

Mechanisms of Right Atrial Pacing Inducing Left Atrial and Left Ventricular Dysfunction Evaluated by Strain Echocardiography

Hsin-Yueh Liang,^{1,2} Wen-Chun Cheng³ and Kuan-Cheng Chang^{1,2}

Background: Electric pacing in the right atrium affects both the atrial depolarization and contraction and may alter the mechanical interaction between atrium and ventricle. Tissue Doppler and strain echocardiography has been validated as accurately depicting regional myocardial motion and deformation, respectively. The purpose of this study was to determine (1) the effect of VDD versus DDD pacing mode on left ventricular (LV) performance and (2) the mechanisms underlying the difference.

Methods: We studied 20 patients with permanent dual-chamber pacemakers. The dual chamber pacemakers were programmed into the VDD and DDD modes, and all Doppler echocardiographic measurement and tissue Doppler imaging were repeatedly obtained in both pacing modes. Atrial synchrony was defined as the time difference between atrial mechanical activation time at the right atrium (RA), left atrial (LA) free walls and the interatrial septum. Atrial strain was measured to represent active atrial contraction.

Results: The mitral inflow time-velocity integral, and diastolic filling period were greater in VDD mode ($p < 0.001$). Atrial strain was significantly higher in VDD mode in the RA ($p = 0.0017$), interatrial septum ($p = 0.0056$) and the LA ($p = 0.015$). Mechanical delay between interatrial septum and LA ($p = 0.04$) and between RA to LA ($p = 0.0014$) were significantly prolonged in DDD mode. Left ventricular outflow tract time-velocity integral was greater in VDD mode ($p < 0.0001$).

Conclusion: In intrinsic atrial rhythm during VDD pacing, atrial contractility and atrial synchrony are preserved, resulting in better LV diastolic filling and LV performance.

Key Words: Atrial synchrony • Pacemaker

INTRODUCTION

Dual-chamber pacing has been shown to improve cardiac output, left ventricular filling pressure and exer-

cise tolerance compared with single-chamber ventricular pacing alone.¹⁻³ Dual-chamber pacemakers can operate in both right-atrial-sensed (VDD) and right-atrial-paced (DDD) modes. In VDD mode, both atria are activated via the intrinsic conduction system. In contrast, both atria are activated by pacing of the right atrial appendage in DDD mode. The atrium serve three important roles, as conduits, reservoirs, and contractile chambers and are part of the preload system. Electric pacing in the right atrium affects both the atrial depolarization and contraction and may alter the mechanical interaction between the atrium and ventricle.^{4,5} Therefore, although the right ventricle is paced at a certain atrio-ventricular interval (AV delay) after right atrial sensing or pacing, the inter-

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¹Division of Cardiology, Department of Medicine, China Medical University Hospital; ²Graduate Institute of Clinical Medical Science, China Medical University; ³Division of Cardiology, Department of Health, Taichung Hospital, Taichung, Taiwan.

Address correspondence and reprint requests to: Dr. Kuan-Cheng Chang, Division of Cardiology, Department of Medicine, China Medical University Hospital, No. 2, Yuh-Der Road, Taichung 40447, Taiwan. Tel: 886-4-2205-2121, ext. 2010; Fax: 886-4-2360-2467; E-mail: kuancheng.chang@gmail.com

atrial mechanical delay is not adjustable, which can significantly affect left-sided atrio-ventricular filling and consequentially left ventricular stroke volume.

Right ventricular (RV) pacing induces LV dyssynchrony and dysfunction, but it is plausible that a similar mechanism exists in the atrium.^{6,7} The purpose of this study was to determine (1) the effect of VDD versus DDD pacing mode on left ventricular (LV) performance; and (2) the mechanisms underlying the differences, using standard Doppler indices, tissue Doppler-derived strain and two-dimensional speckle tracking strain in patients with dual-chamber pacemakers.

METHODS

We studied 20 patients who had been implanted with a permanent dual chamber pacemaker referred for echocardiographic examination based on clinical indication, after having given their informed consent. None of them had atrial fibrillation during examination, admission in recent 6 months because of cardiac disease except conduction disorder, or poor image quality. All the atrial leads were passive-fixation leads placed in the right atrial appendage, and all the ventricular leads were positioned in the right ventricular apex, via transvenous approach under fluoroscopic guidance.

