Adverse Effects of Continuous Ventricular Pacing in Patients with Slower Atrial Fibrillation and Normal Left Ventricular Systolic Function

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Background: Both heart rate irregularity during chronic atrial fibrillation (AF) and ventricular desynchronization imposed by ventricular pacing may compromise ventricular function. We investigated whether heart rhythm regularization achieved through ventricular overdrive pacing (VP) gives additional benefit over rate control alone in patients with AF.

Methods: We studied 27 patients (mean age 72 ± 7 years) with AF and normal left ventricular (LV) systolic function who were implanted with a common VVIR pacemaker. Cardiac function was assessed by using serial echocardiographic conventional, tissue Doppler imaging (TDI) and color M-Mode (CMM) examinations, together with B-type natriuretic peptide (BNP) measurements. Baseline data were obtained during AF (mean heart rate 58 ± 5 beats/minute) with the pacemakers programmed to ventricular mere back-up pacing. These data were compared to the corresponding measurements following a 2-week VP period after the devices had been programmed to a lower rate of 70 beats/min, ensuring most of the time continuing VP.

Results: Continuous VP compared to AF, reduced the LV cardiac index (2.28 ± 0.44 l/min/m² vs 2.33 ± 0.39 l/min/m², $P < 0.05$), increased the LV end-systolic volume (38 ± 14 mL vs 35 ± 11 mL, $P < 0.05$), and decreased the TDI-derived systolic and diastolic mitral velocity (8.1 ± 1.8 cm/s vs 8.3 ± 1.6 cm/s, and 8.1 ± 1.8 cm/s vs 8.3 ± 1.6 cm/s, respectively, both $P < 0.05$) and the CMM-derived transmitral early diastolic flow propagation velocity (37.6 ± 9.2 vs 41.5 ± 9.7 , $P < 0.05$). Following VP, both ratios E/Ea and E/Vp showed a trend toward increase ($P = \text{NS}$), whereas BNP rose up to 25.5% (median value, from 111 pg/mL to 165 pg/mL, $P < 0.01$).

Conclusion: VP may be considered disadvantageous compared to slower AF.

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Heart rate irregularity during atrial fibrillation (AF) has been shown to compromise cardiac function with several mechanisms including beat-to-beat variations in ventricular filling, elevated pressures, reduced cardiac output, inefficient ventricular mechanics, and neurohormonal activation.^{1–3} Pharmacological^{4,5} or interventional therapies^{6–9} influencing the hemodynamic consequences of irregular AF, either do not have any effect or they have not yet been implemented in the clinical practice. So far, little consideration has been paid to the possibility that heart rate regularization might be achieved through simple right ventricular api-

cal overdrive pacing (VP). In a study with mixed population characteristics, short-term VP indicated an improved cardiac output at short-term pacing length cycles in comparison with the same cycle length during AF.¹⁰ In the usual clinical context, if a patient is assigned to pharmacological rate-control strategy to avoid rapid ventricular response, but needs a pacemaker for bradycardia support, it has been not clarified whether or not the use of VP is superior to the underlying slower AF. In this case, it would be of concern if any potential benefits achieved by the regular VP rhythm were thwarted by the

adverse effects of the pacing induced ventricular dyssynchrony.^{11,12}

The purpose of this prospective study was to determine whether or not VP is considered advantageous over irregular AF in patients who have a normal left ventricular (LV) systolic function and an indication for conventional ventricular pacing with rate response (VVIR) pacemaker. This question was investigated by using serial echocardiographic conventional, tissue Doppler imaging (TDI) and color M-Mode (CMM) examinations as well as plasma B-type natriuretic peptide (BNP) measurements in short- as well as in mid-term follow-up evaluation studies.

METHODS

Patients

We prospectively studied 27 ambulatory patients with chronic AF who had been implanted for at least 6 months with a rate-adaptive VVIR pacemaker using standard techniques. Patients had acceptable spontaneous heart rates, but all had standard indication for permanent cardiac pacing to avoid symptomatic intermittent bradycardic episodes of less than 40 beats/min or ventricular pauses of at least 3 seconds. All ventricular leads had been positioned at the right ventricular apex and all devices were since the implantation programmed to ventricular back-up pacing at a lower rate of 50 beats/min and upper rate limit of 130 beats/min.

