri-V pacing. A Tri-V responder was defined as a patient whose percent increase in the $+dP/dt_{Max}$ during Tri-V was >10% compared to that during Bi-V. The baseline clinical variables and RV outflow tract lead location were analyzed to identify the characteristics of Tri-V responders. Ten (31%) patients were classified as Tri-V responders. The LV end-diastolic volume was greater (246±48 vs. 173±53 [ml], $p<0.01$) and RV outflow tract lead was implanted at a higher outflow tract portion ($p<0.05$) in Tri-V responders. A multivariate analysis revealed that only the baseline LV end-diastolic volume (per 50ml greater) predicted the Tri-V responders (OR=2.87; 95% CI=1.03-8.00, $p<0.05$). The area under the receiver-operating characteristic curve for the LV end-diastolic volume was 0.84 ($p<0.01$), and an LV end-diastolic volume >212 ml had a sensitivity of 80% and specificity of 77% to distinguish Tri-V responders. In conclusion, Tri-V provides greater hemodynamic effect for patients with a larger LV end-diastolic volume due to its resynchronization effects on the LV anterior wall.

Keywords: Cardiac resynchronization therapy; hemodynamic study; responders; triple-site ventricular pacing.

Cardiac resynchronization therapy by means of bi-ventricular pacing (Bi-V) is becoming an adjunctive non-pharmacologic therapy for patients with drug-refractory heart failure.[1] However, despite patients being selected on the basis of the QRS duration and echocardiographic parameters, 20-30% of the patients failed to improve, especially in patients with New York Heart Association functional class IV.[2,3] To overcome the inconsistent effects of Bi-V, multi-site pacing techniques have recently been introduced to stimulate a wider area of the myocardium,[4,5] thus enabling a simultaneous left ventricular (LV) contraction. We previously reported the novel technique of ‘‘triple-site ventricular pacing’’ (Tri-V) with a “double-right and single-left” method.[6] However, it is unclear whether or not the Tri-V is more effective than Bi-V in all cardiac resynchronization therapy recipients. The purpose of this study was to clarify these points from acute hemodynamic studies.

Methods

Patients with New York Heart Association functional class III or IV heart failure despite a maximal pharmacologic therapy, LV ejection fraction of <35%, and QRS interval of >120 ms without right bundle branch block were scheduled to receive cardiac resynchronization therapy in our institution. The patients who had atrial fibrillation (n=6), underwent an upgrade from RV apical pacing (n=7), were excluded from this study. Finally, 32 patients who provided written informed consent were enrolled in this study and received Tri-V as the *de novo* cardiac resynchronization therapy. Ethical approval was obtained from the Institutional Ethics Review Committee of our hospital.

The RV and LV leads (stylet-driven leads=11; over-the-wire leads=21) were implanted in the RV apex and anterolateral, posterolateral or lateral cardiac vein, respectively, for a conventional Bi-V system via the standard transvenous approach.[7] Furthermore, for Tri-V, an

additional pacing lead was implanted in the RV outflow tract (Figure 1A). This lead was positioned on the RV septum under fluoroscopic guidance in the left anterior oblique projection[8] to pace the opposite side of the basal/anteroseptal wall of the left ventricle to stimulate the left anterior bundle branch area.[9]

A Y-adaptor (5866-38M, Medtronic Inc.) was connected to the RV channel of the cardiac resynchronization therapy pacemaker (Insync 8040, Insync 8042, Medtronic Inc., Minneapolis, MN) and LV channel of the cardiac resynchronization therapy defibrillator (Insync III Marquis, Concerto, Concerto AT, Medtronic Inc.; and Epic HF, Atlas+HF, St. Jude Medical, Sylmar, CA). The Y-adaptor bifurcated the anode port for the RV apical lead and cathode port for the RV outflow tract lead in the cardiac resynchronization therapy pacemaker and bifurcated the anode port for the RV outflow tract lead and cathode port for the LV lead in the cardiac resynchronization therapy defibrillator in order to use the RV tip-ring electrode as a bipolar pacing and sensing port. When the output of the pacemaker was set at a level greater than the anodal threshold, the ventricle was depolarized simultaneously from either the RV apex and RV outflow tract or RV outflow tract and coronary sinus. A right atrial lead was implanted in the right atrial appendage in all patients.

The relative anatomical location (height) of the RV outflow tract lead to the left ventricle was obtained by the ratio of the longitudinal distance between the tip of the RV apical lead and that of the RV outflow tract lead to the longitudinal diameter of the left ventricle, which was defined as the longitudinal distance between the tip of the RV apical lead and the superior edge of the venogram of the great cardiac vein in the left anterior oblique projection (Figure 1A). The QRS complex in leads I and V1, and R-wave amplitudes in the inferior leads during RV outflow tract pacing were also measured for the assessment of the electrophysiological

characteristics of the RV outflow tract lead (Figure 2). The RVOT lead was considered as being placed in the antero-septal, mid-septal, or postero-septal area when the QRS complex in lead I demonstrated a negative, iso-electric or bi-phasic, and positive polarity, respectively.[10]

With the cardiac resynchronization therapy pacemaker devices, the acute hemodynamic data of the Bi-V was measured under a standard Bi-V setting connecting the RV apical lead directly to the device. After the hemodynamic data was obtained with the Bi-V, the RV apical lead was disconnected from the device and connected to the anodal port of the Y-adaptor and provided Tri-V with the cathode RV outflow tract lead and the hemodynamic data was obtained. With the cardiac resynchronization therapy defibrillator devices, the hemodynamic data was obtained after the leads were connected to the Y-adaptor. Initially, the LV lead was used as the cathode for uni-polar pacing, so that Bi-V pacing was achieved by RV apical bi-polar pacing and LV uni-polar pacing. Subsequently, the left ventricle pacing was switch to a bi-polar pacing mode, so that anodal capture of the RV outflow tract and cathode capture of the left ventricle could be obtained.

After the operation, the peak positive dP/dt ($+dP/dt_{Max}$) as the index of the systolic function and tau as the index of the diastolic function were obtained during baseline (AAI pacing), Bi-V, and Tri-V with a pacing rate 20 bpm higher than the baseline rate using a micromanometer-tipped pigtail catheter (SPC-464D; Millar Instruments, Inc., Houston, TX). The cardiac output was also measured in the latter 19 consecutive patients using a Swan-Ganz catheter (Baxter Healthcare, Irvine, CA). Each pacing session was continued for 5 minutes, with an interval between each pacing configuration of 3 minutes. In the Bi-V and Tri-V, the atrio-ventricular delay was optimized for each configuration tested, as previously reported, to provide the longest transmitral filling time based on a Doppler analysis of the LV filling.[11]

Because we adopted 2 different Y-adaptor settings for cardiac resynchronization therapy pacemaker and cardiac resynchronization therapy defibrillator to provide Tri-V, all hemodynamic data were obtained under bi-ventricular simultaneous pacing, and no adjustments were made to the ventricular-ventricular intervals for the Bi-V and Tri-V to avoid any different left ventricle activation patterns. Any change in the pacing configuration was confirmed by the change in the paced-QRS morphology (Figure 1B). Acute hemodynamic responders were defined as patients whose percent increase in the $+dP/dt_{Max}$ was >10% from AAI pacing to Bi-V (Bi-V responders) or from Bi-V to Tri-V (Tri-V responders).

