Original Research

Unfavourable Effects of Continuous, Atrial-Synchronised Ventricular Pacing on Ventricular Systolic and Diastolic Function in Patients with Normal Left Ventricular Ejection Fraction: Usefulness of Tissue and Colour Doppler Echocardiography

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Introduction: Conventional, atrial-synchronised, right ventricular apical pacing (VP) may compromise ventricular function by causing ventricular desynchronisation. The aim of this study was to evaluate the long-term effects of VP on left and right ventricular systolic and diastolic function.

Methods: We studied 21 clinically stable dual-chamber pacemaker recipients (mean age 68 ± 9 years) with normal left ventricular (LV) systolic function. Patients were in long-term sinus rhythm and had intrinsic ventricular activation with narrow QRS complexes. In an intrapatient model, baseline echocardiographic and tissue Doppler imaging (TDI), colour M-Mode (CMM) examinations, as well as plasma B-type natriuretic peptide (BNP) data, were compared to corresponding measurements following a 3-month period of continuous VP.

Results: Following VP we noted significant increases in LV end-systolic volume (p<0.001) and isovolumic relaxation time (p<0.05), as well as a significant decline in LV systolic function based on ejection fraction (p<0.001) and TDI-Sa (p<0.05). VP was associated with worse LV diastolic function, based on CMM-Vp (p<0.05) and increased E/Vp ratio (p<0.05), but with similar E/Ea ratio and BNP levels (p: NS).

Conclusions: VP appears to impair LV systolic and diastolic function and may predispose to higher LV filling pressures.

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Dual-chamber pacing compared to asynchronous ventricular pacing for patients with sick sinus syndrome has been shown to reduce both hospital admissions related to heart failure and the incidence of atrial fibrillation, as well as improving quality of life.[1-3] Available evidence also suggests an unfavourable linkage between atrial-synchronised right ventricular apical pacing (VP) and an increased risk of heart failure, largely for patients with underlying heart disease.[4-6] It remains to be clarified to what extent the concept of the adverse effects of ventricular desynchronisation imposed by VP could also be applied to patients with normal left ventricular (LV) function. In a recent randomised trial,[7] in which almost the half the patients were without organic heart disease, although there was decreased LV fractional shortening in VP patients compared to those with a normal ventricular activation sequence, the occurrence of congestive

heart failure did not differ between the patient groups. Other studies failed to demonstrate significant haemodynamic or functional changes induced by VP that would imply that VP predisposes to heart failure development in patients with normal LV systolic function.[8-10] In particular, the issue of the effects of VP on cardiac diastolic function has not been fully studied, since previous studies did not employ a comprehensive echo-Doppler assessment including more specific data deriving from tissue Doppler imaging (TDI) and colour M-Mode (CMM) echocardiography.[11,12]

The aim of this study was to evaluate the long-term effects of VP on left and right ventricular systolic and diastolic function in usual dual-chamber pacemaker recipients with normal LV systolic function, using serial echocardiographic Doppler data and measurements of plasma B-type natriuretic peptide (BNP).

Patients and methods

We prospectively studied 21 ambulatory patients, 8 men, 13 women, mean age 66 ± 7 years (range 52-83 years), who underwent conventional dual-chamber pacemaker implantation for sick sinus syndrome at least 6 months prior to entering the study. All patients had intrinsic ventricular activation with normal atrioventricular (AV) conduction (PQ interval ≤220 ms) and had narrow QRS complexes (<120 ms). The devices were programmed at the time of implantation with a non-functional ventricular pacing mode by setting a long AV delay >220 ms. Patients were included in the study if they did not have any history of organic heart disease or heart failure, and if they had a normal LV ejection fraction (≥55%), as assessed by echocardiography, in the absence of regional LV wall contraction abnormalities. Eligible patients were clinically stable as outpatients, they did not take antiarrhythmic drugs, and they had their medications unchanged for at least 3 months prior to entering the study. Patients were excluded if they had abnormal AV conduction, hepatic or pulmonary disease or acute metabolic disorder, renal impairment (serum creatinine concentration >2.0 mg/dl), or symptoms or signs of overt heart failure on the basis of physical examination and chest X-ray. Verification of the stability of the underlying cardiac rhythm was performed by documentation of previous 12-lead electrocardiograms, Holter recordings and interrogation of the intracardiac heart rate as well as event histograms. All pacemakers had an active single activity sensor which was programmed at a medium rate responsive slope.