Protocol

The dual chamber pacemakers were programmed into the VDD and DDD mode, respectively, and all Doppler echocardiographic measurement and tissue Doppler imaging were repeatedly obtained in both pacing modes. All AV delay was programmed shorter than the intrinsic AV delay to ensure right ventricular apex pacing. In DDD mode, the atrial pacing rate was set 10 beats/min above the intrinsic atrial rate.

Echocardiography

A Vivid 7 cardiac ultrasound machine (General Electric, Milwaukee, WI) was used with a 3.5 MHz transducer. Echocardiographic examinations were performed with patients in the left lateral decubitus position. At each mode, an apical 4 chamber view with tissue Doppler imaging and mitral pulsed-wave Doppler examination using a sample volume at the mitral leaflet tip

level were obtained. Pulsed Doppler of the left ventricular outflow tract (LVOT) was acquired from an apical five-chamber view.

Hemodynamics

The mitral annulus and LVOT diameter were assumed unchanged during the study. Thus changes in LVOT-time velocity integral (TVI) were considered reflective of changes in stroke volume. The MV-TVI was used to assess LV diastolic filling. In addition to LVOT-TVI, LV ejection fraction was used to assess LV global systolic function. The diastolic filling period was defined from the onset of transmitral inflow to the subsequent R wave in this study and was expressed as a percentage of the entire cardiac cycle.

Cardiac mechanics

Tissue Doppler and strain echocardiography have been extensively validated as accurately depicting regional myocardial motion and deformation, respectively.⁸⁻¹² Because of less interference by motion or tethering,¹³ strain echocardiography has been demonstrated as being superior to tissue velocity in assessment of regional and global function.¹⁴⁻¹⁶

Modesto et al. have previously shown that strain echocardiography can be used to evaluate atrial systolic function.¹⁷ Strain echocardiography was analyzed using region of interest tracking and the sample size was 6 mm × 6 mm in the atria. Mean temporal resolution was 10 ms. Only tracings with clear systolic and diastolic peaks were analyzed. Atrial strain/strain rate was measured in the right atrial (RA) free wall, interatrial septum and left atrial (LA) free wall in the apical 4 chamber view. The late diastolic atrial strain rate, following P wave of the surface electrocardiogram (ECG), reflects atrial contractility (Figure 1A). The atrial mechanical activation time was defined as the time from the peak of the late diastolic atrial strain rate to the subsequent 'R' wave. The ECG 'R' wave was used as the reference point of electric activity because the 'R' wave is more easily recognized than the 'P' wave. Atrial synchrony was defined as the time difference between atrial mechanical activation times at the RA and LA free walls and the interatrial septum. Active atrial strain, integration of late diastolic atrial strain rate, was measured as a percentage of shortening normalized to the length at the onset of P wave (Figure 1B).

