Ventriculophasic Modulation of Atrioventricular Nodal Conduction in Humans

Allan C. Skanes, MD, FRCP; Anthony S.L. Tang, MD, FRCP

Background—Baroreceptor-mediated phasic changes in vagal tone have been hypothesized to cause ventriculophasic sinus arrhythmia (VPSA). The objectives of this study were to demonstrate ventriculophasic modulation of AV nodal conduction and to substantiate the role of the baroreflex on ventriculophasic AV nodal conduction (VPAVN) by pharmacological perturbation of parasympathetic tone.

Methods and Results—Twelve patients with infra-Hisian second-degree heart block and VPSA were studied. Incremental atrial pacing was performed until AV nodal Wenckebach block at baseline, after phenylephrine infusion, and after atropine. AV nodal conduction curves were constructed for each phase and compared. At baseline, VPAVN was present in 9 of 12 patients on the steep portion of the AV nodal conduction curves. Phenylephrine increased systolic blood pressure from 149 ± 33 to 177 ± 22 mm Hg (P < 0.001) and sinus cycle length from 844 ± 169 to 1010 ± 190 ms (P < 0.001) and shifted the AV nodal conduction curves up and to the right. Phenylephrine induced VPAVN in 2 of 3 patients in whom it was not present at baseline and in 11 of 12 total. Atropine abolished both VPSA and VPAVN in all patients.

Conclusions—VPAVN was demonstrated in patients with infra-Hisian second-degree AV block. It was accentuated by phenylephrine and abolished by atropine, suggesting a baroreflex mechanism for VPSA and VPAVN. (Circulation. 1998;97:2245-2251.)

Key Words: arrhythmia ■ baroreceptors ■ vagus nerve ■ atrioventricular node ■ phenylephrine
ephrine because of baseline systolic hypertension; all had systolic blood pressure \( \geq 180 \text{ mm Hg} \) during baseline 2:1 second-degree heart block. When blood pressure returned to baseline, atropine in sufficient doses to abolish ventriculophasic sinus arrhythmia was given as an intravenous bolus. Measurements during sinus rhythm and incremental right atrial pacing were repeated. This protocol was approved by the institutional review board. After study termination, all patients underwent permanent pacemaker insertion.

At baseline, sinus cycle length and AH intervals were measured. All nine patients with second-degree heart block at baseline had ventriculophasic sinus arrhythmia with sinus cycle length variation of 44±18 ms (Figure 1). For each pacing cycle length, AH intervals were measured in a standard fashion.\(^4,5\) The local His A was measured as the earliest reproducible rapid deflection; the local His was measured as the earliest onset of the His deflection from baseline. As Figure 2 shows, at some paced cycle lengths, the local A could not be measured as the earliest deflection. In these instances, the local A was measured as the first negative deflection at baseline. Once this was the case, all subsequent local A measurements were made in this manner at this pacing cycle length. As such, at each paced atrial rate, beat-to-beat variations in AH interval were measured from a local A identified in the same manner. These measurements were repeated after phenylephrine infusion and atropine. AV nodal conduction curves were constructed by plotting the paced cycle length (AA) interval on the abscissa and the corresponding AH interval on the ordinate. AV nodal conduction curves were constructed for intervals at baseline, after phenylephrine infusion, and after atropine. To assess shifts in AV nodal conduction curves resulting from phenylephrine infusion, three points on each curve were determined and compared: Wenckebach point, AH(s), and AH(l) as described by Page et al.\(^6\) AH(s) refers to the AH interval at the shortest A-A pacing cycle length at which consistent AV nodal conduction was seen at both baseline and with phenylephrine infusion. Likewise, AH(l) refers to the AH interval at the longest A-A pacing cycle length at which consistent AV nodal conduction was seen at both baseline and with phenylephrine infusion.