Patients would be included in the study if they did not have any history of organic heart disease and if they had normal LV systolic function $\geq 50\%$, as assessed by echocardiography. Patients were considered for enrollment in the study if they were clinically stable, were not pacemaker-dependent, had proper pacemaker operation, had narrow QRS complexes < 120 ms during irregular AF and if they had percent intrinsic ventricular conduction before the beginning of the study $> 80\%$. Eligible patients were all on identical and unchanged pharmacological therapy for at least 3 months prior to investigation ensuring adequate rate control, which was defined as ventricular response ranges at rest < 80 beats/min.¹³ This was achieved by the use of first-line agent diltiazem ($n = 27$), in combination with digoxin ($n = 5$) or beta-blocker ($n = 5$). Patients were excluded if they were in New York Heart Association functional class $> II$, had other

rhythm than AF, had clinically significant lung or hepatic disease or renal impairment (serum creatinine concentration > 2.0 mg/dL), had abnormal thyroid function and severe valvular heart disease. Great care was given to exclude patients who had experienced any clinical event after the pacemaker implantation necessitating hospitalization. The stability of heart rhythm was verified on review of the hospital records, 24-hour Holter recordings, when possible, and the stored pacemaker event counters and histograms at the planned follow-up visits.

Study Protocol

The study was designed to assess the effects of short-term (2 hours) and mid-term (minimum 2 weeks) VP on the left and the right ventricular systolic and diastolic function and to compare them with those of slower AF aiming to assess the optimal ventricular rhythm without substantially increasing the patient's heart rate. Patients were examined at rest in supine position under standardized conditions and continuous electrocardiographic monitoring. Clinical, echocardiographic, and BNP indices together with pacemaker check-up were assessed at the following time points: Baseline, short-term, and mid-term. At each evaluation ventricular capture was confirmed on 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.

Baseline studies were performed during AF, with the devices chronically programmed to back-up pacing. For the short-term evaluation pacemakers were programmed to VVIR base rate 70 beats/min and patients were restudied after a 2-hour VP period during which the tolerance of pacing was evaluated. Upon completion of the short-term evaluation, patients were sent home with the pacemaker programmed as VVIR with lower rate limit set at 70 beats/min and the upper rate set at 130 beats/min. Repeat studies for the mid-term evaluation were performed after a minimum 2-week period, during which the medications were kept constant. Patients were asked to express their preferred pacing mode on the basis of direct questioning.

BNP Analysis and Echocardiography

Venous blood samples were obtained after a minimal 30-minute resting period for plasma BNP

measurements using the Triage B-Type Natriuretic Peptide test (Biosite Diagnostics, San Diego, CA, USA), a quantitative fluorescence immunoassay kit.¹⁴ All BNP assays were analyzed after sampling immediately.

Conventional M-mode, two-dimensional and Doppler echocardiography including TDI and CMM were performed using the EnVisor C HD (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 four- and two-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 maximum right atrial (RA) and LA volume was measured by planimetry using the biapical Simpson's rule. The LV stroke volume (SV) and cardiac index (CI) and were calculated using flow velocity integral from pulsed Doppler, and the LV systolic and diastolic volumes (EDV and ESV) and the ejection fraction (EF) were estimated using the Simpson's biplane method. The pulsed-wave Doppler transmitral velocity profile was analyzed to record transmitral peak early diastolic velocity (E) and deceleration time (DT). The LV isovolumetric relaxation time (IVRT) was taken from the end of aortic valve ejection to the onset of LV filling. The severity of mitral regurgitation was quantified on a scale from none (0) to severe (4). The early diastolic flow propagation velocity (CMM-Vp) was measured from CMM images.¹⁵ The average peak systolic (TDI-Sa) and early diastolic (TDI-Ea) velocity of the filling wave was calculated by measuring the septal and lateral mitral annulus velocities. We used the ratios of E/Ea and E/Vp to estimate LV filling pressures.^{14–17} Peak systolic and diastolic tricuspid annulus velocity was obtained by TDI (TDI-RVs and TDI-RVd) to estimate RV function.¹⁸ At least five consecutive measurements were averaged for each echocardiographic parameter by an experienced cardiologist who was unaware of the clinical and BNP data. LV mass index was calculated according to Devereux's formula divided by body surface area.¹⁹