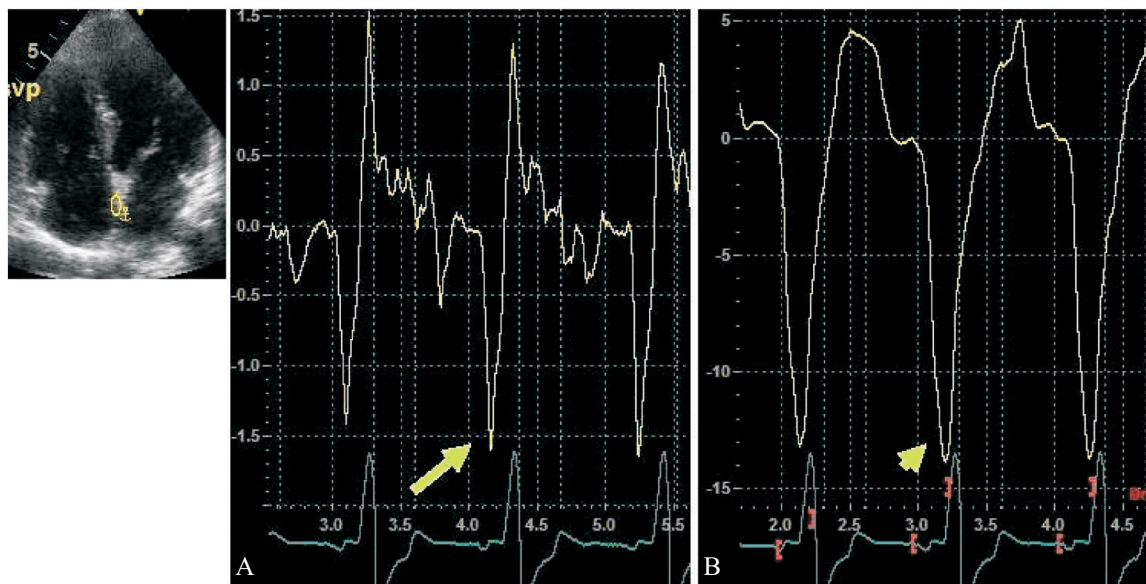


Figure 1. Representative atrial strain rate tracing obtained from the interatrial septum. (A) The late diastolic atrial strain rate (arrow) following P wave of the surface ECG reflects atrial contractility. (B) Integration of the late diastolic atrial strain rate yields active atrial strain (arrow head).

For the purposes of this study, global and regional longitudinal strain, using two-dimensional speckle tracking algorithm, were used to assess LV global and regional function.¹⁸ The global strain was defined as the sum of systolic strain in lateral and septal walls in the apical 4 chamber view. Average strain of each segment was calculated as the global strain divided by 6 segments.

All time delays were corrected for heart rate using the Bazett formula (time delay in ms normalized to the square root of the RR interval in seconds).

Statistics

Data were summarized as mean ± SD or as frequencies. The paired *t* test or the Wilcoxon signed rank test, depending on distribution, was used to compare data between VDD and DDD pacing modes. A *p* value of < 0.05 was considered statistically significant.

RESULTS

Demographic characteristics of the patients enrolled in the study are shown in Table 1. Twenty patients with a mean age of 72 ± 12 years were enrolled. The duration of dual chamber pacemaker implanted was 5.1 ± 3.6 years at the time of enrollment. The mean R-R intervals

in VDD and DDD were 910 ± 138 ms and 834 ± 116 ms, respectively.

Mean, quartile and differences between VDD and DDD pacing modes with respect to the standard echocardiographic measurements are depicted in Table 2. The mitral A-TVI was comparable between the two modes. The MV-TVI (20.5 ± 4.7 vs. 18.9 ± 4.1 cm, *p* < 0.0001), LVOT-TVI (21.7 ± 5.4 vs. 20.0 ± 5.4 cm, *p* < 0.0001), diastolic filling period (451 ± 121 vs. 382 ± 103 ms, *p* < 0.0001) were greater in VDD compared to DDD mode,

Table 1. Demographic characteristics and medication

Age (yrs)	72 ± 12
Female, n (%)	14(70)
Conduction disorder	
Complete AV block	19(95)
Sick sinus syndrome	1(5)
Hypertension	12(60)
Diabetes	6(30)
Heart failure	1(5)
Coronary artery disease documented by coronary angiography	3(15)
Medication, n (%)	
Beta blocker	7(35)
Propafenone	1(5)
Digoxin	1(5)
Amiodarone	1(5)

Table 2. Standard echocardiographic measurement and left ventricular strain

	VDD mean (25%, 75%)	DDD mean (25%, 75%)	p value
PR interval (ms)	175 ± 33 (143, 202)	169 ± 30 (141, 192)	0.07
R-R interval (ms)	910 ± 138 (810, 1018)	834 ± 116 (754, 923)	< 0.0001
A-TVI (cm)	10.1 ± 3.0 (8.2, 11.2)	10.1 ± 2.9 (8.2, 11.2)	0.83
MV-TVI (cm)	20.5 ± 4.7 (17.7, 22.3)	18.9 ± 4.1 (16.7, 20.0)	< 0.0001
LVOT-TVI (cm)	21.7 ± 5.4 (19.3, 23.2)	20.0 ± 5.4 (17.0, 21.9)	< 0.0001
MV-R time (ms)	451 ± 121 (355, 575)	382 ± 103 (304, 497)	< 0.0001
Diastolic filling time (%)	49 ± 7 (43, 56)	45 ± 7 (39, 51)	0.0012
LA EF (%)	57 ± 12 (47, 65)	54 ± 11 (48, 64)	0.11
LV EF (%)	54 ± 6 (50, 58)	53 ± 7 (48, 58)	0.09
Global strain of LV (%)	-67.6 ± 26.4 (-85.8, -51.7)	-59.3 ± 25.1 (-84.0, -41.4)	< 0.0001
Average strain of each segment of LV (%)	-11.3 ± 4.4 (-14.3, -8.6)	-9.9 ± 4.2 (-14.0, -6.9)	< 0.0001