**Statistical Analysis**

All data are presented as mean±SD. Statistical comparison between groups was performed by a two-tailed paired Student’s \( t \) test. A significant difference was accepted if \( P \leq 0.05 \).
AV Nodal Conduction Characteristics

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<th>Patient</th>
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<th>VPAVN-P</th>
<th>AH(s)-B</th>
<th>AH(s)-P</th>
<th>ΔAH(s)</th>
<th>AH(l)-B</th>
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<th>ΔAH(l)</th>
<th>WBP-B</th>
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VPAVN-B and VPAVN-P indicate ventriculophasic AV nodal conduction at baseline and with phenylephrine infusion, respectively; + and −, presence and absence of VPAVN; AH(s)-B and AH(s)-P, AH(s) at baseline and with phenylephrine infusion; AH(l)-B and AH(l)-P, AH(l) at baseline and with phenylephrine infusion; ΔAH(s) and ΔAH(l), AH(s)-P minus AH(s)-B and AH(l)-P minus AH(l)-B; WBP-B and WBP-P, Wenckebach point at baseline and with phenylephrine infusion; ΔWBP, WBP-P minus WBP-B; and NA, phenylephrine not administered. Values are in milliseconds.

Results

Patient Characteristics

Twelve patients, 7 male and 5 female, with a mean age of 68 ± 16 years were studied. Of the 12 patients, 10 had no preexisting cardiac disease and were not taking cardiac medication at the time of presentation or study. Two patients had preexisting cardiac disease. One patient (patient 10; see the Table) had known mild rheumatic mitral stenosis and paroxysmal atrial fibrillation. For this reason, the patient was taking digoxin and furosemide. The digoxin was discontinued after presentation with second-degree heart block and 2 days before the electrophysiological study. The second patient (patient 11; the Table) was known to have congestive heart failure on the basis of coronary artery disease and previous myocardial infarction, type II diabetes controlled by diet, and mild renal dysfunction with a serum creatinine of 210 μmol/L. This patient was not taking medication known to affect autonomic tone or AV nodal conduction.

Ventriculophasic AV Nodal Conduction

Ventriculophasic AV nodal conduction referred to a consistent pattern of fluctuation of AH intervals at a steady-state atrial pacing rate at which the arterial pressure wave was followed by the longer AH interval. Figure 2A shows an example of 2:1 infra-Hisian heart block at atrial paced cycle length of 840 ms. Ventriculophasic AV nodal conduction was present with alternating AH intervals of 120 and 130 ms. The beat with the longer AH interval was preceded by the arterial pressure. The amount of AH changes caused by ventriculophasic modulation of AV nodal conduction was 10 ms. When higher degrees of AV block occurred, the longest AH interval was again recorded after the arterial pressure wave. The AH interval of the next two beats shortened progressively (190 to 180 ms). The amount of AH changes caused by ventriculophasic AV nodal conduction was 20 ms. Ventriculophasic changes in the AH interval were said to exist if this variation in AH interval was ≥ 5 ms and consistent from cycle to cycle.

Baseline Measurements

At baseline, the mean sinus cycle length was 844 ± 69 ms. All patients had ventriculophasic sinus arrhythmia of 44 ± 18 ms. No patient had ventriculophasic AV nodal conduction in sinus rhythm. During incremental atrial pacing, ventriculophasic AV nodal conduction was noted in 9 of 12 patients (patients 1 through 9; the Table). The maximal AH interval variation caused by ventriculophasic modulation of AV nodal conduction was between 5 and 20 ms, with a mean of 13.3 ± 6.1 ms. The ventriculophasic changes occurred on the steep portion of the AV nodal conduction curves (Figure 3). As illustrated in Figure 2A and 2B, the amount of AH variation caused by ventriculophasic AV nodal conduction increased with increasing atrial paced rate.

