The acute effect of atrioventricular pacing on sympathetic nerve activity in patients with normal and depressed left ventricular function

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Segerson NM, Wasmund SL, Daccarett M, Fabela ML, Hammond CH, Stoddard G, Smith ML, Hamdan MH. The acute effect of atrioventricular pacing on sympathetic nerve activity in patients with normal and depressed left ventricular function. Am J Physiol Heart Circ Physiol 295: H1076–H1080, 2008. First published June 27, 2008; doi:10.1152/ajpheart.91404.2007.—Although modest elevations in pacing rate improve cardiac output and induce reflex sympathoinhibition, the threshold rate above which hemodynamic perturbations induce reflex sympathoexcitation remains unknown. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressures (MAP) and sympathetic nerve activity (SNA) were measured during normal sinus rhythm (NSR) and atrioventricular (AV) sequential pacing in 25 patients. Pacing was performed at 100, 120, and 140 beats/min with an AV interval of 100 ms. Patients were divided into two groups based on normal or abnormal left ventricular ejection fraction (LVEF): group 1 (n = 11; mean LVEF, 55%) and group 2 (n = 14; mean LVEF, 31%). In group 1, relative to NSR, SBP decreased an average of 2%, 3%, and 8% at 100, 120, and 140 beats/min (P < 0.001), respectively. DBP and MAP increased 9%, 15%, and 15% (P = 0.001) and 3%, 6%, and 5% [P = not significant (NS)], respectively. In group 2, SBP reductions were even greater, with an average decrease of 4%, 8%, and 16% (P < 0.001). Whereas DBP increased 9%, 9%, and 8% at 100, 120, and 140 beats/min (P = NS), MAP increased 3% and 2% at 100 and 120 beats/min but decreased 3% at 140 beats/min (P = 0.001). SNA recordings were obtained in 11 patients (6 in group 1 and 5 in group 2). In group 1, SNA decreased during all rates, with a mean 21% reduction. In group 2, however, SNA decreased at 100 and 120 beats/min (49% and 38%) but increased 24% at 140 beats/min. Patients with depressed LVEF exhibited altered hemodynamic and sympathetic responses to rapid sequential pacing. The implications of these findings in device programming and arrhythmia rate control await future studies.

right ventricular (RV) pacing induces an iatrogenic left bundle branch block that prohibits normal left ventricular (LV) contractile mechanics. Specifically, there is a reduction in LV chamber efficiency, LV peak dP/dt, and isovolumetric relaxation time (1, 7). These hemodynamic perturbations are associated with increased levels of cardiac sympathetic activity (1) and an increased risk of hospitalization and mortality, particularly in patients with depressed LV ejection fraction (LVEF) (11). As the pacing rate increases, the rate-mediated increase in cardiac output overcomes the RV pacing-induced hemodynamic perturbations, resulting in a net increase in blood pressure (BP) and reflex sympathoinhibition (9). Additional increases in pacing rates, however, result in a decrease in cardiac output and reflex sympathoexcitation (8). The cutoff rate above which sympathoexcitation is noted in patients with normal and depressed LV function is unknown.

In the present study, we sought to evaluate the effects of atrioventricular (AV) sequential pacing at different rates on BP, central venous pressure (CVP), and sympathetic nerve activity (SNA) in patients with normal and depressed LV function. Understanding the hemodynamic and sympathetic responses to pacing should greatly enhance our ability to adequately program pacemakers and devices, particularly in patients with depressed LV function.

MATERIALS AND METHODS

Study patients. This study was performed at the University of Utah in Salt Lake City and the Veterans Affairs Medical Centers in Dallas and Salt Lake City. This study was approved by the local institutional review boards. Informed consent was obtained from all patients, and all procedures were in accordance with institutional guidelines. All patients referred for an electrophysiological study between April 2003 and March 2007 were screened. Patients who were not in normal sinus rhythm (NSR) at the time of the study were excluded. A total of 25 patients were enrolled and form the material of this study. Patients were divided into two groups based on the presence or absence of contractile dysfunction, defined as a LVEF ≤50%. Hereafter, patients with preserved LVEF are referred to as group 1 (n = 11) and patients with contractile dysfunction are referred to as group 2 (n = 14).

Electrophysiological studies. Patients were studied in the drug-free postabsorptive state after informed consent was obtained. Two quadripolar catheters were inserted percutaneously and positioned in the high lateral right atrium and RV apex. Atrial and ventricular pacing thresholds were measured, and pacing was performed at twice the diastolic pacing threshold. In addition, a catheter was placed in the right atrium for CVP measurements and a 5-French sheath was placed in the femoral artery for continuous BP monitoring.