A-TVI = time-velocity integral of the late mitral (A) wave; EF = ejection fraction; LA = left atrium; LV = left ventricle; LVOT-TVI = time-velocity integral of the LV outflow tract velocity; MV-R time = onset of mitral inflow to the subsequent R wave; MV-TVI = time-velocity integral of the early and late mitral inflow Doppler waves (E and A); PR interval = onset of P wave to ventricular pacing spike on ECG.

respectively. There was no significant difference in LA (57 ± 12 vs. 54 ± 11%, $p = 0.11$) and LV (54 ± 6 vs. 53 ± 7%, $p = 0.09$) ejection fraction between two modes.

LA mechanics including LA contractility and synchrony were further evaluated in order to investigate potential mechanisms underlying these hemodynamic differences. Active atrial strain was significantly higher in VDD compared to DDD pacing modes in the RA (-28.6 ± 9.2 vs. -25.9 ± 6.3%, $p = 0.0017$), interatrial septum (-15.9 ± 4.8 vs. -13.5 ± 4.3%, $p = 0.0056$) and the LA (-15.2 ± 6.2 vs. -13.3 ± 5.4%, $p = 0.015$), respectively. The intra-right-atrial synchrony, shown by time difference between atrial mechanical activation at the RA and interatrial septum, was similar in the two pacing modes (27 ± 14 vs. 33 ± 11 ms, $p = 0.075$). However, the atrial mechanical delays between interatrial septum and LA (44 ± 12 vs. 34 ± 13 ms, $p = 0.04$) and between RA to

LA (78 ± 25 vs. 61 ± 22 ms, $p = 0.0014$) were significantly prolonged in DDD mode compared to VDD mode (Table 3).

In VDD mode, global strain of LV in apical 4-chamber view was greater than in DDD mode (-67.6 ± 26.4 vs. -59.3 ± 25.1, $p < 0.0001$) (Table 2). Regional strain near RV pacing sites was less than other remote sites in both modes (Figure 2).

Inter- and intra-observer variability showed good agreement (Figure 3) in measurement of time delay (93% and 92%, respectively) and strain (97% and 96%, respectively).

DISCUSSION

The atria are not simply passive conduits for blood

Table 3. Atrial mechanics and mechanical dyssynchrony

	VDD mean (25%, 75%)	DDD mean (25%, 75%)	<i>p</i> -value
Regional active atrial strain			
Right atrium (%)	-28.6 ± 9.2 (-35.5, -25.0)	-25.9 ± 6.3 (-30.7, -21.9)	0.0017
Interatrial septum(%)	-15.9 ± 4.8 (-18, -12.5)	-13.5 ± 4.3 (-17.1, -10.0)	0.0056
Left atrium (%)	-15.2 ± 6.2 (-20.2, -9.6)	-13.3 ± 5.4 (-18.6, -8.8)	0.015
Intra- and inter-atrial mechanical dyssynchrony (ms)			
RA to IAS	27 ± 14 (15, 37)	33 ± 11 (27, 44)	0.075
RA to LA	61 ± 22 (43, 72)	78 ± 25 (55, 96)	0.0014
IAS to LA	34 ± 13 (25, 42)	44 ± 22 (28, 59)	0.004

IAS, interatrial septum; LA, left atrium; RA, right atrium.

