Characteristics of the Acute Rise of Atrial Natriuretic Factor During Ventricular Pacing*

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**Background:** Previous studies have shown that peripheral venous levels of atrial natriuretic factor (ANF) are elevated during ventricular pacing as a result of asynchrony of atrial and ventricular contraction. However, the pattern by which ANF rises following institution of ventricular pacing has not been fully established and its physiologic consequences are unclear.

**Methods:** Eight ambulatory patients in stable condition with dual-chamber pacemakers were studied. The pacemaker was reprogrammed from the dual-chamber to the ventricular pacing mode for 3 h, during which serial measurements were made of BP, heart rate and rhythm, levels of ANF, and plasma renin activity (PRA).

**Results:** ANF levels rose markedly but slowly following the onset of ventricular pacing, reaching levels as high as 694% of control. The rise occurred over the course of 120 min, at which time the average value for the group plateaued at 82.5 ± 22.1 fmol/mL (mean ± SEM) vs 25.3 ± 4.5 fmol/mL at control (p < 0.01); there was, however, marked variability in individual responses. By contrast, levels of PRA remained remarkably stable. Average BP changes were small, although there was a trend in the later part of the study for systolic pressure to decrease.

**Conclusions:** ANF levels rise markedly but gradually after institution of ventricular pacing and, hence, acute pacing studies must account for this delay in their design. The physiologic importance of the rise in ANF should be evaluated further since the rise in peptide levels may be associated with a decrease in systolic BP.

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**Key words:** artificial pacing; atrial natriuretic factor

**Abbreviations:** ANF = atrial natriuretic factor; PRA = plasma renin activity

It is known that levels of atrial natriuretic factor (ANF) are elevated during ventricular (VVI) pacing, and since the peptide has natriuretic, diuretic, and vasodilator properties, it has been implicated in the pathophysiology of pacing-induced hypotension and pacemaker syndrome. Furthermore, levels of ANF at rest and during stress have been used to evaluate the physiologic performance of various pacing modalities.

It is, therefore, surprising that the characteristics of the time course and the pattern by which ANF rises following the onset of ventricular pacing have not been fully established; additionally, the physiologic role of the hormone in this setting has remained unclear. This study was designed to characterize the acute rise of ANF following the onset of ventricular pacing and to establish at what point the levels stabilized, so that future studies could be planned accordingly. In addition, observations were made on the response of the BP and urinary output.

**Materials and Methods**

**Patients**

Eight ambulatory patients with dual-chamber pacemakers (five men and three women; mean ± SEM age, 66 ± 3 years; range, 51 to 77 years) were studied. The pacemakers were chronically programmed to the dual-chamber (DDD) mode. Indications for implantation were ativoventricular block in six patients, sinus node dysfunction in one patient, and both conditions in another patient. Two subjects had no associated organic heart disease. Among the remaining six subjects, four patients had aortic regurgitation, two patients had hypertensive cardiovascular disease, one patient had coronary artery disease, and two patients had previously undergone cardiac surgery (aortic valve replacement in one patient and coronary bypass grafting in the other patient). All eight patients were in stable condition in New York Heart Association functional class I or II. Exclusion criteria included the presence of chronic, sustained atrial arrhythmias.
symptomatic valvular heart disease, overt congestive heart failure, and severe pulmonary or systemic hypertension. Informed consent was obtained from all patients according to a protocol approved by the Committee on Human Rights in Research of the Cornell Weill Medical College.

Protocol

Patients arrived fasting on the day of the study, bringing a completed urine collection from the preceding 24 h and having withheld the morning doses of diuretics and cardioactive medications, except for digoxin (one patient). The study began between 8:05 AM and 9:10 AM. Patients were observed in the supine position throughout the study, except for designated periods of standing. An indwelling catheter was placed in a forearm vein for blood drawing, and a cardiac monitor was attached. Since the study involved prolonged periods of observation, patients were allotted equally between two experimental sequences in order to identify any potential effects of time on the study findings; they were not told which sequence would be followed. The four patients in group 1 followed a sequence of control observation in the DDD mode, which consisted of 5 min standing and 30 min supine; this was followed by VVI pacing for 180 min supine and 5 min standing, and then a recovery period in the DDD mode consisting of 60 min supine and 5 min standing. The four patients in group 2 were observed in the control DDD period, which was followed by pacemaker interrogation without reprogramming and, hence, continuation of the DDD mode for an additional 60 min. Following this, VVI pacing was instituted for 180 min. Periods of standing were included at times analogous to the first sequence. During VVI, the pacemaker rate was programmed to exceed the control rate by an average of 3 ppm (range, 0 to 10 ppm). In one instance, the pacing rate had to be increased from 75 to 80 ppm at 60 min of the VVI pacing period because of interference from the native rhythm. BP was measured at frequent intervals; blood for ANF was drawn frequently during VVI pacing and at the conclusion of each experimental period; blood for plasma renin activity (PRA) and 10 mL for storage was drawn at the end of each experimental period.