Measurements. Effenter, postganglionic muscle SNA was recorded from the left peroneal nerve as previously described (10). Briefly, a sterile microelectrode was inserted into a fascicle of the peroneal nerve near the fibular head. The nerve signals were amplified, filtered (700 to 2,000 Hz), rectified, and discriminated. Raw nerve signals were integrated to produce a mean voltage display for quantitative analysis. Muscle sympathetic nerve bursts during sinus rhythm were readily recognized by their tight temporal relationship to the sinus cardiac cycle, their increasing frequency during Valsalva maneuvers, the occurrence of large bursts accompanying premature ventricular beats, and the failure to respond to arousal stimuli or stroking of the skin in the region of innervation. The SNA was quantified as the total

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area under the curve of filtered nerve recordings during bursts. CVP and arterial BP measurements were obtained directly from the previously inserted catheter and sheath into the right atrium and femoral artery, respectively. Both SNA and hemodynamic variables were expressed as percent changes relative to their respective values during sinus rhythm before pacing began; thus “0%” depicts no change from the prepacing baseline.

Experimental protocol. After acceptable recordings of SNA, BP, CVP, and heart rate were obtained, the following protocol was performed. Two minutes of baseline recordings were obtained, followed by three 2-min segments of AV sequential pacing with predetermined rates (100, 120, and 140 beats/min) and an AV interval equal to 100 ms. The order in which these pacing rates were performed was chosen at random with a 1-min recovery and 1-min repeat baseline before each pacing segment. All measurements were performed during the last minute of baseline and AV pacing. AV pacing was chosen rather than single chamber pacing to prevent asynchronous atrial contraction during ventricular pacing, which is known to perturb sympathetic activity (2, 5).

Analysis and statistics. The total area under the curve of SNA bursts was calculated during the final minute of each pacing period, allowing 1 min of pacing to reach steady state before analysis. Mean systolic peaks [systolic BP (SBP)], mean diastolic troughs [diastolic BP (DBP)], and mean arterial pressure (MAP) were ascertained from the digitalized pressure tracing using commercially available software (Chart v5.5; ADInstruments, Colorado Springs, CO). The percent change for each of these variables was then calculated relative to the period of sinus rhythm preceding each pacing segment.

Population distributions are given as means ± SD unless otherwise specified. To assess interactions between pacing rates and physiological measurements, while accounting for the correlation introduced from the use of within-subject repeated measures, generalized least squares linear random effects models were fitted. For hemodynamic parameters, only primary effects were included in the models. In the SNA model, the effect of rate on SNA was graphically different only at 140 beats/min. Therefore, a continuous rate variable was not appropriate as an independent variable since the effect was not linear. Thus two indicator variables were used for rate: 120 vs. 100 beats/min and 140 vs. 100 beats/min. The group was included as another independent variable (group 2 vs. group 1, which was depressed vs. normal LVEF). Finally, a group × rate-140 interaction term was added.

The rate-120 indicator variable was eliminated in a backward stepwise fashion, leaving one rate indicator variable (140 vs. both 100 and 120 beats/min combined). This permitted a simple interpretation for the interaction term. The interaction term now represents the additional change in SNA for group 2 specific to the 140 beats/min rate, beyond the change attributable to the group difference in SNA.

Statistical significance was defined as $P < 0.05$. All statistical calculations were performed using Stata v9.0.

RESULTS

Clinical characteristics. A total of 25 patients were enrolled with hemodynamic data obtained in all 25 patients. SNA recordings were successfully obtained in 11 subjects. The population included 21 men and 4 women and averaged 60 ± 14 yr of age. The race distribution was 17 Caucasian, 6 Black, 1 Hispanic, and 1 Pacific Islander. Group 1 (LVEF > 50%) included 11 patients with a mean LVEF = 55 ± 4.2%, and group 2 (LVEF ≤ 50%) included 14 patients with a mean LVEF = 31 ± 8%, with 12 having an ischemic etiology for their contractile dysfunction. There were no significant demographic differences between groups 1 and 2. The mean age of the 11 patients with adequate SNA recordings was 51 ± 13 yr. Six of these patients were in group 1 and 5 were in group 2.