Statistics

Data are presented as mean $\pm$ SD. Patients were used as their own control. Nominal data are presented as percentage of patients, and nonparamet-

ric parameters were compared by Fisher's exact test or Wilcoxon test. Values obtained in each individual at the short- and mid-term visits were related to those obtained in the same patient at baseline. Data were analyzed by one-way repeated measures of variance with post hoc adjustment using the Student-Newman-Keuls test. BNP levels are expressed as median values (25–75%). A P value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Twenty-seven patients with mean age of 72 ± 7 years (range, 65–91 years) were evaluated in this study. Information on their clinical characteristics is summarized in Table 1. Nineteen of these patients (70%) were male. Nine patients (33%) reported a history of well-controlled arterial hypertension by taking antihypertensive drugs. Four patients had type 2 diabetes and were taken on oral hypoglycemic agent. Patients were in chronic AF for 35 ± 29 months (range, 9–120 months) at the time of enrollment, and had baseline average resting ventricular rate of 58 ± 5 beats/min (range, 47–64 beats/min). None of the patients had a history of thromboembolism. Patients had LV mass index 105 ± 24 g/m², septal thickness 9.7 ± 1.2 mm, and posterior wall thickness 9.8 ± 1.0 mm.

Table 1. Baseline Patient Characteristics

Age (years)	72 $\pm$ 7
Sex, n, male/female	19/8
Atrial fibrillation/flutter, n	27/0
AF duration (months)	35 $\pm$ 29
Underlying heart disease, n (%):	
Arterial hypertension	9 (33)
Mitral regurgitation grade 1 or 2	7 (26)
None	11 (41)
Diabetes mellitus, n (%)	4 (15)
NYHA class I or II, n (%)	27 (100)
Mean heart rate during AF (beats/min)	58 $\pm$ 5
Medications, n (%):	
Diltiazem	27 (100)
ACE inhibitor	8 (30)
Beta blocker	5 (19)
Digoxin	5 (19)
Diuretic	4 (15)
Warfarin	27 (100)
Left ventricular ejection fraction (%)	61 $\pm$ 6

Data are given as means $\pm$ SD unless specified otherwise. ACE = angiotensin-converting enzyme; AF = atrial fibrillation; LV = left ventricular; NYHA = New York Heart Association functional class.

The percentage of VP during the short-term evaluation at rest was in all patients 100%. VP increased the baseline QRS duration of 90 ± 16 ms to 156 ± 18 ms ($P < 0.001$). Compared with baseline AF, there was no significant effect of VP on mean blood pressure (105 ± 6 mmHg vs 103 ± 5 mmHg, $P = \text{NS}$). All patients completed the follow-up evaluation at a mean of 15.6 ± 1.0 days (range, 14–17 days). On average, percentage of VP for all patients over the 2-week period was $74 \pm 8\%$ (range, 65–89%).

Baseline AF was associated with palpitations in 11 patients (41%) and dyspnea in eight patients (30%). Six patients (22%) complained of palpitations at the beginning of VP, which however disappeared before the end of short-term pacing period. Three patients (11%) reported symptomatic improvement with continuing VP. At the study conclusion, when patients were generally asked which mode they

preferred, eight patients expressed preference for VP, six patients felt worse with VP, whereas the rest were undecided.

Echocardiographic Parameters and BNP Levels

The effects of short- and mid-term VP on the echocardiographic variables and the BNP levels are shown in Table 2. Overall, VP was found to have an unfavorable impact on the cardiac function compared to AF. No significant changes were noted between the two pacing modes in the left and the right atrial and ventricular sizes and volumes except from a significant increase in ESV following short-term as well as mid-term VP (from 35 ± 11 mL at baseline to 38 ± 13 mL and 38 ± 14 mL, respectively, both $P < 0.05$).