In seven of the eight subjects, all freely voided urine was collected before the control period, at the end of each experimental period and at any point during the study that the subject needed to void. No urinary catheters were placed, and no IV fluid or forced oral intake was employed. Urine flow rates during the study were calculated from the volume voided and the time elapsed since a prior output of urine. For the urine collection of the previous day, the flow rate was calculated by dividing the volume by the 24-h period.

Assays

Blood for ANF determination was drawn directly from the indwelling venous cannula into prechilled Vacutainer tubes (Becton Dickinson; Rutherford, NJ) containing potassium ethylenediamine tetra-acetic acid and then transported on ice to the laboratory; samples were processed and underwent radioimmunoassay according to previously described procedures21; values are expressed as femtomoles per milliliter. PRA was determined by radioimmunoassay as previously described,22 and values are expressed as nanograms per milliliter per hour.

Statistical Methods

Group data are expressed as the mean ± SEM. Group means were compared using Mann-Whitney and Wilcoxon signed-rank tests for nonnormally distributed data. Serial hormonal and BP measurements were compared to control values using analysis of variance for repeated measures in conjunction with tests of multiple comparisons. Associations between relative changes in BP and hormonal values were tested with linear regression and standard Pearson correlation. All p values are two tailed and considered significant below the 0.05 level.

Results

Clinical Findings

All patients completed the protocol without complications. Marked hypotension precluded measurement of BP in one patient at 5 min of standing during VVI pacing and in another patient during the recovery DDD period. In the control period, the cardiac rhythm consisted of AV sequential dual chamber pacing in four patients, atrial synchronous ventricular pacing in three patients and normal sinus rhythm in one patient. Thus, four patients had electronic atrial stimulation (average rate, 71/min) and four patients had native atrial activation (average rate, 70/min). During VVI pacing, there was dissociated atrial activity in seven patients and retrograde atrial activation in one patient; the atrial rate averaged 65.0/min and the ventricular rate averaged 73.5/min.

ANF Rise

Peripheral venous levels of ANF began to rise within minutes of VVI pacing (Fig 1, 2); however, they rose gradually and, surprisingly, they continued to climb until 120 min of pacing, at which point they plateaued, with values of 82.5 ± 22.1 fmol/mL at 120 min (p < 0.01 vs control), 81.4 ± 17.9 fmol/mL at 150 min (p < 0.01 vs control), and 78.5 ± 17.8 fmol/mL at 180 min (p < 0.01 vs control).

![Figure 1. ANF rise and BP changes during VVI pacing. Average ANF values (left ordinate) and average systolic BP (SBP) and diastolic BP (DBP) [right ordinate] in relation to the pacing modality. *Statistically significant inverse correlation (r = 0.88, p < 0.004).](http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21979/)
Although each patient showed a rise in ANF, there was large variability among the individual responses (Fig 2), with the maximal increments ranging from 40% to as much as 694% of control values. The return of ANF values to baseline was complete by 60 min of recovery in the dual chamber mode (26.2 ± 4.1 fmol/mL at recovery vs 21.8 ± 3.7 fmol/mL at control) for the four patients in group 1 in whom the recovery measurement was available by experimental design. There was no important influence of the duration of the study on the results obtained, as the only difference between group 1 and group 2 patients was that the latter reached plateau values at 120 min of VVI pacing and the former at 90 min.

Finally, the four patients who had electronic atrial stimulation in the DDD mode had an average control value of 24.0 ± 6.6 fmol/mL, which was not significantly different than the control value of 26.6 ± 7.0 fmol/mL for the four patients with native atrial activity. This result, which is in accordance with other studies, argues against the supposition that the electronic stimulus itself acts to increase ANF.

Changes in PRA

In contrast to the changes in ANF during VVI pacing, PRA remained remarkably stable. The control value averaged 1.3 ± 0.4 ng/mL/h in the DDD mode, compared with 1.1 ± 0.2 ng/mL/h after 180 min of VVI pacing. For the four patients in group 1, the recovery level was 1.1 ± 0.2 ng/mL/h vs 1.8 ± 0.6 ng/mL/h at control (p = not significant).

BP

Serial changes in the average, supine BP of the group were small and did not attain statistical significance (Fig 1). Individual responses, however, were more heterogeneous; therefore, correlations were sought between relative changes in BP and ANF levels. The analysis showed that during the later phase of the VVI pacing period, changes in the systolic BP tended to inversely reflect changes in ANF. Thus, at 120 min, there was a nonsignificant inverse correlation between relative changes in systolic BP and ANF (r = −0.49, p = 0.22), which became statistically significant at 150 min of VVI pacing (r = −0.88, p < 0.004; Fig 1, 3). The patient with retrograde atrial activation had more pronounced changes in BP than the other patients. He showed a decrease in systolic BP at every measured point of the VVI pacing period and a maximal decrease of 20% of the control value at 150 min of pacing. The ANF rise exhibited by this patient, identified by the open circles in Figure 2, was more prompt and sustained than the other patients and reached a peak increment of 652% of control value at 150 min.