Baseline echocardiography was performed with a Vivid 7 system (GE, Vingmed Ultrasound, Horten, Norway) before the procedure. The LV end-diastolic and end-systolic volumes, and ejection fraction were assessed by a biplane Simpson's equation using the apical four- and two-chamber views. The severity of the mitral regurgitation was graded from color-flow Doppler images as none, mild (jet area/left atrial area; <20%), moderate (20% to 45%), and severe (>45%).[12] Myocardial tissue velocity curves using color-coded tissue doppler images were obtained placing the sample volume on 12 LV segments, the basal and mid-ventricular segments of the anteroseptal, anterior, lateral, posterior, inferior, and inferoseptal walls. Intraventricular dyssynchrony was identified with a parameter derived from the tissue doppler images: the standard deviation of the time to peak myocardial systolic velocity (Ts) for the 12 LV segments (Ts-SD).[13]

Continuous variables are expressed as the mean±SD. An analysis of variance (ANOVA) was used when comparisons involved >2 groups. When group differences were found, a one-way ANOVA was followed by the Scheffe's method to test the significance of the difference among the means in all groups. Categorical variables were compared by a chi-square

analysis and Yates' correction, if necessary. Univariate and multivariate logistic regression analyses were used to identify predictors of Tri-V responders. All parameters with a significance <0.05 in the univariate analysis were entered into the multivariate model. A receiver operating characteristic curve analysis was used to determine the ability of the LV end-diastolic volume to predict Tri-V responders. A p value <0.05 was considered significant.

Results

A transvenous Tri-V system was successfully implanted in all patients (Table 1). When the pacing mode was changed from AAI pacing to Bi-V and from Bi-V to Tri-V, the changes in the paced-QRS morphologies were detected by the 12-lead ECG in all patients (Figure 1B). During the change from Bi-V to Tri-V, a reduction in the S-wave amplitude of ≥0.2 mV (n=29) or increase in the R-wave amplitude of ≥0.2 mV (n=1) in any of the inferior leads was observed in 30 (94%) patients. Furthermore, a reduction in the R-wave amplitude of ≥0.2 mV (n=2) or appearance of an S-wave from the R-wave or increase in the S-wave amplitude of ≥0.2 mV (n=21) in any of leads V1 to V3 was observed in 23 (72%) patients. Because the pacing thresholds obtained after connecting the leads to the Y-adaptor have higher thresholds compared to the uni-polar configuration, the thresholds were measured after the lead was connected to the Y-adaptor.[14] Mean threshold was 1.49±0.97 V at a 0.56±0.37 ms pulse width for the RV apical lead, 1.81±1.01V at a 0.52±0.37 ms pulse width for the RV outflow tract lead, and 2.90±1.65 V at a 0.56±0.34 ms pulse width for the LV lead, respectively.

In patients undergoing cardiac resynchronization therapy pacemaker (n=20), the threshold of the anodal RV apical lead was 1.83±1.15 V at a 0.64±0.42ms pulse width and that of the cathode RV outflow tract lead was 1.66±0.93 V at 0.62±0.44 ms. In contrast, in 12 patients undergoing cardiac resynchronization therapy defibrillator, the threshold of the anodal RV

outflow tract lead was 2.04±1.21 V at a 0.35±0.15 ms pulse width and that of the cathode LV lead was 2.93±0.74 V at 0.39±0.11 ms. In 7 patients undergoing cardiac resynchronization therapy defibrillator, the threshold of the cathode LV lead was higher compared to that of the anodal RV outflow tract lead. Regarding the short refractoriness of anodal pacing, pacing-induced ventricular tachyarrhythmias were not observed in any patients. The procedure and fluoroscopy time were 176±47 min and 36.7±19.1 min, respectively.

The $+dP/dt_{Max}$ increased more during Bi-V-than during AAI pacing ($p<0.01$), and it further increased when changed from Bi-V to Tri-V ($p<0.05$; Figure 3A). Conversely, the tau improved in the order of AAI pacing, Bi-V, and Tri-V, and there was a significant difference between the AAI pacing and Tri-V ($p<0.01$; Figure 3B). The total QRS duration during Tri-V was the shortest and cardiac output was the greatest among the 3 different pacing configurations (Figure 3C, 3D).

An acute hemodynamic study demonstrated that 18 patients (56%) who obtained a >10% increase in the $+dP/dt_{Max}$ during Bi-V than that during AAI pacing were Bi-V responders, and the remaining 14 (44%) were Bi-V non-responders (Table 1; Figure 4). Among the 18 Bi-V responders in whom the percent increase in the $+dP/dt_{Max}$ was >10% from AAI pacing to Bi-V, a further percent increase in the $+dP/dt_{Max}$ of >10% from Bi-V to Tri-V (Tri-V responders) was obtained in 6 (33%) patients. On the other hand, in the 14 Bi-V non-responders, 4 (29%) responded to Tri-V (Tri-V responders). Thus, further hemodynamic improvement from Bi-V to Tri-V was found in 10 (31%) patients, and they were compared with the remaining 22 (69%) Tri-V non-responders.

During the study, 8 patients were on inotropic support. There was no significant difference in the percent increase of the $+dP/dt_{Max}$ from Bi-V to Tri-V (9.0±9.4 vs. 5.8±11.3 [%];

p=0.47) or the LV end-diastolic volume (218±86 vs. 220±85[ml]; p=0.96) between these patients and the remaining 24 who did not received inotropic support. Within 1 month after receiving Tri-V, 6 (75%) patients receiving inotropic support could be weaned off the inotropic support.

In both Tri-V responders and non-responders, the magnitude of the $+dP/dt_{Max}$ and cardiac output was greater with an order of Tri-V>Bi-V>AAI pacing (Figure 5A, and 5D). The percent increase in the $+dP/dt_{Max}$ from AAI pacing to Bi-V was 15.2% in Tri-V responders, which also did not significantly differ from Tri-V non-responders (14.2%; p=0.87). In both groups, the magnitude of the tau, or total QRS duration was smaller with an order of Tri-V>Bi-V>AAI pacing (Figure 5B, and 5C). There was no significant difference in the tau among the 3 pacing configurations in Tri-V non-responders. However, in Tri-V responders, the tau was significantly smaller during Tri-V than AAI pacing ($p<0.01$; Figure 5B).

In the adjusted multivariate analysis, the baseline LV end-diastolic volume (per 50ml greater) was the only independent predictor for identifying acute Tri-V responders (OR=2.87; 95% CI=1.03-8.00, $p<0.05$; Table 2). By a receiver operating characteristic curve analysis, a LV end-diastolic volume of 212 ml was the threshold value for predicting Tri-V responders with an 80% sensitivity and 77% specificity (Figure 6).

Only a minor coronary sinus dissection occurred during the LV lead implantation in 2 patients (6.3%). There were no major complications such as a coronary sinus rupture or cardiac tamponade. In one (3%) patient, the LV lead dislodged 3 days after the operation, and it was re-positioned.

