Effects of Atropine and Pirenzepine on Heart Rate Turbulence

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Background: It has been shown that mortality risk in patients after myocardial infarction could be estimated by heart rate turbulence (HRT), a short-term change in heart rate after ventricular premature beat (VPB), presumably caused by baroreceptor mechanism. We sought to determine whether pharmacological blockade with atropine, or augmentation of vagal tone with pirenzepine given in small doses would influence HRT.

Methods: In 30 patients with normal echocardiogram, and without signs or symptoms of coronary artery disease, after electrophysiologic examination or radiofrequency ablation for supraventricular arrhythmias was completed, turbulence onset (TO) and turbulence slope (TS) in basal state, after 1.3 mg IV pirenzepine and finally, after atropine in dose of 0.04 mg/kg of body weight were compared.

Results: As assessed by Friedman ANOVA test both pirenzepine and atropine caused a significant change in both TO ($P < 0.01$) and TS ($P < 0.01$). The mean basal TO of $-3.6 \pm 2.9\%$, changed after pirenzepine to $-5.99 \pm 5.6\%$ ($P < 0.01$), and after atropine it changed to $-3.3 \pm 18.1\%$ ($P < 0.01$). The mean basal TS of 18.6 ± 10.1 ms/R-R interval increased after pirenzepine to 26.8 ± 19.9 ms/R-R interval ($P < 0.05$), and decreased after atropine to 1.2 ± 0.8 ms/R-R interval ($P < 0.01$). Mean cycle length increased after pirenzepine from 706.8 ± 106.8 to 830 ± 151.9 ms ($P < 0.01$), and decreased after atropine to 454.2 ± 58.1 ms ($P < 0.01$).

Conclusion: A conclusion could be drawn that vagomymetic manipulation with intravenous pirenzepine increases HRT; vagal blockade with atropine decreases HRT. This finding suggests that a normal vagal innervation of heart is a prerequisite for the phenomenon of HRT. **A.N.E. 2006;11(1):34-37**

heart rate turbulence; atropine; pirenzepine; mechanism

A recently emerged measurement of mortality risk after myocardial infarction, heart rate turbulence (HRT), refers to short-term variation of heart rate after ventricular premature beat (VPB). In a work of Schmidt,¹ it has been shown that attenuation or absence of HRT implies an enlarged risk of death in patients after myocardial infarction. The suggested mechanism of HRT involves a hemodynamically inefficient VPB, which triggers a short-term perturbation in vagal and sympathetic output, mediated through baroreflex activity.²⁻⁴ Hence, the precondition for normal HRT should be the preserved vagal innervation of heart.⁵ In this study, we sought to determine the effects of vagolytic and vagomymetic

medication on HRT in patients presumably free of structural heart disease.

METHODS

The study was conducted at two specialized cardiovascular clinics, after the ethics committee of both hospitals approved the study protocol.

After giving written informed consent, 30 patients underwent electrophysiological study clinically indicated for assessment and management of supraventricular arrhythmias. Patients with atrial fibrillation, more than 6 VPB/min, signs or symptoms of coronary artery disease, or abnormal

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echocardiogram, as well as contraindications for atropine were excluded. All patients were mildly sedated with midazolame. After standard electrophysiological examination or ablation of supraventricular tachycardia was completed, a study protocol was performed as follows.

A diagnostic catheter placed in the right ventricle was used for induction of VPB. Ten VPB were induced at twice diastolic threshold, and at approximately 75% of sinus cycle length, first in baseline state, then after giving pirenzepine in dose 1.3 mg IV, and finally, after atropine in dose 0.04 mg/kg body weight. Continuous ECG was recorded and later analyzed on a standard digital system (Lab Duo, Bard Electrophysiology, Lowell, MA). After giving a medication and before induction of VPB a 2-minute recording of ECG has been accomplished, in order to determine the effect of drugs on cycle length.

Turbulence onset (TO) was calculated for each VPB, according to a formula previously described.¹ In brief, TO was defined as the difference between the mean of the first two sinus R-R intervals after the compensatory pause and the last two sinus R-R intervals before the VPB, expressed as a percentage; the measurements were subsequently averaged for each patient and in each condition. Turbulence slope (TS) was defined as the maximum positive slope of a regression line assessed over any sequence of five subsequent sinus rhythm R-R intervals within the tachogram RR1, RR2, RR3, ... RR15, where RR_i is the average of *i*th sinus rhythm R-R interval after the compensatory pause of a singular VPB, and was expressed in ms/R-R interval. TS was calculated for each patient in each condition. Values for TO < 0% and for TS > 2.5 ms/R-R interval, were considered normal.

The significance of change of TO and TS after giving pirenzepine and atropine was determined by the Friedman ANOVA test; the effect of pirenzepine and atropine on TS and TO, as well as on cycle length, was evaluated by Wilcoxon rank test.

RESULTS

A total of 30 patients (16 women) were studied. The mean age was 48 ± 20 . The indication for study was atrioventricular nodal reentry tachycardia in 18, atrioventricular tachycardia in WPW syndrome in 10, and isthmus dependent atrial flutter in 2 patients. The mean left ventricular ejection fraction was $57 \pm 4.5\%$.