We could only estimate urinary flow rates since urinary catheters were not employed. When measured from freely voided urine, the maximal flow rate of 2.41 mL/min during VVI pacing was markedly higher than the average flow rate of the preceding day of 1.21 mL/min calculated from the 24-h collection.

**DISCUSSION**

**Temporal Pattern of ANF Elevation**

This study demonstrates that ANF exhibits a gradual, although marked, rise following the onset of ventricular pacing, requiring an average of 120 min before group values stabilize and, even after that
interval, individual values continue to show considerable fluctuation. The return to baseline on resumption of DDD pacing is complete by 1 h. Although several previous studies\(^1-7,9,10\) have found elevated ANF levels during VVI pacing, short periods of pacing of 10 to 15 min were generally used. A few studies\(^8,11-13\) employed a 30- to 60-min acute pacing period. The current findings demonstrate that ANF continues to rise beyond those time periods, reaching markedly elevated levels before stabilizing. Given the magnitude of the elevation, the peptide may exert physiologic effects on BP, and even on urinary output, that are not detectable with shorter periods of observation. Additionally, if ANF levels are used as a gauge of the physiologic performance of various pacing modalities, sufficiently long periods of VVI pacing should be incorporated into study designs to avoid operating on the ascending limb of the ANF rise curve (Fig 1).

The gradual ANF rise contrasts with the immediate rise in intra-atrial pressure which follows VVI pacing. Ventricular pacing results in an immediate increase in mean atrial pressure in conjunction with the appearance of cannon waves\(^23\) due to inappropriately timed atrial contractions occurring against partly or fully closed atrioventricular valves. Rapid ventricular pacing studies\(^24,25\) that have directly measured atrial pressure and ANF have confirmed that the peaking of ANF levels occurs well after the prompt rise in atrial pressure. The discordance arises because the proximate stimulus to ANF release appears to be atrial stretch rather than atrial pressure.\(^26,27\) Thus, the gradual ANF rise suggests that atrial distention after the start of VVI pacing occurs slowly at a rate determined by the interplay between the pressure pulses (cannon waves) and the compliance characteristics of the atria.

Seven of the eight patients in this study had dissociated atrial activity, and one patient had retrograde VA conduction. The ANF rise seen in the latter patient was more abrupt and sustained than in the others. Retrograde VA conduction leads to consistent, repetitive atrial contraction against closed atrioventricular valves. Dissociated atrial activity, instead, results in atrial contraction occurring randomly in relation to the position of the atrioventricular valves. Consequently, atrial pressure and distention are more marked in patients with VA conduction during ventricular pacing, and the resultant ANF levels are more elevated than in patients with dissociated atrial activity.\(^11,12\)

**Changes in PRA**

The remarkable stability of PRA levels in the presence of marked ANF elevation is noteworthy. In VVI pacing, there are two opposing factors influencing PRA levels. The rise in ANF opposes the release of PRA,\(^14\) whereas the decrease in cardiac output caused by this pacing modality stimulates it. The absence of a detectable change in plasma renin levels after an adequate period of observation suggests that these opposing influences effectively balance each other.

**BP Changes**

The average BP changes of the group during this study were small compared to the marked ANF elevations; still, some patients exhibited considerable decrease in BP, particularly the systolic level. In the later part (120 min and 150 min) of the ventricular pacing period, the relative change in BP bore a modest inverse relationship to the relative ANF increment (Fig 1, 3). These findings are consistent with those of Papadopoulos et al,\(^11\) who reported a 12.77% decrease in systolic BP and a 10.50% decrease in diastolic BP, associated with a 215.95% increase in ANF levels after just 30 min of VVI pacing in 25 patients. The occurrence of the hypotension after only 30 min of pacing is likely the result of the fact that the patients in that study were selected for the presence of retrograde atrial activation, which was present in only one of the eight patients in the current study.

The delayed hypotensive trend associated with the ANF rise in our study is consistent with a causal association, since the hormone would have had time to exert its known vasodilatory, natriuretic, and capillary transudating effects.\(^14\) However, beyond any direct pathophysiologic involvement, the ANF rise might also reflect the degree of activation of neurohumoral vasodilatory atrial mechanisms\(^28-30\) which, combined with a decrease in cardiac output,\(^31-36\) may explain the hypotension induced by VVI pacing.

In addition to hemodynamic changes, atrial distention also commonly causes a diuresis.\(^37\) Although this study was not designed to assess the urinary response to ventricular pacing, it was apparent that several patients exhibited a significant diuresis during VVI pacing and the entire study group appeared to show an increase in urinary flow rates. Given the known decrease in cardiac output during VVI pacing, this preliminary observation is of considerable interest.

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