Study protocol

The study was designed to assess the short-term (2 hours) and long-term (minimum 3 months) VP effects on left and right ventricular systolic and diastolic function and to compared them to baseline intrinsic ventricular activation. Clinical, echocardiographic and BNP measurements, together with pacemaker interrogation, were assessed at the following three time points: baseline, short-term and long-term. At each follow-up evaluation ventricular capture was confirmed on a standard 12-lead electrocardiogram, and the number of sensed and paced events was retrieved from the pacemaker event counters. Written informed consent was obtained from all patients. The local research ethics committee approved the study protocol.

Baseline studies were performed during intrinsic ventricular activation with the devices programmed to back up ventricular pacing. To achieve permanent and complete ventricular capture, the AV delay of the devices was programmed shorter, at rate adaptive values of 90-160 ms. For the short-term evaluation, patients were re-studied after a 2-hour resting period during which their tolerance to VP was evaluated. Upon completion of the short-term evaluation, patients were sent home with the device's rate-response function being active, the AV delay set to 90-160 ms, and the lower and upper rate limits left unchanged throughout the study at uniform values of 60 and 125 beats/min. Patients were asked to express their preferred pacing mode on the basis of direct questioning.

BNP analysis and echocardiography

Patients were examined in a supine position after a minimum period of 30 minutes under standardised conditions and continuous ECG monitoring. Venous blood samples were obtained for plasma BNP measurement using a quantitative fluorescence immunoassay kit, the Triage B-Type Natriuretic Peptide test (Biosite Diagnostics, San Diego CA, USA).[13] All BNP assays were analysed immediately after sampling.

Conventional M-mode, 2-dimensional and Doppler echocardiography, including TDI and CMM were performed using the commercially available EnVisor C HD machine (Philips Medical Systems,

Andover MA, USA), operating at 2.5 MHz. All standard measurements were obtained from parasternal long- and short-axis views and apical 4- and 2-chamber views. M-mode was obtained for left and right ventricular end-diastolic diameters (LV-EDD and RV-EDD), left atrium dimension (LA), and interventricular septum and posterior wall thickness. The LV cardiac output (CO) was calculated from the systolic integral velocity in the outflow tract. The LV end-systolic and end-diastolic volumes (LV-EDV and LV-ESV), and the ejection fraction (LV-EF) were estimated using Simpson's biplane method. The pulsed-wave Doppler transmitral velocity profile was performed to record transmitral peak early (E) and late diastolic velocity (A), the deceleration time (DT) and the E/A ratio. The LV isovolumic relaxation time (IVRT) was measured with continuous wave Doppler as the interval between the end of ejection and the onset of mitral inflow. The propagation velocity of early flow into the LV cavity (CMM-Vp) was measured from CMM images. The peak systolic and early diastolic velocities of the filling wave were measured by TDI at the septal and lateral mitral annulus in order to calculate the average TDI-Sa and TDI-Ea, respectively. The TDI-Sa index has been shown to reflect global LV contractility.[14] We used the ratios E/Ea and E/Vp to estimate LV filling pressures.[11,12] Peak systolic and diastolic tricuspid annulus velocities were obtained from TDI (TDI-RVs and TDI-RVd) to evaluate right ventricular function.[15] At least three consecutive measurements were averaged for each echocardiographic parameter by an experienced cardiologist who was unaware of the clinical data.

Statistical analysis

Results are presented as mean ± standard deviation. Patients were used as their own controls. One-way analysis of variance with post-hoc adjustment using the Student-Newman-Keuls test was performed to compare baseline, short-term and long-term pacing data. BNP levels are expressed as median values (25%-75%). A p-value <0.05 was considered statistically significant.