The hemodynamic effects of pacing rate. In group 1, relative to NSR, SBP decreased an average of 2%, 3%, and 8% at 100, 120, and 140 beats/min (1.4% decrease per 10 beats/min increase; $P < 0.001$). DBP and MAP increased an average of 9%, 15%, and 15% ($P = 0.001$) and 3%, 6%, and 5% ($P = 0$ not significant (NS)), respectively. In group 2, relative to NSR, a greater reduction in SBP was noted compared with that of group 1, with an average decrease of 4%, 8%, and 16% at 100, 120, and 140 beats/min (2.9% drop per 10 beats/min increase; $P < 0.001$). Whereas DBP increased 9%, 9%, and 8% at 100, 120, and 140 beats/min ($P = NS$), MAP increased 3% and 2% at 100 and 120 beats/min but decreased 3% at 140 beats/min ($P = 0.001$). A summary of the BP changes in group 1 and group 2 is provided in Fig. 1.

In group 1, CVP decreased an average of 1, 1, and 2 mmHg during pacing at 100, 120, and 140 beats/min, respectively. In group 2, no change in CVP was noted at 100 and 120 beats/min with a slight increase of 2 mmHg at 140 beats/min. None of the CVP changes was statistically significant.

The effects of pacing rate on SNA. Sample tracings of SNA during baseline and rapid pacing from a patient with normal LVEF (group 1) and a patient with depressed LVEF (group 2) are provided in Figs. 2 and 3, respectively. In group 1, SNA...

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Fig. 1. The mean changes in blood pressure (BP) parameters in group 1 (A) and group 2 (B). The reference point (0%) for each measurement is the BP during sinus rhythm before pacing. Multivariable models showed rate effected an increase in systolic BP (SBP: $P < 0.001$) and a decrease in diastolic BP (DBP: $P < 0.001$) in group 1, with mean arterial pressure (MAP) not significantly effected. In group 2, rate exhibited even greater effects on SBP but had less effect on DBP ($P = 0$ not significant (NS)). MAP increased 3% and 2% at 100 and 120 beats/min (bpm) but decreased 3% at 140 beats/min ($P = 0.001$). LVEF, left ventricular ejection fraction.
decreased during all pacing rates, with a mean reduction of 21% relative to sinus rhythm. In group 2, SNA decreased during pacing at 100 and 120 beats/min (49% and 38%, respectively) but increased by 24% at 140 beats/min. Although the confidence intervals (CIs) about the point estimate of the mean SNA at rate 140 beats/min in group 2 cross zero, the combined effect on SNA of 140 beats/min pacing and contractile dysfunction was statistically significant in the multivariable model; that is, pacing at 140 beats/min in group 2 increased SNA by 67% (95% CI 4.0; 131%), \( P = 0.04 \), beyond the group differences at 100 and 120 beats/min. A summary of the SNA changes in both groups is provided in Fig. 4. Surprisingly, there were no significant correlations between SNA and any arterial pressure parameters, suggesting that other autonomic feedback mechanisms might be involved.

**DISCUSSION**

The main findings from this study are: 1) in patients with normal LV contractile function, AV sequential pacing at rates ranging between 100 to 140 beats/min resulted in progressive increases in mean BP with concomitant sympathoinhibition; and 2) in patients with impaired contractile function, increases in mean BP and sympathoinhibition were noted at 100 and 120 beats/min; however, a decrease in mean BP and a trend toward increased sympathetic activity were noted at 140 beats/min. Our findings strongly suggest that AV sequential pacing at 140 beats/min should be avoided in patients with depressed LV function.

**Hemodynamic changes during AV sequential pacing.** The hemodynamic changes associated with AV sequential pacing have been reported in several studies (3–6, 9). The factors at play include the AV relationship, pacing rate, and cardiac...
function. At any given rate, the timing of atrial systole has been shown to impact the hemodynamic response with closely coupled atrial and ventricular systole, resulting in increases in atrial and pulmonary pressures and a decrease in the cardiac index (3, 4). At rates ≤100 beats/min, increases in BPs have been noted presumably due to rate-mediated increases in cardiac output (9). However, at faster rates, decreases in diastolic filling result in decreases in the cardiac index and BP (5). The threshold above which a decline in the cardiac index and BP is observed depends greatly on cardiac function. Our findings suggest that in patients with normal LVEF, AV pacing with rates up to 140 beats/min results in an increase in mean BP. However, in patients with a depressed LVEF, an increase in mean BP was observed at 100 and 120 beats/min with a decrease noted at 140 beats/min, suggesting that such rates should be avoided in this patient population.