Discussion

The results of the present study which examined the acute hemodynamic responses to both Bi-V and Tri-V demonstrated the following findings: 1) 31% of the cardiac

resynchronization therapy candidates demonstrated a further improvement in the $+dP/dt_{Max}$ with a >10% increase in the $+dP/dt_{Max}$ from Bi-V to Tri-V, whereas the remaining 69% of the patients did not, 2) those Tri-V responders also exhibited an improvement in the tau during the Tri-V, and there was a significant difference between the AAI pacing and Tri-V, 3) the baseline LV end-diastolic volume was the independent predictor of Tri-V responders, and 4) no potential complications occurred during the Tri-V implantation. These findings indicate that the device implantation for Tri-V with a "double-right and single-left" method was feasible, and that greater beneficial effects with Tri-V can be achieved in selected patients with a greater LV end-diastolic volume.

In the cardiac resynchronization therapy recipients, the latest segmental LV contraction was observed not only in the LV lateral wall but also in the anterior wall.[15] Previous studies demonstrated that dyssynchrony in the LV anterior wall still remained after the conventional Bi-V and Tri-V could resolve the residual dyssynchrony.[6,16] In the conventional Bi-V, the contraction of the LV anterior wall begins after the activation waveform reaches from the lateral pacing site, and the conduction time from the lateral pacing site to the LV anterior wall increases proportionally as the distance between the 2 sites increases.[16] Therefore, in patients with a large left ventricle, there may be a fair possibility that the LV dyssynchrony could not be resolved with conventional Bi-V from the RV apex and LV lateral wall. This may explain the reason why an enlarged left ventricle is a predictor of a lack of a response to Bi-V.[17] In contrast, when pacing under Tri-V settings, the left ventricle wall was simultaneously activated from the RV apex, RV outflow tract and LV free wall, thus enabling a better contraction.[6,16] This may explain the reason why an enlarged left ventricle is a predictor of a lack of a response to Bi-V[17] and why it became the independent predictor of Tri-V responders in this study.

In the present study, the $+dP/dt_{Max}$ significantly improved from baseline to Bi-V, and its % increase was 14%, which was comparable with the previous studies.[18] Our study demonstrated that, in patients with an enlarged left ventricle, additional hemodynamic improvement could be obtained with Tri-V even after the conventional Bi-V. On the contrary, in the Tri-V non-responders who often had relatively smaller left ventricle, the LV dyssynchrony might have almost effectively resolved with the Bi-V. Therefore, because of the equivalent effectiveness of Bi-V from baseline, additional and apparent improvements in the LV dyssynchrony and contraction might not be obtained with Tri-V in non-responders.

Recent studies reported that the Tri-V method, consisting of "double-left, single-right" pacing, resulted in a significant reduction in the New York Heart Association functional class, LV ejection fraction, and mechanical dyssynchrony.[4] It is difficult to compare our data with that of the previous study because of the differences in the study design and patient characteristics. However, the implantation success rate of 85% in the previous report[4] was much lower than that in our study (100%). We think that the procedural success of the "double-left, single-right" method would strictly depend upon the anatomy of the coronary veins. Unless there were 2 proper coronary veins with an appropriate area of the left ventricle and a proper distance between those veins, a satisfactory benefit of the Tri-V would not be achieved. On the contrary, in the "double-right, single-left" method we applied in this study, it was easier to implant the pacing lead at the planned and optimal portion in the RV outflow tract and coronary veins. Therefore, a"double-right, single-left" method may be more feasible and safer than a "double-left, single-right" method.

Our results indicate that, when a patient had an enlarged left ventricle (especially with an LV end-diastolic volume of >212 ml), additional improvement in the hemodynamics could be

obtained with Tri-V. Previous studies have shown that the prognostic importance of LV remodeling and LV enlargement proportionally increases the morbidity and mortality regardless of the etiology of the heart failure,[19,20] and cardiac resynchronization therapy has had limited efficacy for the prognosis in patients with a greater LV end-diastolic dimension.[17] Therefore, this technique may be recommended as an alternative therapy to Bi-V for patients with an enlarged left ventricle. Conversely, in the patients with a moderately enlarged left ventricle, Bi-V might be sufficient to resolve the LV dyssynchrony and improve the hemodynamics.

This study was mainly limited by the study design and only short-term hemodynamic changes were evaluated. A considerable number of seriously ill patients were included in this study (Table 1) with approximately 25% of the patient having required inotropic support. To minimize the influence of this situation, we adopted the percent increase in the $+dP/dt_{Max}$ to define the Tri-V responders. Although there was no significant difference in the % increase of the $+dP/dt_{Max}$ between the patients who received the inotropic support and those who did not in this study, it might not be appropriate to assess the hemodynamics of the patients who received inotropic support together with those who did not. Furthermore, neither a 6 min walk nor cardiopulmonary exercise testing were performed, and only the acute hemodynamic improvement was evaluated. Finally, in spite of a high prevalence of seriously ill patients, approximately 30 % of those turned out to be Tri-V responders. We believe that Tri-V is an alternative therapeutic option for hoping to improve the hemodynamic condition of seriously ill patients with an enlarged left ventricle. However, the number of patients analyzed was small. Therefore, further randomized studies with a larger sample size and long-term follow-up may be needed to clarify the long-term outcomes and the optimal method for Tri-V.

References

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-1853.
2. Reuter S, Garrigue S, Barold SS, Jais P, Hocini M, Haissaguerre M, Clementy J. Comparison of characteristics in responders versus nonresponders with biventricular pacing for drug-resistant congestive heart failure. *Am J Cardiol* 2002;89:346-350.
3. Cleland J, Freemantle N, Ghio S, Fruhwald F, Shankar A, Marijanowski M, Verboven Y, Tavazzi L. Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response a report from the CARE-HF (Cardiac Resynchronization in Heart Failure) Trial. *J Am Coll Cardiol* 2008;52:438-445.
4. Leclercq C, Gadler F, Kranig W, Ellery S, Gras D, Lazarus A, Clementy J, Boulogne E, Daubert JC. A randomized comparison of triple-site versus dual-site ventricular stimulation in patients with congestive heart failure. *J Am Coll Cardiol* 2008;51:1455-1462.
5. Pappone C, Rosanio S, Oreto G, Tocchi M, Gulletta S, Salvati A, Dicandia C, Santinelli V, Mazzone P, Veglia F, Ding J, Sallusti L, Spinelli J, Vicedomini G. Cardiac pacing in heart failure patients with left bundle branch block: impact of pacing site for optimizing left ventricular resynchronization. *Ital Heart J* 2000;1:464–469.
6. Yoshida K, Seo Y, Yamasaki H, Tanoue K, Murakoshi N, Ishizu T, Sekiguchi Y, Kawano S, Otsuka S, Watanabe S, Yamaguchi I, Aonuma K. Effect of triangle ventricular pacing on haemodynamics and dyssynchrony in patients with advanced heart failure: a comparison study with conventional bi-ventricular pacing therapy. *Eur Heart J* 2007;28:2610-2619.