Table 2. Echocardiographic Parameters and BNP Levels

	AF, baseline	VVIR, short term	VVIR, mid term	P (AF vs VVIR midterm)
LV-EDD (mm)	49 ± 4	—	51 ± 6	NS
RV-EDD (mm)	40 ± 5	—	41 ± 6	NS
LA (mm)	47 ± 6	—	47 ± 6	NS
LA (mL)	113 ± 56	—	112 ± 53	NS
RA (mL)	89 ± 46	—	91 ± 44	NS
EDV (mL)	91 ± 24	93 ± 26	89 ± 28	NS
ESV (mL)	35 ± 11	$38 \pm 13^*$	38 ± 14	<0.05
LV-EF (%)	61 ± 6	60 ± 6	61 ± 7	NS
SV (mL)	78 ± 16	$60 \pm 10^\dagger$	63 ± 11	<0.05
CI (L/min/m ²)	2.33 ± 0.39	$2.17 \pm 0.35^\dagger$	2.28 ± 0.44	<0.05
Peak E (cm/s)	95 ± 16	$90 \pm 21^\dagger$	95 ± 15	NS
DT (ms)	199 ± 68	189 ± 57	191 ± 50	NS
IVRT (ms)	102 ± 25	$113 \pm 30^\dagger$	114 ± 22	<0.01
TDI-Sa (cm/s)	7.7 ± 1.0	$7.2 \pm 0.8^*$	7.4 ± 1.2	<0.05
TDI-Ea (cm/s)	8.3 ± 1.6	$8.0 \pm 1.8^*$	8.1 ± 1.8	<0.05
TDI-RVs (cm/s)	12.3 ± 1.6	11.8 ± 1.7	11.9 ± 2.1	NS
TDI-RVd (cm/s)	11.3 ± 2.5	$10.2 \pm 1.9^\dagger$	10.7 ± 2.5	<0.01
CMM-Vp (cm/s)	41.5 ± 9.7	$37.3 \pm 10.3^*$	37.6 ± 9.2	<0.05
E/Ea	11.7 ± 2.2	11.6 ± 3.0	12.0 ± 2.4	NS
E/Vp	2.36 ± 0.44	2.53 ± 0.71	2.61 ± 0.47	NS
MR grade	0.5 ± 0.6	0.6 ± 0.6	0.7 ± 0.7	NS
BNP (pg/mL)				
Median (25%-75%)	111 (83–222)	110 (84–224)	165 (115–247)	<0.01

P column shows P values for comparison of AF baseline and VVIR pacing mid-term.

* $P < 0.05$, $^\dagger P < 0.01$, and $^\ddagger P < 0.01$, refer to differences between AF baseline and VVIR pacing short-term.

AF = atrial fibrillation; BNP = B-type natriuretic peptide; CI = cardiac index; CMM = Color M-Mode; 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; IVRT = isovolumetric relaxation time; LA = left atrium; LV = left ventricular; MR = mitral regurgitation; RA = right atrium; RV = right ventricular; RVs = peak systolic tricuspid annulus velocity; RVd = peak diastolic tricuspid annulus velocity; Sa = TDI mean peak systolic myocardial velocity; SV = stroke volume; TDI = Tissue Doppler imaging; Vp = transmitral early diastolic flow propagation velocity.

For systolic function, short-term VP for 2 hours significantly reduced the SV and the CI (from 78 ± 16 mL to 60 ± 10 mL and from 2.33 ± 0.39 l/min/m² to 2.17 ± 0.35 l/min/m², respectively, both $P < 0.05$), decreased the TDI-Sa (from 7.7 ± 1.0 cm/s to 7.2 ± 0.8 cm/s, $P < 0.05$) and increased the ESV (from 35 ± 11 mL to 38 ± 13 mL, $P < 0.05$). After 2 weeks of VP, there was also a significant reduction of SV and the CI (from 78 ± 16 mL to 63 ± 11 mL and from 2.33 ± 0.39 l/min/m² to 2.28 ± 0.44 l/min/m², respectively, both $P < 0.05$) and a significant decline in TDI-Sa (from 7.7 ± 1.0 cm/s to 7.4 ± 1.2 cm/s, $P < 0.05$), whereas the ESV significantly increased from 35 ± 11 mL to 38 ± 14 mL ($P < 0.05$).

For diastolic function, short-term VP significantly decreased the Peak E wave (from 95 ± 16 cm/s to 90 ± 21 cm/s, $P < 0.01$), the TDI-Ea (from 8.3 ± 1.6 to 8.0 ± 1.8 cm/s, $P < 0.05$), the TDI-RVd (from 11.3 ± 2.5 cm/s to 10.2 ± 1.9 cm/s, $P < 0.01$) and the CMM-Vp (from 41.5 ± 9.7 cm/s to 37.3 ± 10.3 cm/s, $P < 0.05$), and significantly increased the IVRT (from 102 ± 25 ms to 113 ± 30 ms, $P < 0.01$). After 2 weeks of VP, the TDI-Ea, the TDI-RVd and the CMM-Vp were still significantly reduced (8.1 ± 1.8 cm/s, 10.7 ± 2.5 cm/s and 37.6 ± 9.2 cm/s, respectively, $P < 0.05$ vs baseline), the IVRT was also found prolonged (114 ± 22 ms, $P < 0.01$ vs baseline), but there were no more significant changes in Peak E.