**Sympathetic changes during AV sequential pacing.** Taylor et al. (9) evaluated muscle SNA in 13 patients with dual-chamber pacemakers during 3 min of ventricular pacing and AV sequential pacing at a rate equal to 60 and 100 beats/min. Sympathetic activity decreased with cardiac pacing, and the decline was greater with AV pacing when compared with ventricular pacing. These findings were true in patients with normal and depressed LVEF. We have previously evaluated the effects of AV sequential pacing at a rate of 175 beats/min on BP, CVP, and muscle SNA in 11 patients with dual-chamber pacemakers (5); LV function was normal in seven patients, mildly depressed in two patients, and moderately depressed in two patients. Sympathetic activity increased in all seven patients in whom successful SNA recordings were obtained, and the increase in SNA was significantly greater during closely coupled atrial and ventricular systole compared with long R-P tachycardia. Although these two studies clearly showed sympatohihibition at rates ≤100 beats/min and sympathoexcitation at a rate of 175 beats/min, the effects of AV sequential pacing at rates >100 and <175 beats/min remain
Fig. 4. The mean changes in SNA in both groups. The reference point (0%) for each measurement is the SNA during sinus rhythm before pacing. SE estimates are indicated with whisker bars. In a multivariable model, the combined effect of pacing at 140 beats/min and left ventricular dysfunction (group 2) increased SNA by 67% (95% confidence interval 4.0, 131%), P = 0.04, relative to all other observations.

unclear. More importantly, the cutoff rate above which we see a shift from sympato-inhibition to sympato-excitation is unknown. In the present study, we found that the effects of AV sequential pacing on SNA differed depending on the presence of normal or abnormal LVEF. In patients with normal LVEF, AV sequential pacing with rates up to 140 beats/min resulted in a decrease in sympathetic activity, whereas in patients with depressed LVEF, sympato-inhibition was noted at 100 and 120 beats/min with a shift toward sympato-excitation at 140 beats/min. The absence of a significant change in CVPs and the reciprocal changes noted between BP and SNA suggest that this is an arterial baroreceptor-mediated mechanism.

Clinical implications. In patients with dual-chamber pacemakers or implantable defibrillators, AV sequential pacing is commonly used with a rate exclusively mediated by sensor-driven programming. To our knowledge, no previous studies have evaluated the effects of AV pacing on sympathetic activity at the commonly used upper sensor rates of 120 and 140 beats/min. The findings from the present study suggest that in patients with normal LVEF, AV sequential pacing with rates up to 140 beats/min is acceptable and even favorable as far as the hemodynamic and sympathetic responses are concerned. However, in patients with depressed LVEF, AV sequential pacing at rates greater than 120 beats/min should be avoided due to the decrease in BP and reflex sympatho-excitation. Increased sympathetic activity in patients with depressed LVEF has long been recognized as being detrimental both as far as arrhythmogenesis and as a contributing factor to the vicious cycle of heart failure decompensation. Therefore, in patients with depressed LVEF, it is preferable to limit the upper sensor rate to 120 beats/min.

Limitations. There are several limitations of this study. First, our findings might not apply to AV sequential pacing with different AV delays. We used a short AV delay to guarantee ventricular capture. Previous studies suggested that a short AV delay resulted in better hemodynamics compared with that of longer AV delays due to increases in filling time. Therefore, we doubt that the results would be significantly different with longer AV delays. Second, we used RV pacing, and our findings could certainly be different with biventricular pacing. However, our data are relevant to clinical practice since RV pacing is commonly used in patients with an indication for pacing despite the presence of LV dysfunction unless the patient has baseline electrical dysynchrony or underwent AV junction ablation. Third, our study was performed with the patients in the supine position at rest, and the results are likely to be different in the upright position and during exercise. Nonetheless, our findings represent a reference and impetus for future studies including measurements during exercise. Finally, our sample size was small. However, this limitation is implicit in the difficulty of these human experiments. Statistical significance was nonetheless achieved, even after adjusting for repeated within-subject measures, but this sample size does not allow for an analysis of other potential clinical covariates.

Conclusion
When compared with patients with normal contractile function, patients with depressed LVEF exhibited strikingly different rate responsiveness in their hemodynamic and sympathetic responses to rapid AV sequential pacing. The implications of the present findings in device programming and arrhythmia rate control in these patients await future studies.

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REFERENCES