7. Hansky B, Vogt J, Gueldner H, Lamp B, Tenderich G, Krater L, Heintze J, Minami K, Horstkotte D, Koerfer R. Left heart pacing--experience with several types of coronary vein leads. *J Interv Card Electrophysiol* 2002;6:71-75.
8. Balt JC, van Hemel NM, Wellens HJ, de Voogt WG. Radiological and electrocardiographic characterization of right ventricular outflow tract pacing. *Europace* 2010;12:1739-1744.
9. Pachon JC, Pachon EI, Albornoz RN, Pachon JC, Kormann DS, Gimenes VM, Medeiros PT, Silva MA, Sousa JE, Paulista PP, Souza LC, Jatene AD. Ventricular endocardial right bifocal stimulation in the treatment of severe dilated cardiomyopathy heart failure with wide QRS. *Pacing Clin Electrophysiol* 2001;24:1369-1376.
10. Dixit S, Gerstenfeld EP, Callans DJ, Marchlinski FE. Electrocardiographic patterns of superior right ventricular outflow tract tachycardias: distinguishing septal and free-wall sites of origin. *J Cardiovasc Electrophysiol* 2003;14:1-7.
11. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, Lin H, Kong SL, Lam YM, Hill MR, Lau CP. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;105:438-445.
12. Bonow RO, Carabello BA, Kanu C, de Leon AC, Jr., Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients

With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006;114:e84-231.

13. Yu CM, Zhang Q, Fung JW, Chan HC, Chan YS, Yip GW, Kong SL, Lin H, Zhang Y, Sanderson JE. A novel tool to assess systolic asynchrony and identify responders of cardiac resynchronization therapy by tissue synchronization imaging. *J Am Coll Cardiol* 2005;45:677-684.
14. Rho RW, Patel VV, Gerstenfeld EP, Dixit S, Poku JW, Ross HM, Callans D, Kocovic DZ. Elevations in ventricular pacing threshold with the use of the Y adaptor: implications for biventricular pacing. *Pacing Clin Electrophysiol* 2003;26:747-751.
15. Becker M, Kramann R, Franke A, Breithardt OA, Heussen N, Knackstedt C, Stellbrink C, Schauerte P, Kelm M, Hoffmann R. Impact of left ventricular lead position in cardiac resynchronization therapy on left ventricular remodelling. A circumferential strain analysis based on 2D echocardiography. *Eur Heart J* 2007;28:1211-1220.
16. Yoshida K, Yokoyama Y, Seo Y, Sekiguchi Y, Aonuma K. Triangle ventricular pacing in a non-responder to conventional bi-ventricular pacing. *Europace* 2008;10:502-504.
17. Diaz-Infante E, Mont L, Leal J, Garcia-Bolao I, Fernandez-Lozano I, Hernandez-Madrid A, Perez-Castellano N, Sitges M, Pavon-Jimenez R, Barba J, Cavero MA, Moya JL, Perez-Isla L, Brugada J. Predictors of lack of response to resynchronization therapy. *Am J Cardiol* 2005;95:1436-1440.
18. Auricchio A, Ding J, Spinelli JC, Kramer AP, Salo RW, Hoersch W, KenKnight BH, Klein HU. Cardiac resynchronization therapy restores optimal atrioventricular mechanical timing in heart failure patients with ventricular conduction delay. *J Am Coll Cardiol*

2002;39:1163-1169.

19. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Levy D. Left ventricular dilatation and the risk of congestive heart failure in people without myocardial infarction. *N Engl J Med* 1997;336:1350-1355.

20. Lee TH, Hamilton MA, Stevenson LW, Moriguchi JD, Fonarow GC, Child JS, Laks H, Walden JA. Impact of left ventricular cavity size on survival in advanced heart failure. *Am J Cardiol* 1993;72:672-676.

Figure Legends

Figure 1. (**A**) The ratio of the longitudinal distance between the tip of the right ventricular (RV) apical lead and that of the RV outflow tract lead (a) to the longitudinal diameter of the left ventricle (b), which was defined as the longitudinal distance between the tip of the RV apical lead and the superior edge of the venogram of the great cardiac vein in the left anterior oblique (LAO 45°) projection. The ratio of the longitudinal distance was 0.82 in this patient. (**B**) Representative ECG changes from baseline (AAI pacing), during bi-ventricular pacing (Bi-V), and triple-site ventricular pacing (Tri-V). Note that a reduction in the S-wave amplitude of >0.2 mV in all the inferior leads and the appearance of an S-wave in the R-wave in leads V2 to V3 were observed during the change from Bi-V to Tri-V. RV=right ventricular.

Figure 2. Representative lead locations and 12 lead ECGs during pacing from the lead in the right ventricular (RV) outflow tract in 2 patients who received triple-site pacing. Note that the location of the RV outflow tract lead is higher and the R-wave amplitude in lead II is greater in the responder (**A**) than in the non-responder (**B**). RV=right ventricular.

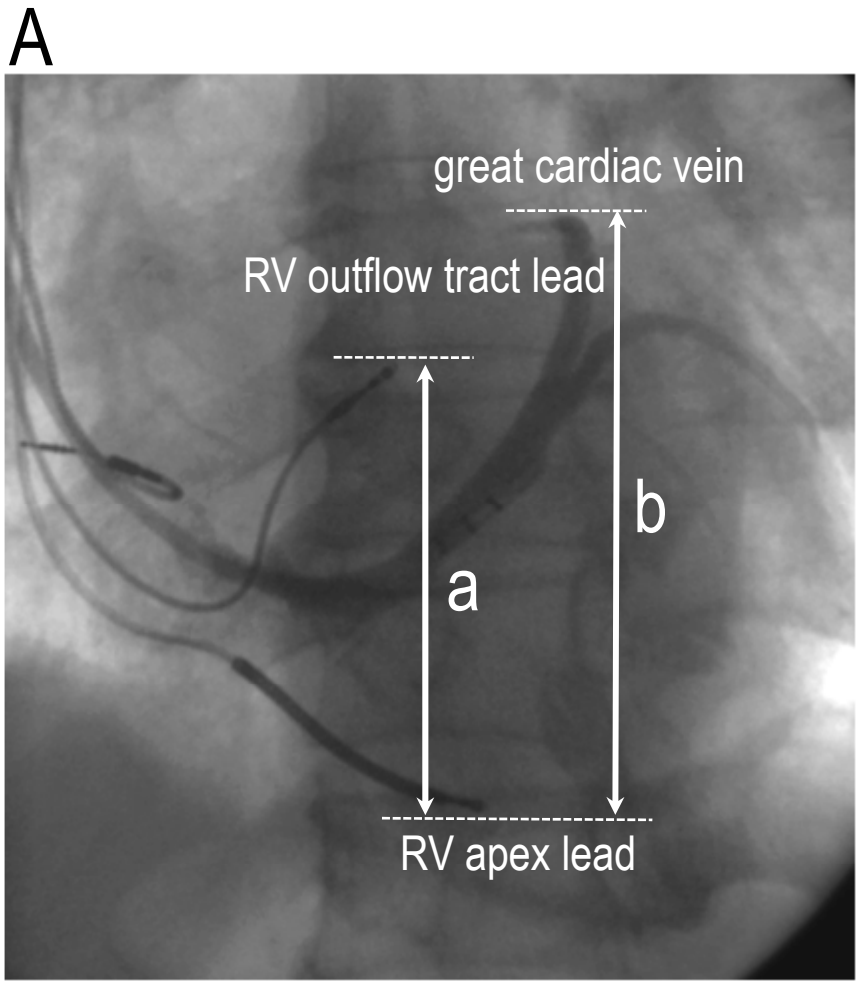
Figure 3. Changes in the peak positive dP/dt_{Max} (**A**), tau (**B**), and total QRS duration (**C**) in 32 patients at baseline (AAI pacing), during bi-ventricular pacing (Bi-V), and during triple-site ventricular pacing (Tri-V). (**D**) The changes in the cardiac output obtained in 19 patients. $^{*}p<0.05$, $^{+}p<0.01$, $^{\S}p<0.0001$ compared with baseline. ‡$p<0.05$, $^{¶}p<0.01$, $^{\#}p<0.001$ compared with Bi-V.