Results

Patient characteristics

Patients had undergone dual-chamber pacemaker implantation 7.8 ± 1.5 months (range, 6-11 months) be-fore entering the study. Ventricular leads were placed in the right ventricular apex region while screw-in atrial leads were positioned in the right atrial appendage. Before pacemaker implantation, patients had mean PR interval 190 ± 16 ms and QRS complex 95 ± 14 ms. At baseline evaluation, patients had LV mass index 109 ± 19 g/m^2, septal thickness 9.2 ± 1.1 mm, and posterior wall thickness 9.1 ± 0.9 mm. Baseline cumulative percent atrial pacing was 85 ± 11% (range 65-97%) and ventricular pacing 6 ± 4% (range 1-13%).

Ventricular pacing during the short-term evaluation was 100%, inducing significant prolongation of the QRS duration to 162 ± 24 ms (p<0.001 vs. baseline) without affecting mean blood pressure measurements (105 ± 6 mmHg vs. 103 ± 5 mmHg, respectively, p: NS). Patients completed the follow-up evaluation at a mean of 3.5 ± 0.5 months (range, 3-4 months). Over the long-term evaluation, the cumulative percentage for atrial pacing was 82 ± 13% (range 50-85%) and for ventricular pacing 98 ± 2% (range 96-100%).

No complications linked to the pacing system function were noted, and all patients maintained AV pacing throughout the study period. With regard to symptoms, 3 patients (14%) complained of palpitations at the beginning of VP. At the end of the study, similar numbers of patients expressed preference for the rhythm with intrinsic ventricular activation (6 patients) and for VP (4 patients), while the rest expressed no particular preference.

Echocardiographic parameters and BNP levels

The effects of VP on the echocardiographic variables and the BNP levels are shown in Table 1. Overall, short-term VP did not change any variable from baseline significantly.

At long-term follow-up, VP did not significantly change atrial, or right and left ventricular dimensions (p: NS). Regarding systolic function, VP resulted in a significant increase of LV-ESV (p<0.001) and a reduction of LV-EF (p<0.001), but was not associated with significant changes in CO. Regarding TDI, VP was associated with a significant reduction in mean TDI-Sa (p<0.05), but not in TDI-RVs (p: NS). Regarding diastolic function, VP resulted in a significant increase of IVRT (p<0.05), whereas DT showed a non-significant trend to higher values (p: 0.06). No significant changes were noted in peak Doppler E and A velocities, TDI-Ea or TDI-RVd (p: NS). In ad-

Table 1. Echocardiographic parameters and B-type natriuretic peptide (BNP) levels.

	Narrow QRS	Paced QRS, short-term	Paced QRS, long-term	p (Narrow QRS vs. Paced QRS, long-term)
HR (beats/min)	63 ± 6	64 ± 6	64 ± 5	NS
LV-EDD (mm)	50 ± 4	-	51 ± 4	NS
RV-EDD (mm)	37 ± 4	-	38 ± 5	NS
LA (mm)	39 ± 5	-	40 ± 4	NS
LV-EDV (ml)	81 ± 17	77 ± 16	75 ± 28	NS
LV-ESV (ml)	30 ± 8	29 ± 9	34 ± 8[1]	<0.001
LV-EF (%)	64 ± 5	62 ± 7	59 ± 5[2]	<0.001
CO (l/min)	4.6 ± 0.6	4.3 ± 0.7	4.6 ± 0.9	NS
E/A	0.92 ± 0.26	0.89 ± 0.33	1.10 ± 0.56	NS
DT (ms)	209 ± 37	225 ± 36	227 ± 48	NS
IVRT (ms)	112 ± 27	127 ± 28	127 ± 29	<0.05
MR (4-grade score)	0.5 ± 0.5	0.6 ± 0.5	0.6 ± 0.5	NS
TDI-Sa (cm/s)	7.6 ± 1.6	7.6 ± 1.7	6.8 ± 1.4[2]	<0.05
TDI-Ea (cm/s)	7.0 ± 1.7	6.6 ± 1.4	6.7 ± 1.6	NS
TDI-RVs (cm/s)	13.3 ± 2.1	12.9 ± 3.3	12.4 ± 2.1	NS
TDI-RVd (cm/s)	9.2 ± 1.6	8.8 ± 2.5	10.4 ± 2.2[2]	NS
CMM-Vp (cm/s)	35.0 ± 9.3	31.4 ± 6.8	29.8 ± 6.9	<0.05
E/Ea	9.5 ± 2.1	9.6 ± 2.1	10.6 ± 2.5	NS
E/Vp	1.9 ± 0.6	1.8 ± 0.6	2.4 ± 0.6	<0.05
BNP (pg/ml) median (25%-75%)	81 (38-143)	62 (32-130)	132 (27-186)[3]	NS