The ratios E/Ea and E/Vp, indicative of LV filling pressures, exhibited a trend toward increase, particularly did not significantly change following neither short-term nor mid-term VP ($P = \text{NS}$). The plasma BNP levels were found elevated up to 25.5% on the mid-term evaluation ($P < 0.01$).

DISCUSSION

This study showed that VP may be harmful to patients with AF, since the price paid for the relative rhythm regularization may be confounded by some hemodynamic considerations. In essence, our results comply, though to a lesser degree, with the already proven detrimental effects of asynchronous or synchronous RV pacing over native sinus rhythm on ventricular function.^{20,21} As evidence-based guidelines for or against the use of VP in patients with AF are lacking, our results may help the decision-making physician to optimize pacemaker programming in setting the de-

vice's low rate limit to a minimum, just to ensue needed pacing.

Previous experimental and clinical studies have highlighted the persistent adverse effects of irregular cycle lengths on ventricular performance compared to the regular cycle lengths at the same average rate.¹⁻³ However, there is no agreement that rate regularization per se confers symptomatic and functional advantages. Whereas rate regularization contributed to the benefits of atrioventricular junction ablation and pacing,^{6,7} no ventricular pacing study^{8,22} has demonstrated improvement in symptoms or ejection fraction. Since heart rate irregularity itself does appear more disadvantageous at shorter ventricular cycle lengths,^{22,23} patients with well-controlled ventricular rates, such as our patient population, may be satisfactorily treated. In this regard, irregular rate control was better than regular paced rhythm following His-bundle ablation²⁴ when compared at relative high heart rates of approximately 85 beats/min. Our trial design permitted comparison of VP to intrinsic AF most of the time, by setting the initial pacemaker's base rate low, a programming that is usually implemented in clinical practice.

In this study, VP was associated with some unfavorable effects on the left and right ventricular function, not only acutely but in the mid-term evaluation as well. First, VP seems to affect LV contractility adversely in patients with AF, even though this was not evident by evaluating the traditional LV ejection fraction. The stroke volume and the cardiac index were found significantly decreased following both short-term and mid-term evaluation despite the pacing-induced increase in the heart rate. This is in agreement with the significantly reduced TDI-Sa parameter during VP, which is considered to be an indicator of global left ventricular systolic function.²⁵ Considering diastolic function, the combination of the increased IVRT with the coinciding decreases in TDI-Ea and CMM-Vp may be interpreted to suggest long-term pacing effect toward impaired LV relaxation. It is noteworthy that, VP affected the diastolic function of the right ventricle, as documented by the significant decreases in TDI-RVd,¹⁶ only short-term, which may indicate adaptation to longer lasting pacing. Of particular concern was the finding of the progressively increased E/Ea and E/Vp ratios, indicating that VP may lead to higher LV filling pressures.

The effect of VP on BNP was also considerable. While the BNP levels did not change significantly

following VP acutely, they increased 25.5% by continuing VP and without causing any symptoms. Since elevated BNP levels have been recognized, regardless of the patient's symptoms, as not only to reflect the degree of ventricular dysfunction but also to correlate with LV pressures and prognosis,^{26,27} it could be argued that a longer duration of VP might trigger higher BNP increments with possible unforeseen consequences.

Finally, a definitive judgment about patient acceptance or possible symptomatic benefit resulting from VP could not be drawn. Some patients preferred VP over annoying irregular AF, whereas others experienced gradual adaptation to continual VP. These observations are consistent with a report, which did not demonstrate improved quality of life with ventricular response pacing in order to regularize ventricular rate during AF.⁹

Study Limitations

In our study TDI- and CMM-derived indices were surrogate to LV filling pressures, but invasive measurements might have offered a more accurate hemodynamic profile to substantiate our conclusions. However, in the clinical setting it is not feasible to routinely subject outpatients to catheterization. Besides, one could argue that our observations mainly apply to resting conditions. However, beyond pharmacologic rate control, our patients were given the possibility to have physiologic heart rate responses during exercise with the use of the rate-adaptive mode. In addition, our results are to be interpreted in consideration that a longer period of VP may impart different effects on the cardiac function. Last, functional measurement might be more clinically appropriate than echocardiographic comparisons to document the benefit of either programming. On the other hand, by evaluating BNP, which have been shown to play a role as marker of functional capacity,¹⁴ our finding of higher BNP levels following VP may indicate disadvantage compared to spontaneous AF on an ambulatory level.