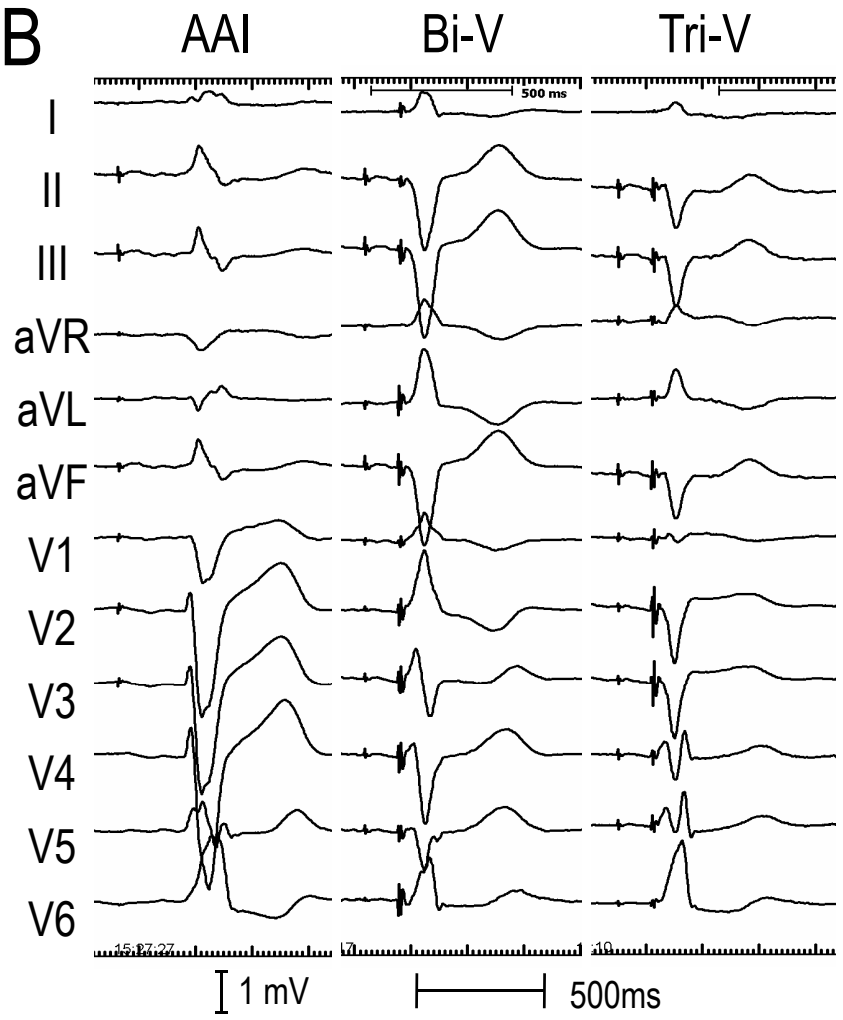
Figure 4. Flow diagram and results of the acute hemodynamic study. Bi-V=bi-ventricular pacing; Tri-V=triple-site ventricular pacing

Figure 5. Changes in the peak positive $+dP/dt_{Max}$ (**A**), tau (**B**), and total QRS duration (**C**) in 10 Tri-V responders (•) and 22 non-responders (▲) at baseline (AAI pacing), during bi-ventricular

pacing (Bi-V), and during triple-site ventricular pacing (Tri-V). (**D**) Changes in the cardiac output obtained in 8 Tri-V responders (•) and 11 non-responders (▲). $^{*}p<0.05$, $^{+}p<0.01$, $^{\S}p<0.001$, ‡$p<0.0001$ compared with baseline. $^{¶}p<0.01$ compared with Bi-V.

Figure 6. The areas of the receiver operating characteristic curves of the left ventricular end-diastolic volume.