[1]p<0.001, [2]p<0.05, and [3]p<0.01 refer to differences between Paced QRS, short-term vs. Paced QRS, long-term.

A – transmitral late diastolic velocity; CMM – colour M-Mode; CO – cardiac output; DT – early filling deceleration time; E – transmitral early diastolic velocity; Ea – TDI mean early transmitral diastolic velocity; EDD – end-diastolic diameter; EDV – end-diastolic volume; EF – ejection fraction; ESV – end-systolic volume; HR – heart rate; IVRT – isovolumic relaxation time; LA – left atrium; LV – left ventricular; MR – mitral regurgitation; E – transmitral early diastolic velocity; RA – right atrium; RV – right ventricular; RVd – peak diastolic tricuspid annulus velocity; RVs – peak systolic tricuspid annulus velocity; Sa – TDI mean peak systolic myocardial velocity; TDI – tissue Doppler imaging; Vp – transmitral early diastolic flow propagation velocity.

dition, there was a significant reduction of the CMM-Vp index (p<0.05) with VP, suggesting advanced diastolic dysfunction. Both ratios E/Ea and E/Vp, indicative of LV filling pressures, increased following VP and the value of E/Vp was significantly greater (p<0.05).

The plasma BNP levels changed little in response to acute VP (p: NS) and showed a tendency to increase after longer lasting VP (p: NS). Following long-term VP, 16 patients (76%) exhibited BNP levels below 100 pg/ml. Interestingly, the remaining five patients, with BNP levels higher than 100 pg/ml, also had baseline levels above 100 pg/ml.

Discussion

Preventing cardiac dysfunction in pacemaker therapy has recently become a worthwhile goal in itself. The results of this study indicate an unfavourable link between VP and LV systolic and diastolic function in patients with a normal LV-EF. Since ventricular dysfunction has a major impact on prognosis, our study suggests that even when AV synchrony is preserved, VP should be avoided as much as possible.

Considering ventricular systolic function, our findings of decreased LV-EF and TDI-Sa indexes following VP are in agreement with those of previous studies in which ventricular stimulation was found to affect the LV contractile efficiency negatively.[9,16,17] Based on our data, it could be argued that the reduced systolic function following VP might be attributed to the significantly higher end-systolic volume, resulting in an unfavourable rightward movement of the ventricular pressure-volume loop. With the newly introduced TDI-derived RVs index[15] a similar negative impact of VP on right ventricular systolic function could not be demonstrated.

Abnormalities in diastolic function are increasingly recognised to play, if not a primary, a major contributory role in heart failure development.[18] To the best of our knowledge, this is the first analysis of diastolic cardiac function through the integrated use

of TDI and CMM Doppler echocardiography in dual-chamber pacemaker patients. Based on the conventional Doppler evaluation, in agreement with the few available data,[19,20] our findings of notable prolongations of DT and IVRT following VP suggest retardation of LV relaxation. It is important to consider that the progression of diastolic dysfunction is usually accompanied by both impaired LV relaxation and progressive elevation of LV filling pressures, which carry a dismal prognosis. The integration of TDI and CMM Doppler information facilitates the exact characterisation of the degree of diastolic dysfunction and helps to predict the intracardiac filling pressures non-invasively. Evidence has been provided that the TDI-Ea and CMM-Vp indexes relate to LV relaxation,[21] whereas the ratios E/Ea and E/Vp correlate with LV filling pressures.[11,12] Therefore, our findings of decreased TDI-Ea and CMM-Vp and increased E/Ea and E/Vp ratios in response to longer lasting VP add strength to the assumption that VP is associated with progressively worse diastolic dysfunction. However, other conventional echocardiographic data which precluded a restrictive transmittal pattern (i.e. prolonged DT and IVRT, normal E/A ratio) together with E/Ea ratio values not exceeding 15,[12] imply that VP does not lead to severely reduced LV compliance and pronounced increases of LV filling pressures. In this study, through the TDI-RVd index,[15] we have also shown that VP may not negatively affect right ventricular diastolic function.