REFERENCES

1. Clark DM, Plumb VJ, Epstein AE, et al. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. *J Am Coll Cardiol* 1997;30:1039-1045.
2. Daoud EG, Weiss R, Bahu M, et al. Effect of an irregular ventricular rhythm on cardiac output. *Am J Cardiol* 1996;78:1433-1436.
3. Lau CP, Leung WH, Wong CK, et al. Haemodynamics of induced atrial fibrillation: A comparative assessment with sinus rhythm, atrial and ventricular pacing. *Eur Heart J* 1990;11:219-224.
4. Hagens VE, Van Veldhuisen DJ, Crijns HJ, et al. Implication from randomized trials of rate and rhythm controls on management of patients with persistent atrial fibrillation. *Ann Noninvasive Electrocardiol* 2006;11:170-186.
5. The Atrial Fibrillation Follow-up Investigation on Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825-1833.
6. Ozcan C, Jahangir A, Friedman PA, et al. Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. *N Engl J Med* 2001;344:1043-1051.
7. Jensen SM, Bergfeldt L, Rosenquist M. Long-term follow-up of patients treated by radiofrequency ablation of the atrioventricular junction. *Pacing Clin Electrophysiol* 1995;18:1609-1614.
8. Simpson CS, Yee R, Lee JK, et al. Safety and feasibility of a novel rate-smoothing ventricular pacing algorithm for atrial fibrillation. *Am Heart J* 2001;142:294-300.
9. Tse HF, Newman D, Ellenbogen KA, et al. Effects of ventricular rate regularization pacing on quality of life and symptoms in patients with atrial fibrillation (Atrial fibrillation symptoms mediated by pacing to mean rates [AF SYMPTOMS study]). *Am J Cardiol* 2004;94:938-941.
10. Vankawala V, Markabawi B, Dainiak S, et al. Left ventricular function in atrial fibrillation during overdrive pacing. *Am Heart J* 2002;143:827-832.
11. Tse H-F, Lau CP. Long-term effect of right ventricular pacing on myocardial perfusion and function. *J Am Coll Cardiol* 1997;29:744-749.
12. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: Executive summary. *Circulation* 2001;104:2118-2150.
13. Tse HF, Lau CP. Long-term effect of right ventricular pacing on myocardial perfusion and function. *J Am Coll Cardiol* 1977;29:744-749.
14. De Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. *Lancet* 2003;362:316-322.
15. Rivas-Gotz C, Manolios M, Thohan V, et al. Impact of left ventricular ejection fraction on estimation of left ventricular filling pressures using tissue Doppler and flow propagation velocity. *Am J Cardiol* 2003;91:780-784.
16. Nagueh SF, Middleton KJ, Kopelen HA, et al. Doppler tissue imaging: A noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997;30:1527-1533.
17. Ommen S, 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.
18. 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.
19. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J Cardiol* 1986;57:450-458.
20. Wilkoff BL, Cook JR, Epstein AE, et al. Dual Chamber and VVI Implantable Defibrillator Trial Investigators.

- 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.
21. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. Multicenter Automatic Defibrillator Implantation Trial II Investigators. *N Engl J Med* 2002;346:877-883.
22. Sawayama T, Nezuo S, Tsuda T, et al. Noninvasive evaluation of diastolic filling patterns in patients with atrial fibrillation by ejection time and preceding cycle length. *Am J Cardiol* 1980;45:1005-1012.
23. Gosselink AT, Blanksma PK, Crijns HJ, et al. Left ventricular beat-to-beat performance in atrial fibrillation: Contribution of Frank-Starling mechanism after short rather than long RR intervals. *J Am Coll Cardiol* 1995;26:1516-1521.
24. Levy T, Walker S, Mason M, et al. Importance of rate control or rate regulation for improving exercise capacity and quality of life in patients with permanent atrial fibrillation and normal left ventricular function: A randomized controlled study. *Heart* 2001;85:171-178.
25. 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.
26. Maisel AS, Koon J, Krishnaswamy P, et al. Utility of B-natriuretic peptide as a rapid, point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. *Am Heart J* 2001;141:367-374.
27. Maeda K, Tsutamoto T, Wada A, et al. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. *Am Heart J* 1998;135:825-832.