Effect of Phenylephrine Infusion

Phenylephrine was infused at a mean dose of 1.3 ± 0.4 mg/kg in nine patients, which increased systolic blood pressure by 27.6% from 149 ± 33 to 177 ± 22 mm Hg (P < 0.001). Sinus cycle length increased by 19.7% from 860 ± 162 to 1010 ± 190 ms (P < 0.001). Of the nine patients who had 2:1 distal heart block during sinus rhythm at baseline study, three did not receive phenylephrine because of systolic hypertension as stated above. Of the remaining six who received phenylephrine, two developed 1:1 conduction during phenylephrine infusion. Hence, only four patients had 2:1 heart block at baseline and during phenylephrine infusion while in sinus rhythm and before atrial pacing. In these four patients, ventriculophasic sinus arrhythmia increased from a mean of 31 ± 10 to 73 ± 42 ms (P = 0.12).
The paced atrial cycle length at which AV nodal Wenckebach occurred increased by 14.4% from $386 \pm 93$ to $441 \pm 119$ ms ($P < 0.03$). Ventriculophasic AV nodal conduction was noted in 8 of 9 patients who received phenylephrine and in 11 of 12 of the total group. The maximal AH interval variation caused by ventriculophasic modulation of AV nodal conduction in the patients who received phenylephrine was $13.8 \pm 4.4$ ms (range, 10 to 20 ms). Six patients who had ventriculophasic AV nodal conduction (VPAVN) at baseline also received phenylephrine. In this group, the magnitude of VPAVN at baseline was $10.0 \pm 5.5$ ms; after phenylephrine, a similar magnitude was seen (11.7±5.2 ms). As noted above, 3 patients did not receive phenylephrine infusion because of hypertension. Phenylephrine infusion brought out ventriculophasic AV nodal conduction in 2 of 3 patients (patients 10 and 11; the Table) in whom it was not present at baseline (Figure 4). Ventriculophasic changes were seen on the steep portion of the AV nodal conduction curve. Furthermore, phenylephrine caused AV nodal conduction curves to shift up and to the right as evidenced by the increase in AV nodal Wenckebach point from $385.6 \pm 93.3$ to $443.3 \pm 117.3$ ms ($P < 0.05$), AH(l) from $63.9 \pm 200.0$ to $82.2 \pm 36.2$ ms ($P < 0.03$), and AH(s) from $138.9 \pm 40.4$ to $171.7 \pm 34.8$ ms ($P < 0.01$).

In one patient (patient 12; the Table) who had no ventriculophasic AV nodal conduction at baseline, phenylephrine at a dose of 1.2 mg/kg did not induce ventriculophasic AV nodal conduction. Yet sinus cycle length increased from 910 to 1160 ms, and systolic blood pressure increased from 148 to 190 mm Hg. There was only a minimal corresponding shift in the AV nodal conduction curve as evidenced by minimal changes in AH(s), AH(l), or Wenckebach point (patient 12; the Table and Figure 5). This is in contrast to the two patients (patients 10 and 11) who had ventriculophasic AV nodal

**Figure 3.** Representative AV nodal conduction curve from a patient with ventriculophasic AV nodal conduction both at baseline and with phenylephrine infusion. AV nodal conduction curves at baseline, with phenylephrine infusion, and after atropine infusion are indicated by circles, triangles, and squares, respectively. Note the presence of ventriculophasic AV nodal conduction on the steep portion of the curves. To indicate the paced AA interval on the conduction curve at which Wenckebach was seen, we arbitrarily chose a corresponding AH interval of 250 ms, which represents the upper limits of our conduction curves. Wenckebach point refers to the paced A-A cycle length at which AV nodal Wenckebach occurred. To distinguish these points from the remainder of the AV nodal conduction curve, Wenckebach points are illustrated as stipple-filled symbols. Points in sinus rhythm and Wenckebach points (WBPs) are indicated. Note that phenylephrine caused the AV nodal conduction curve to shift up and to the right. Atropine caused the curve to shift down and to the left. Filled symbols represent points at which ventriculophasic AV nodal conduction was recorded; open symbols, points at which no ventriculophasic AV nodal conduction was recorded.

**Figure 4.** Representative AV nodal conduction curve from a patient who had ventriculophasic AV nodal conduction induced by phenylephrine infusion. No ventriculophasic AV nodal conduction was seen at baseline. Phenylephrine infusion shifted the curve up and to the right and induced ventriculophasic AV nodal conduction on the steep portion of the curve. Atropine was not given to this patient. Symbols as in Figure 3.
conduction provoked by phenylephrine infusion. These two patients had substantial shifts in their AV nodal conduction curves. This is consistent with a disparate effect of baroreflex-mediated vagal influence on the sinus node and AV node. The single patient without ventriculophasic AV nodal conduction was 69 years old, had no known cardiac disease, was on no medication that would alter the autonomic tone, and had no history of hypertension.