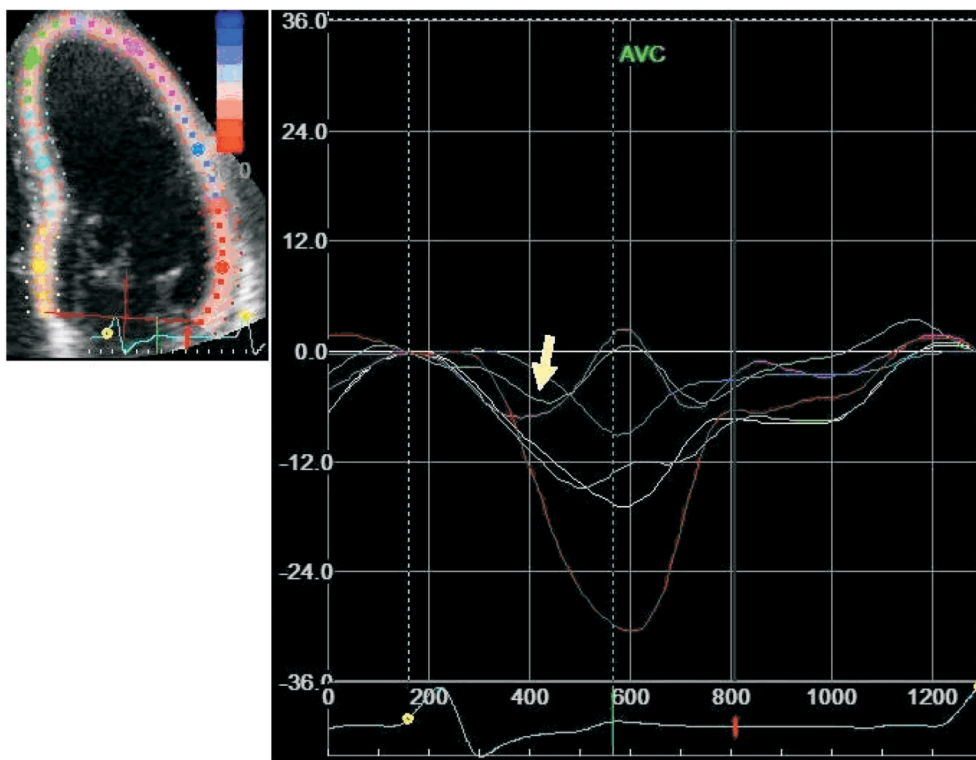


Figure 2. Global strain of LV measured by two-dimensional speckle tracing algorithm. Regional strain (green on the left panel) near the pacing sites (arrow) was decreased compared to the remote sites.

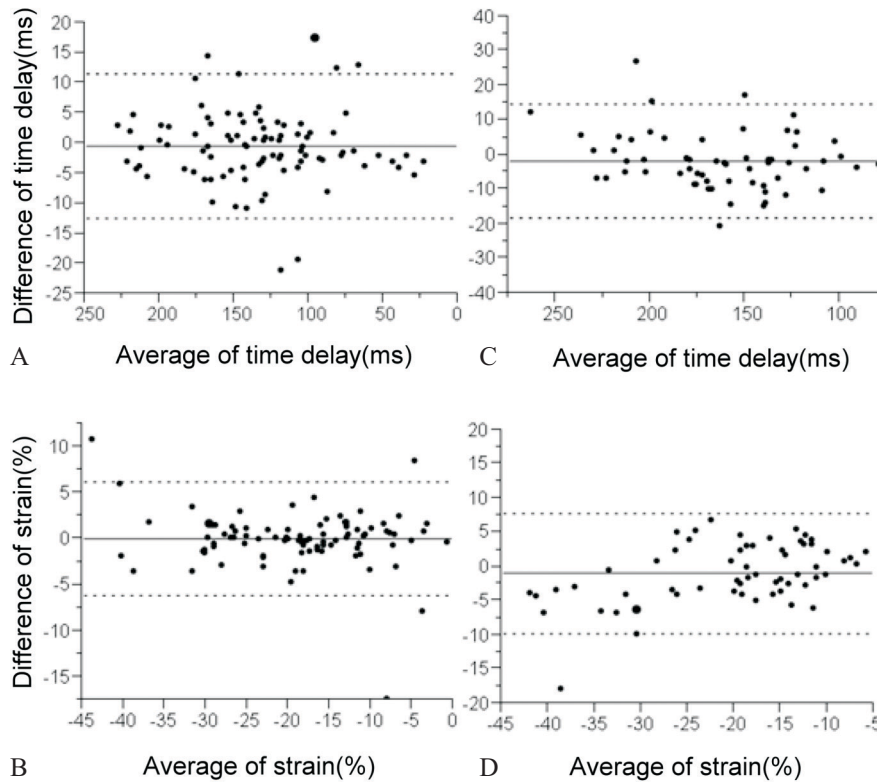


Figure 3. Bland-Altman analysis of intra (A, B)- and inter (C, D)-observer's variability in measurement of time delay and strain.

but contribute actively to ventricular filling. In this study, we demonstrated the presence of atrial mechanical dysfunction and dyssynchrony in the DDD mode, using strain echocardiography. In addition, we presented hemodynamic and mechanics evidence indicating that these atrial mechanical abnormalities result in reduced transmitral filling and consequentially lower ventricular stroke volume and systolic strain in the DDD mode. These multiple lines of evidence suggest that VDD pacing in dua-chamber pacemaker provides a more favorable mechanical and hemodynamic profile compared to DDD mode.