Figure 1. Effects of pirenzepine on TS (top) and TO (bottom) are shown. Basal values are shown on the left part of the diagram, and values after pirenzepine on right part. TS = turbulence slope; TO = turbulence onset.

At a baseline, the mean cycle length was 706.8 ± 106.8 ms, the mean TO was $-3.6 \pm 2.9\%$, and mean TS was 18.5 ± 10.1 ms/R-R interval. TO was normal in 27 patients, abnormal values being 0%, 2%, and 0.4%. Value for TS was abnormal in 1 patient with 2.4 ms/R-R interval.

As assessed by Friedman ANOVA test, pirenzepine and atropine caused a significant change in both TO ($P < 0.01$) and TS ($P < 0.01$).

After pirenzepine was given, mean cycle length changed from 706.8 ± 106.8 to 830 ± 151.9 ms ($P < 0.01$); mean TO decreased from $-3.6 \pm 2.9\%$ to $-5.99 \pm 5.6\%$ (Fig. 1). This change was again statistically significant ($P < 0.01$). However, there were still abnormal values in 3 patients: 2% in patient number 10 remained the same, in patient 7 TO worsened from 0% to 0.7%, and in patient 18 from

Figure 2. Effect of atropine on TS (top) and TO (bottom). Values before (left) and after atropine (right) are shown. Abbreviations as in Figure 1.

previously normal -7% shifted to abnormal 6% . Patient number 16 changed from abnormal 0.4% to normal -14% .

Mean TS after pirenzepine increased to 26.8 ± 19.9 ms/R-R interval ($P < 0.05$). All patients had normal TS after pirenzepine, including patient number 1, in whom TS changed from 2.4 to 10.2 ms/R-R interval (Fig. 1).

After atropine was given, mean cycle length decreased to 454 ms ($P < 0.01$), mean TO increased to $-3.3 \pm 18.1\%$ ($P < 0.01$), and mean TS decreased to 1.2 ± 0.8 ms/R-R interval ($P < 0.01$) (Fig. 2). TS remained in normal range after atropine only in 2 patients: patient number 9 with 2.6 ms/R-R interval, and patient number 6 with 4.24 ms/R-R interval; in all other patients TS became less than 2.5 ms/R-R interval after atropine was given.

DISCUSSION

The principal finding of this study is that in population presumed to be free of structural cardiac disease, vagomymetic manipulation with intravenous pirenzepine increases TS and decreases TO; secondly, vagal blockade with atropine decreases TS and increases TO.

This finding suggests that normal vagal innervation of heart is a prerequisite for the phenomenon of HRT. As suggested in other studies, the mechanism of the HRT could be as follows. The first event after a VPB is a sudden drop of blood pressure caused by incomplete filling of the left ventricle by the time of the VPB. This drop in blood pressure acts on baroreceptors in great arteries and causes a decrease in neural output to the centers in central nervous system. As a consequence of it, efferent vagal activity decreases, and heart rate increases. Next phase consists of a short-term increase in blood pressure, caused by increased sympathetic discharge, which is due to the same initiating event of transient hypotension; this stimulates baroreceptors, and as a consequence, increases efferent vagal activity from central nervous system to heart, causing a decrease in heart rate.

By giving atropine, vagal activity becomes diminished, and, as previously shown,⁵ shifts parameters of HRT, TS, and TO, to abnormal values. In our patient population this finding has been confirmed. Conversely, by giving a vagomymetic drug, an increase in TS and decrease in TO could be expected. Pirenzepine, a muscarinic blocker, has been previously shown to possess paradoxical vagomymetic effect in small doses, due to its predominant action on presynaptic M1 receptors.^{6,7} In our study, pirenzepine given intravenously in small dose significantly increases cycle length, increases TS, and decreases TO, which is a likely effect of increased vagal tone.

A correlation between impaired autonomic innervation of heart and risk of arrhythmic death in patients after myocardial infarction has been proven.⁸ Therefore, a manipulation of sympathetic influence on heart may reduce the risk of serious arrhythmias. In several studies it has been shown that vagomymetic medication changes indices of impaired autonomic heart innervation after MI, such as heart rate variability and baroreflex sensitivity, but it was not shown that this effect was associated with a decrease in mortality in this patients.^{9,10} In our study, pirenzepine shifted HRT

parameters to more positive values in presumably healthy persons. It is not clear whether this effect could be shown in persons with obvious structural heart disease and pathologic HRT. Even if such an effect could be shown, it remains highly speculative whether a treatment with vagomymetic medication such as pirenzepine could decrease a risk of death in patients with structural heart disease.

In our study it has been shown that previously suggested normal values for HRT descriptors, TO < 0%, and TS > 2.5 ms/R-R interval do apply to our patient population, with few exceptions. There were 3 exceptions for TO which makes 10% of examined patients, and 1 exception for TS (3.3%). These results are consistent with findings from previous studies in apparently healthy adults¹¹ that the incidence of false positive HRT result in persons without significant structural heart disease is high for TO, but not for TS, when cutoff points as in our study are used.

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