A
great cardiac vein
RV outflow tract lead
a
b
RV apex lead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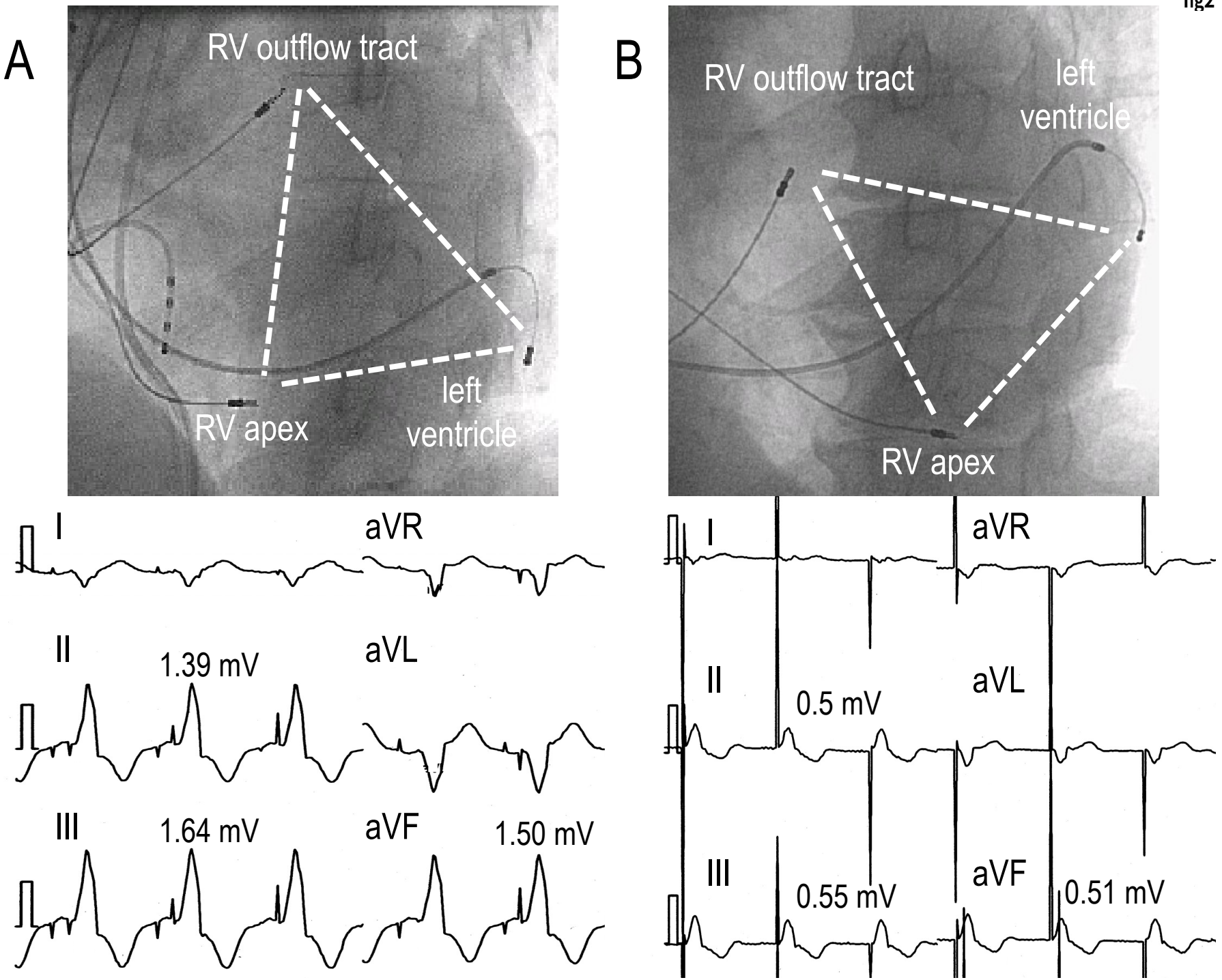