The evaluation of BNP in this investigation could possibly add valuable adjunctive diagnostic and prognostic information in VP patients, since elevations of BNP have been associated with increased LV filling pressures. It has been suggested that BNP values of 25-62 pg/mL might be used to rule out isolated diastolic abnormalities seen on echocardiography, regardless of whether the patient has symptoms of heart failure.[22] Our finding of a wide spread of baseline BNP values during intrinsic ventricular activation agrees very well with the likelihood of pre-existing diastolic abnormalities that is expected in a such an elderly pacemaker population.[18,21,22] Some previous studies showed that VP does not significantly affect BNP levels in patients with preserved LV-EF.[23,24] Our study showed increased BNP levels following longer lasting VP, even though four fifths of our patients had values lower than the established cutoff of 100 pg/ml, which was the level of greatest sensitivity and specificity for diagnosing heart failure.[25] This, in

agreement with the abovementioned echo-Doppler data, supports the concept that VP does not cause severe LV dysfunction in patients with a normal LV-EF. On the other hand, patients with baseline BNP >100 pg/ml had a further BNP increase following longer lasting VP, which was not related to symptomatic status. In the clinical setting this suggests that VP may be deleterious in patients with high baseline BNP levels.

Study limitations

Although we did not individualise the AV delay in our patients, we chose the optimal reported range,[26] which has been shown to offer a haemodynamic advantage at rest and during exercise. Secondly, one could criticise our results for applying only to resting conditions. Nonetheless, it could be argued that even this moderate degree of worse LV function would gradually turn to a more severe one during exercise. Lastly, mitral TDI measurements in this study were obtained from the medial and lateral annulus according to a concept which has been applied in previous landmark studies.[11,12] We did not perform TDI measurements of the inferior and anterior aspects, which would have been of some additive value for the global characterisation of patients with normal LV function, owing to time-consuming methodological constraints.

Conclusions

Our findings suggest that VP in patients with normal LV systolic function is associated not only with reduced LV systolic function, but also with a moderate degree of worsening LV diastolic function, possibly triggering higher LV filling pressures. It is particularly worrying that reliance on potential discomfort symptoms with VP appears to be inadequate, since both modes of pacing were equally well-tolerated. Our results attain preventive significance, since it might be argued that such elderly pacemaker patients with possibly pre-existing diastolic abnormalities[18] may be more vulnerable to the progression of ventricular dysfunction[27] over time as a result of VP itself. As a practical implication, concerted efforts should be made to maintain a normal activation sequence, particularly in patients with high BNP levels. In general, although a short AV delay is legitimate in current clinical practice, a longer AV interval should be preferred in order to minimise VP.

References

1. Andersen HR, Thuesen L, Bagger JP, et al: Prospective randomized trial of atrial versus ventricular pacing in sick-sinus syndrome. Lancet 1994; 344: 1523-1528.

2. Connolly SJ, Kerr CR, Gent M, et al: Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. N Engl J Med 2000; 342: 1385-1391.

3. Lamas GA, Lee KL, Sweeney MO, et al: Mode Selection Trial in Sinus-Node Dysfunction. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med 2002; 346: 1854-1862.

4. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al: MOde Selection Trial Investigators. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003; 107: 2932-2937.

5. Wilkoff BL, Cook JR, Epstein AE, et al: Dual chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual chamber And VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002; 288: 3115-3123.

6. Moss AJ, Zareba W, Hall WJ, et al: Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002; 346: 877-883.

7. Nielsen JC, Kristensen L, Andersen HR, et al: A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. J Am Coll Cardiol 2003; 42: 614-623.