It is well known that pacing of the RA appendage significantly worsens interatrial conduction delay, as reflected by the prolonged P-wave duration on the surface ECG, and interatrial conduction time on intracardiac electrograms.^{4,19,20} Cha et al. measured LA and LV pressure directly, using Millar catheter, to define optimal mechanical LA-to-LV delay. They found shorter mechanical LA-to-LV delay, suggestive of increased interatrial conduction delay, in the DDD mode.⁵ Previous studies have shown that RA pacing significantly in-

creases interatrial mechanical delay by M mode and Doppler echocardiography.^{4,21} However, M mode has its limitations since it can only interrogate a limited number of ventricular and/or atrial walls.²¹ Similarly, transmitral Doppler signals are the result of net pressure gradients between the atrium and the ventricle; the timing of Doppler signals does not necessarily correspond to the timing of atrial mechanical activation.⁴ In contrast, tissue Doppler and strain imaging have high spatial and temporal (> 200 frames/s) resolution and depict regional mechanical events directly in virtually any segment of the heart. Matsumoto et al. has shown increased time delay of peak strain in atrial segments, indicating atrial dyssynchrony, during right atrial appendage pacing.²² Our data demonstrated that DDD mode resulted in significant intra-left atrial and inter-atrial mechanical delays, indicating increased intra-left atrial and inter-atrial dyssynchrony.

The significance of LA contribution to LV filling and overall LV performance has been previously noted in animal and clinical studies. Furthermore, in one animal study, atrial pacing has been shown to reduce LV

stroke volume without significant differences in remote regional LV strain.²³ In patients with cardiac resynchronization therapy, right atrial pacing causes decreased LVOT-TVI and diastolic filling time.²⁴ In our study, DDD pacing resulted in sub-optimal ventricular diastolic filling and consequently stroke volume compared to VDD mode. In addition, we also demonstrated atrial mechanical dysfunction, as reflected by decreased active atrial strain, in DDD mode. The mitral A-TVI was comparable between the two modes and seemed not concordant with the above mechanism. Two potential reasons for this discrepancy could be that (1) fusion of mitral E and A waves makes it difficult to separate LV filling into two distinct diastolic phases accurately, and (2) atrial systolic dysfunction is linked to atrial diastolic mechanics, which has influence on left atrial function as conduit and reservoir.

LV global strain along its long axis during systole can be used to assess whole-LV systolic performance, validated by dP/dt.¹⁸ In the present study, although LVEF was not statistically different between VDD and DDD modes, the more sensitive strain measurements demonstrated statistically significant differences in global strain of LV, indicating that LV systolic function is indeed lower in DDD mode. By RV apex pacing, decreased regional strain near pacing sites (apex) compared to remote region (middle and base) has been demonstrated in animal study.²⁵ Our data supports that contention, indicating that RV apex pacing has an unfavorable impact on the LV performance.

As suggested by the present study, atrial abnormality in DDD mode causes decreased LV preload and consequently reduced LV systolic mechanics, resulting in sub-optimal LV performance compared to VDD mode.

LIMITATIONS

The sample size was small. This study was performed with patients at rest, and its findings may not hold true during activity. Regarding global strain, only 6 representative segments in the 4-chamber view rather than all 16 segments of the LV were used.²⁶ There is a small chance that some of the changes in atrial or ventricular performance can be attributed to the 10 bpm difference in heart rate between the two pacing modes. Al-

though our data suggest VDD pacing as the preferred mode of pacing, prevention of atrial fibrillation by increased base rate by atrial pacing may necessitate DDD pacing.^{27,28}

CONCLUSION

Intrinsic atrial activation during VDD pacing preserves atrial contractility and atrial synchrony, resulting in better LV diastolic filling, stroke volume and LV systolic mechanics. Our data suggest VDD as the preferred mode in dual-chamber pacemakers.

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