**Effect of Atropine**

Atropine in a mean dose of $1.3 \pm 0.4 \text{ mg}$ was given as an intravenous bolus to 10 of 12 patients. Two patients did not receive atropine because of glaucoma. Atropine shortened sinus cycle length by $33\%$ from 1010 $\pm 190$ to 658 $\pm 109 \text{ ms} (P<0.001)$ and reduced the Wenckebach point by $25\%$ from 443 $\pm 125$ to 334 $\pm 65 \text{ ms} (P<0.005)$. Atropine abolished ventriculophasic sinus arrhythmia and ventriculophasic changes in AV nodal conduction in all patients.

**Discussion**

The major finding of this study is the demonstration of ventriculophasic AV nodal conduction in patients with second-degree infra-Hisian heart block. This ventriculophasic modulation of AV nodal conduction was seen at baseline in 9 of 12 patients with second-degree infra-Hisian heart block and ventriculophasic sinus arrhythmia. When not seen at baseline, it could be induced by phenylephrine infusion in 2 of the 3 remaining patients. Thus, all patients except 1 exhibited this phenomenon. This is the first description of phasic modulation of AV nodal conduction in a model of intact baroreflex.

**Previous Animal Studies**

The phasic effects of baroreceptor-mediated fluctuations in vagal tone on the SA and AV nodes have been studied in animal models. In these studies, brief burst stimulation of the vagal effenter were meant to simulate those caused by stimulation of the baroreflex in response to beat-to-beat fluctuations in arterial pressure.7,8 Burst vagal stimulation was found to cause sinus node slowing in a phase-dependent manner.9-11 At the level of the AV node, most studies found that dromotropic effects were balanced by effects on the sinus node so that 1:1 conduction was maintained over a wide spectrum of stimulation frequencies.12,13 When the input to the AV node was fixed by atrial pacing, however, a direct negative dromotropic response was seen in AV nodal conduction.14 This response of the AV node to postganglionic vagal stimulation during atrial pacing was also found to be phase-dependent.12 Hence, these studies would predict that in the intact reflex, phasic fluctuations in blood pressure would cause phase-dependent changes in AV nodal conduction. Animal studies have used direct fluctuations in blood pressure to cause baroreflex-mediated changes in vagal tone.15-17 Despite measurements on a beat-to-beat basis of AV nodal conduction in these studies, phasic changes in AV nodal conduction were limited by the development of high-degree heart block. Therefore, beat-to-beat fluctuations in AV intervals secondary to the baroreflex were superimposed on typical Wenckebach changes in the AV interval. Furthermore, AH intervals, which better reflect AV nodal conduction, were not measured. Hence, phasic fluctuations in the AH interval on a beat-to-beat basis in isolation of other effects have not been studied previously.

**Previous Human Studies**

Baroreceptor-mediated effects on AV nodal function have been studied in humans. Mancia et al,18 using intravenous nitroglycerin and phenylephrine boluses to cause fluctuations in blood pressure, studied the effect of the baroreflex on the AH and HV intervals both during sinus rhythm and during atrial pacing. As in animal studies, increases in blood pressure were accompanied by sinus slowing. There was little change in AH or HV intervals during sinus rhythm. During atrial pacing, which fixed the input to the AV node, the AH interval changed in direct relation to the blood pressure. Hence, tonic increases in baroreceptor-mediated vagal tone influenced AV nodal conduction in humans. Page et al9 studied the effects of tonic increases in vagal output via a
baroreceptor-mediated mechanism on the AV nodal conduction curve in 10 patients being investigated for syncope or presyncope. Phenylephrine caused an increase in sinus cycle length in all patients and was noted to shift the AV nodal conduction curve up and to the right in 8 of 10 patients. Hence, phenylephrine was found to induce a vagal-mediated effect on AV nodal conduction in these patients. Neither of these studies in humans described the effects of phasic changes in baroreflex-mediated vagal tone on AV nodal conduction.