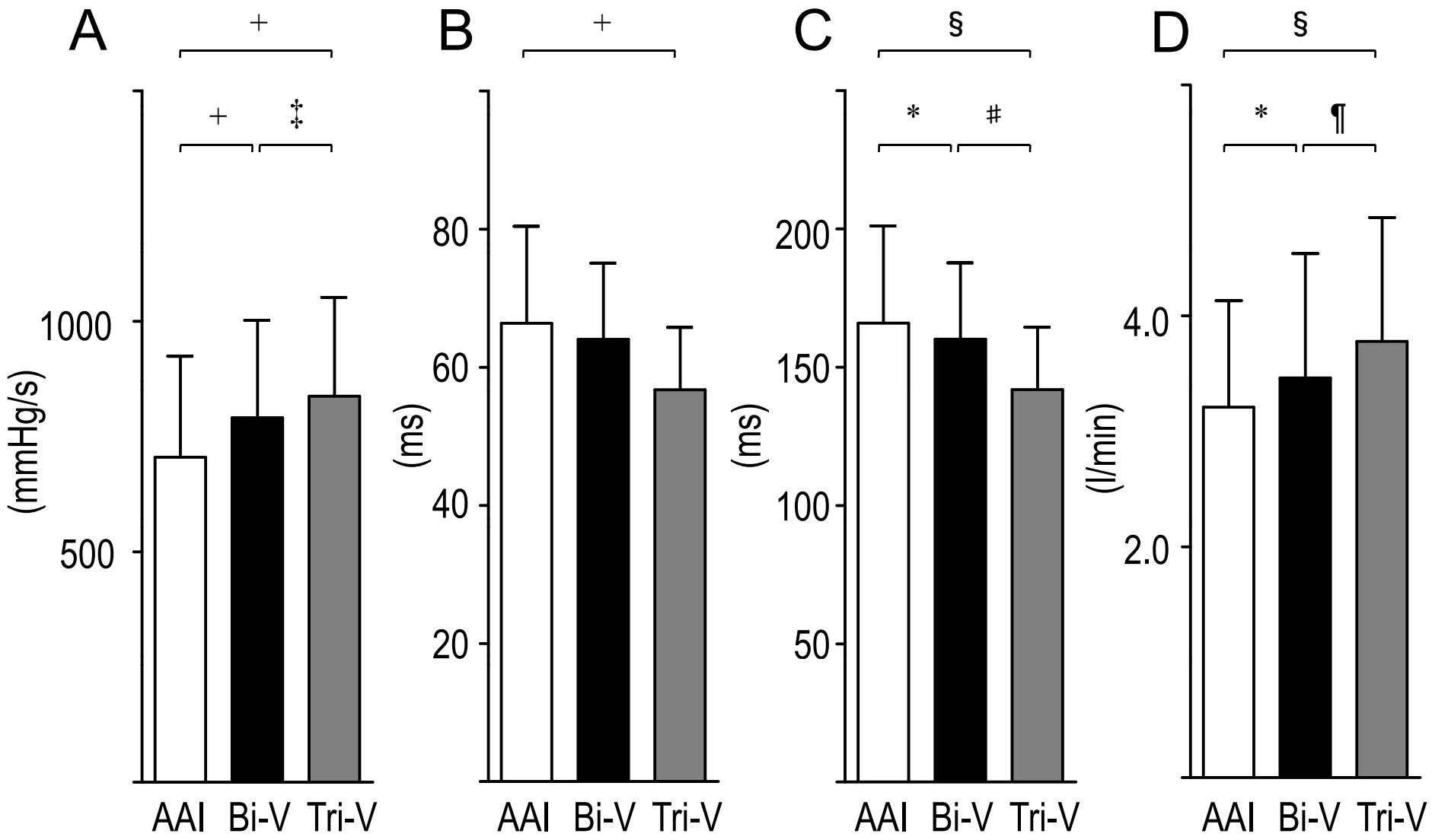
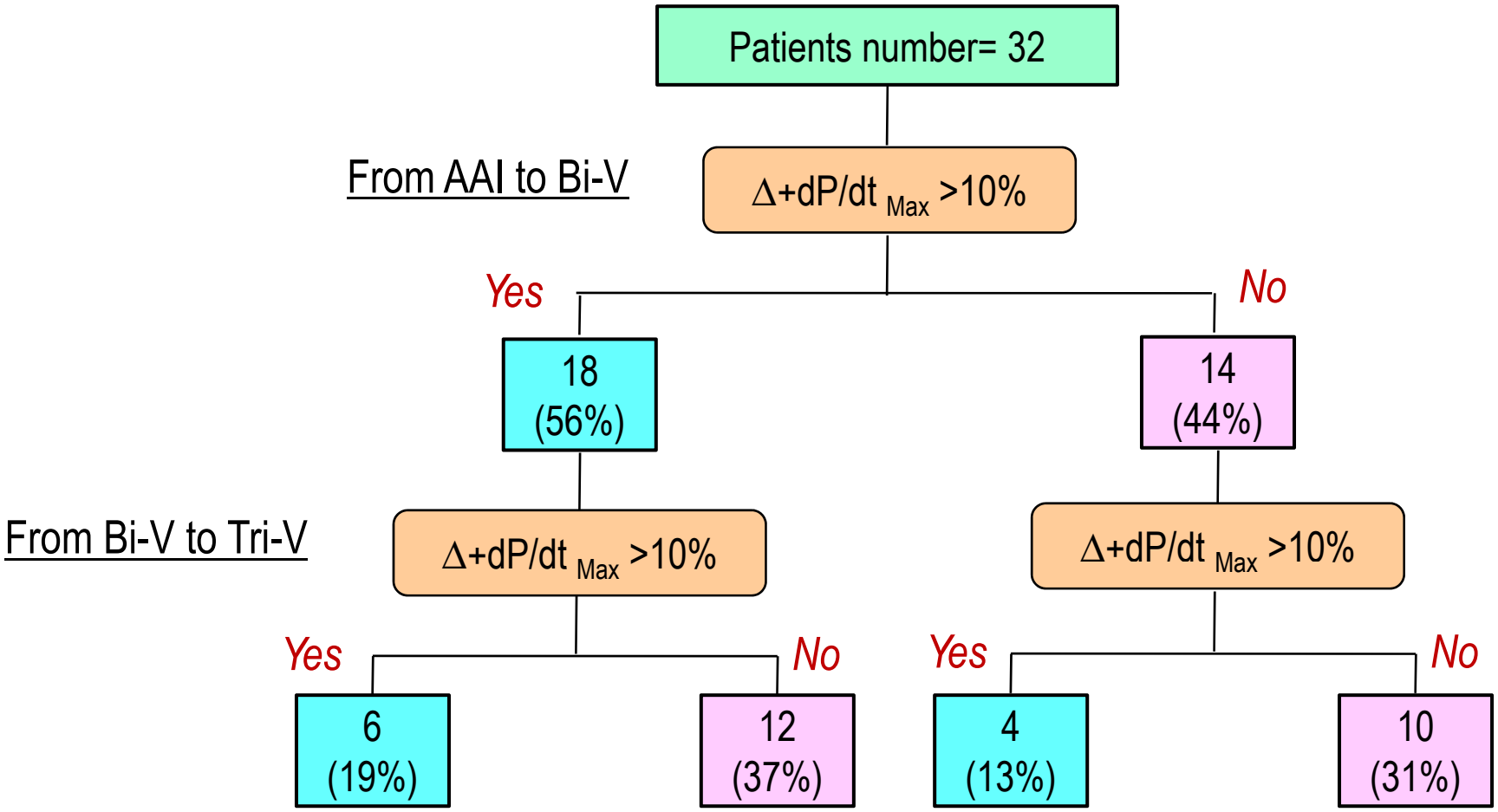
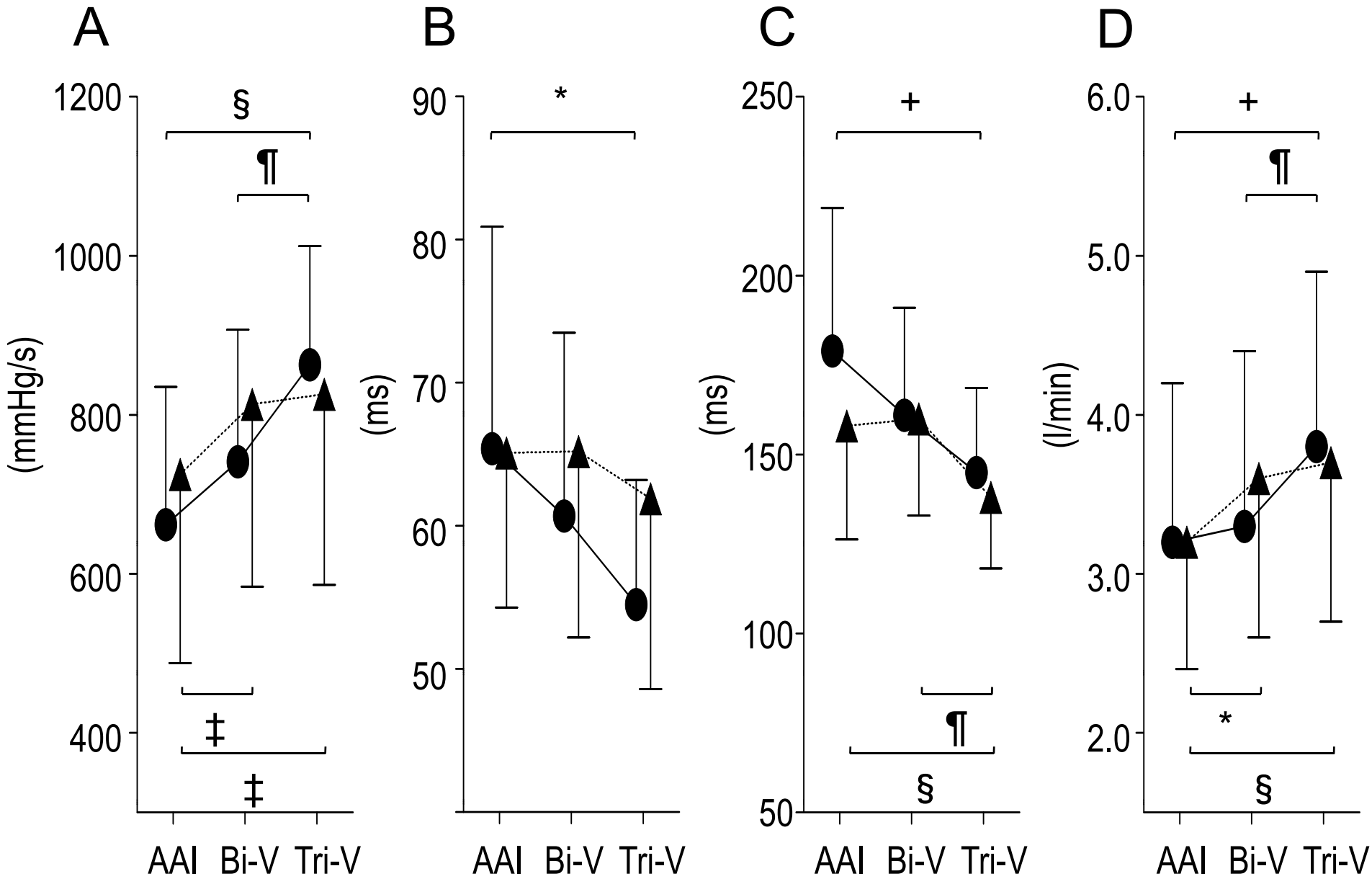
V5
V6
1 mV
500ms