8. Lau CP, Tai YT, Leung WH, et al: Rate adaptive pacing in sick sinus syndrome: effects of pacing modes and intrinsic conduction on physiological responses, arrhythmias, symptomatology and quality of life. Eur Heart J 1994; 15: 1445-1455.

9. Vardas PE, Simantirakis EN, Parthenakis FI, et al: AAIR versus DDDR pacing in patients with impaired sinus node chronotropy: an echocardiographic and cardiopulmonary study. Pacing Clin Electrophysiol 1997; 20: 1762-1768.

10. Schwaab B, Kindermann M, Schatzer-Klotz D, et al: AAIR versus DDDR pacing in the bradycardia tachycardia syndrome: a prospective, randomized, double-blind, crossover trial. Pacing Clin Electrophysiol 2001; 24: 1585-1595.

11. Garcia MJ, Ares MA, Asher C, et al: Color M-Mode flow velocity propagation: an index of early left ventricular filling that combined with pulsed Doppler peak E velocity may predict capillary wedge pressure. J Am Coll Cardiol 1997; 29: 448-454.

12. Ommen SR, Nishimura RA, Appleton CP, et al: Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000; 102: 1788-1794.

13. De Lemos JA, McGuire DK, Drazner MH: B-type natriuretic peptide in cardiovascular disease. Lancet 2003; 362: 316-322.

14. Alam M, Wardell J, Anderson E, et al: Characteristics of mitral and tricuspid annular velocities determined by pulsed wave Doppler tissue imaging in healthy subjects. J Am Soc Echocardiogr 1999; 12: 618-628.

15. Meluzin J, Spinarova L, Dusek L, et al: Prognostic importance of right ventricular function assessed by Doppler tissue imaging. Eur J Echocardiography 2003; 4: 262-271.

16. Leclercq C, Gras D, Le Helloco A, et al: Hemodynamic importance of preserving the normal sequence of ventricular activation in permanent cardiac pacing. Am Heart J 1995; 129: 1133-1341.

17. Jutzy RV, Feenstra L, Pai R, et al: Comparison of intrinsic versus paced ventricular function. Pacing Clin Electrophysiol 1992; 15: 1919-1922.

18. Vasan RS, Benjamin EJ, Levy D: Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 1995; 26: 1565-1574.

19. Rosenqvist M, Isaaz K, Botvinick EH, et al: Relative importance of activation sequence compared to atrioventricular synchrony in left ventricular function. Am J Cardiol 1991; 67: 148-156.

20. Stojnic BB, Stojanov PL, Angelkov L, et al: Evaluation of asynchronous left ventricular relaxation by Doppler echocardiography during ventricular pacing with AV synchrony (VDD): comparison with atrial pacing (AAI). Pacing Clin Electrophysiol 1996; 19: 940-944.

21. Sohn DW, Chai IH, Lee DJ, et al: Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol 1997; 30: 474-480.

22. Hammerer-Lercher A, Ludwig W, Falkensammer G, et al: Natriuretic peptides as markers of mild forms of left ventricular dysfunction: effects of assays on diastolic performance of markers. Clinical Chemistry 2004; 50: 1174-1183.

23. La Villa G, Padeletti L, Lazzeri C, et al: Plasma levels of natriuretic peptides during ventricular pacing in patients with a dual chamber pacemaker. Pacing Clin Electrophysiol 1994; 17: 953-958.

24. Horie H, Tsutamoto T, Ishimoto N, et al: Plasma brain natriuretic peptide as a biochemical marker for atrioventricular sequence in patients with pacemakers. Pacing Clin Electrophysiol 1999; 22: 282-290.

25. Maisel AS, Krishnaswamy P, Nowak RM, et al: Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 18: 161-167.

26. Lau C-P, Wong C-K, Leung W-H, et al: Superior cardiac hemodynamics of atrioventricular synchrony over rate responsive pacing at submaximal exercise: Observations in activity sensing DDDR pacemakers. Pacing Clin Electrophysiol 1990; 13: 1832-1837.

27. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW: Progression of systolic abnormalities with isolated diastolic heart failure and diastolic dysfunction. Circulation 220; 105: 1195-2120.