Our study is unique in that it is the first clear delineation of a phasic modulation of AV nodal conduction in a model of intact baroreflex. Patients with distal infra-Hisian second-degree heart block serve as a unique model in which to study beat-to-beat variations in the AH interval with and without the influence of ventricular systole and therefore the baroreflex. A consistent relationship was found between the AH interval and the preceding QRS complex and arterial pulse. During 2:1 infra-Hisian heart block, the longer AH interval followed the arterial pressure wave and was typically recorded two beats after a QRS complex. This latency consisted of a delay from electrical activation (QRS) to mechanical cardiac output (arterial pulse) and baroreflex latency. This baroreflex latency has previously been shown in animal studies to be approximately 500 ms. In higher degrees of infra-Hisian AV block, the longest AH interval was recorded after the arterial pressure wave; it progressively shortened until the next arterial pulse. This is in keeping with animal studies that demonstrated that the effects of postganglionic brief vagal bursts were maximal in the first beat and dissipated over 5 to 10 beats.

Of 12 patients, 9 had ventriculophasic AV nodal conduction at baseline. Of 3 patients who did not have ventriculophasic AV nodal conduction at baseline, phenylephrine was able to induce it in 2. One patient never exhibited ventriculophasic changes at the AV node, despite the fact that the reflex was intact and operative in this patient. This patient had ventriculophasic sinus arrhythmia at baseline when she presented in 2:1 infra-Hisian heart block. Furthermore, phenylephrine was able to cause a vagal-mediated increase in sinus cycle length. Despite this, no ventriculophasic AV nodal conduction was seen, and the AV nodal conduction curves before and after phenylephrine were virtually superimposable, suggesting that the reflex vagal stimulation had minimal effect on the AV node. Atropine shifted the AV nodal conduction curve down and to the left, suggesting that the AV node was functioning under the influence of some degree of vagal tone. Page et al. using a similar method of autonomic perturbation, found a similar result in 2 of their patients who had sinus slowing with phenylephrine-induced increases in blood pressure. However, AV nodal conduction curves in these patients also remained unchanged. This is consistent with a disparate effect on the SA and AV node, which is known to exist in response to fluctuations in baroreflex-mediated vagal tone in animals and humans.

In all cases in which ventriculophasic AV nodal conduction was seen, it was noted on the steep portion of the AV nodal conduction curve and increased in an absolute amount as the paced atrial rate was increased until Wenckebach occurred. This phenomenon has been noted in models using brief vagal stimuli in dogs. Salata et al. found that the phase-dependent changes in AV nodal conduction were also cycle length dependent; the variation in the AH interval was increased as the paced cycle length decreased. The study by Page et al. found that phenylephrine caused a shift in the AV nodal conduction curve from baseline that was greatest at shorter paced cycle lengths; hence, the vagal-mediated effects of phenylephrine were greatest on the steep portion of the curve. It is therefore not surprising to find a greater vagal-mediated effect inducing ventriculophasic AV nodal conduction on the steep portion of the curve. Atropine abolished both ventriculophasic sinus arrhythmia and ventriculophasic changes in AV nodal conduction in all patients. The ability to accentuate or provoke ventriculophasic changes with phenylephrine and to abolish the effects with atropine strongly suggests a baroreflex-mediated mechanism. Other interacting factors may contribute to the vagal-mediated modulation of the AV node. Vagal stimulation has been shown to cause a shift in the site of sinus nodal pacemakers and a change in the spread of conduction from the SA node to AV node. Furthermore, AV nodal conduction has been shown to be modulated by a change in the relative contributions of the crista terminalis and interatrial septal inputs. In our study, AH measurements were recorded during atrial pacing from the high right atrium; thus, the site of earliest atrial activation was fixed, and the inputs to the AV node were unlikely to shift significantly. Therefore these factors were unlikely to make a significant contribution to our results.

**Clinical Significance**

Ventriculophasic modulation of AV nodal conduction may be important during atrial fibrillation. As in this study, ventriculophasic effects on the AV node have been difficult to demonstrate in sinus rhythm because vagal-mediated sinus slowing reduces the subsequent cycle length of the input to the AV node, thereby attenuating any direct vagal-mediated slowing in AV nodal conduction. During atrial fibrillation, however, the irregular ventricular rate and resultant fluctuations in cardiac output are expected to produce similarly irregular fluctuations in baroreflex-mediated vagal tone. Two recently published studies have demonstrated that rapid fluctuations of vagal tone can contribute to the irregularity of the ventricular response during atrial fibrillation. Although the baroreflex was not investigated directly, it is reasonable to expect that ventriculophasic modulation of AV nodal conduction contributes to the complex dynamics of AV nodal function during atrial fibrillation.

**References**


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