fig2


A
RV outflow tract
RV apex
left ventricle
I
aVR
II
1.39 mV
aVL
III
1.64 mV
aVF
1.50 mV
B
RV outflow tract
left ventricle
RV apex
I
aVR
II
0.5 mV
aVL
III
0.55 mV
aVF
0.51 mV


A
B
C
D
+
+
‡
§
*
#
¶
1000
500
(mmHg/s)
80
60
40
20
(ms)
200
150
100
50
(ms)
4.0
2.0
(l/min)
AAI
Bi-V
Tri-V


Patients number= 32
From AAI to Bi-V
Δ+dP/dt Max >10%
Yes
No
18
(56%)
14
(44%)
From Bi-V to Tri-V
Δ+dP/dt Max >10%
Δ+dP/dt Max >10%
Yes
No
Yes
No
6
(19%)
12
(37%)
4
(13%)
10
(31%)


A
B
C
D
(mmHg/s)
(ms)
(ms)
(l/min)
1200
1000
800
600
400
90
80
70
60
50
250
200
150
100
50
6.0
5.0
4.0
3.0
2.0
§
¶
‡
‡
*
+
¶
§
+
¶
*
§
AAI
Bi-V
Tri-V
AAI
Bi-V
Tri-V
AAI
Bi-V
Tri-V
AAI
Bi-V
Tri-V

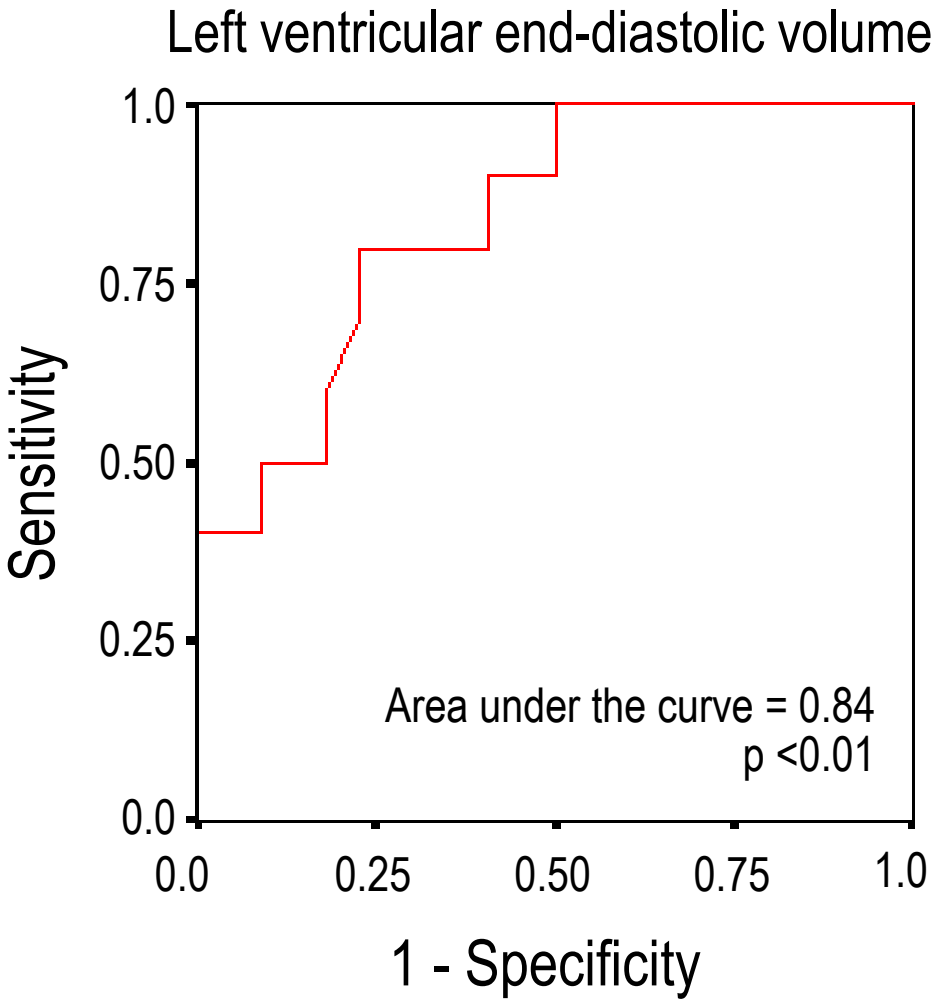

Left ventricular end-diastolic volume
Sensitivity
1.0
0.75
0.50
0.25
0.0
Area under the curve = 0.84
p <0.01
0.0
0.25
0.50
0.75
1.0
1 - Specificity

Table 1. Clinical and procedural characteristics of the patients

Variable	All patients (n=32)	Responders (n=10)	Non-responders (n=22)	*p value*
Age (years)	65±13	71±9	63±15	0.2
Men	27 (84%)	9 (90%)	14 (64%)	0.2
NYHA class III/IV	18/14	6/4	12/10	0.8
Ischemic/non-ischemic	4/28	2/8	2/20	0.4
Systolic blood pressure (mmHg)	96±11	98±7	95±13	0.6
Heart rate (beats/min)	72±16	69±15	63±17	0.5
Concomitant disease and general condition				
Chronic kidney disease	28 (88%)	10 (100%)	18 (82%)	0.3
Chronic hepatic failure	5 (16%)	1 (10%)	4 (18%)	0.9
Mechanical ventilation	7 (22%)	2 (20%)	5 (23%)	0.9
Inotropic support	8 (25%)	2 (20%)	6 (27%)	0.9
Heart Failure Hospitalization within 1 month	24 (75%)	8 (80%)	16 (73%)	0.9
Medications				
Beta-blockers	20 (63%)	5 (50%)	15 (68%)	0.3
Angiotensin converting enzyme inhibitor/ receptor blocker	17 (53%)	5 (50%)	12 (55%)	0.8
Amiodarone	22 (69%)	6 (60%)	16 (73%)	0.5
QRS duration at baseline (msec)	167±35	180±40	162±31	0.6
Left ventricular ejection fraction (%)	25±8.2	25±8.3	25±8.4	0.9
Left ventricular end-diastolic volume (ml)	195±61	246±48	173±53	<0.001
Moderate to severe mitral regurgitation	7 (22%)	2 (20%)	5 (23%)	0.9
Ratio of longitudinal distance	0.80±0.12	0.88±0.06	0.76±0.13	<0.05
Polarity of the QRS complex in lead I during pacing from the right ventricular outflow tract				0.8
Negative	15 (47%)	11 (50%)	4 (40%)	
Isoelectric or bi-phasic	15 (47%)	10 (45%)	5 (50%)	
Positive	2 (6%)	1 (5%)	1 (10%)	
R-wave amplitude during pacing from the right ventricular outflow tract lead (mV)				
Lead II	1.04±0.51	1.29±0.59	0.93±0.44	0.09
Lead III	1.18±0.56	1.36±0.71	1.09±0.48	0.2
Lead aVF	1.10±0.53	1.31±0.64	1.01±0.46	0.1
Left ventricular lead position				0.2
Lateral or postero-lateral	29 (91%)	8 (80%)	21 (95%)	
Antero-lateral	3 (9%)	2 (20%)	1 (5%)	
Ts-SD	39.0±15.0	38.4±14.0	39.0±15.8	0.9

The values are reported as the mean±standard deviation or number of patients (%). A responder was defined as a patient whose percent increase in the $+dP/dt_{Max}$ during triple site pacing was >10% that during bi-ventricular pacing in the acute hemodynamic study. Chronic kidney disease and chronic hepatic failure were defined as an estimated glomerular filtration rate of <60 ml/min/1.73m^2 and serum total bilirubin level of >2 mg/dl, respectively. The ratio of the longitudinal distance indicates the ratio of the longitudinal distance between the tip of the right ventricular apex lead and that of the right ventricular outflow tract lead to the longitudinal diameter of the left ventricle, which was defined as a longitudinal distance between the tip of the right ventricular apex lead and the superior edge of the venogram of the great cardiac vein in the left anterior oblique projection. Ts-SD=standard deviation of the time to the peak myocardial systolic velocity for the 12 LV segments by tissue Doppler imaging.[11]

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