Impact of Preceding Ventricular Premature Beats on Heart Rate Turbulence

Hung Yi Chen, M.D.

From the Department of Cardiology, Heping Branch, Taipei City Hospital, Taiwan

Background: Heart rate turbulence (HRT) has recently been introduced as a noninvasive tool for studying autonomic dysfunction. It presented short time fluctuation of sinus cycle length following single ventricular premature contraction (VPC). However, HRT parameters may be influenced by different factors. This study aimed to evaluate the possible influence of VPC frequency on HRT.

Methods: 24-h Holter recording was performed in patients with VPCs initially detected by 12-lead electrocardiography (ECG) in the outpatient department. The numbers of VPCs in 2- and 5-minute durations preceding each VPC tachogram were calculated. The HRT parameters and the numbers of the VPCs preceding VPC tachograms were analyzed.

Results: There were 23,122 available VPC tachograms from 107 healthy subjects included in the study. The turbulence onset (TO) value increased and the turbulence slope (TS) value decreased as VPC's frequency increased. The TO values rapidly increased when the number of VPCs was >15 beats in the 2-minute and >35 beats in the 5-minute durations. There was also a prominent decrease in TS values when the VPCs reached 14 and 30 beats in the 2- and 5-minute durations, respectively.

Conclusion: Physiologic baroreflex may be attenuated under intensive stimulation, which is evidenced by blunted HRT parameters by frequent VPCs. Physiologic response to VPC's frequency may be related to baroreflex fatigue and is demonstrated as a sigmoid curve.

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INTRODUCTION

Heart rate turbulence (HRT) is a recently introduced representation of the biphasic physiologic response of sinus rhythm to a single ventricular premature contraction (VPC). The variations consist of an initial acceleration and a subsequent sinus deceleration. Its two parameters as defined by Schmidt et al. are turbulence onset (TO) and turbulence slope (TS). Blunted HRT parameters are more predictive of mortality in myocardial infarction patients.¹

Several studies have evaluated this physiological phenomenon and baroreflex sensitivity is currently the hypothesized mechanism.^{2,3} However, false positive HRT values in healthy subjects had been reported.⁴ Further studies illustrate possible factors that may influence the two parameters.^{5,6} This study aimed to find the relationship between HRT values and the numbers of the VPCs preceding HRT tachograms in subjects with structural

normal hearts in order to determinate the impact of VPC frequency on HRT.

METHODS

From January 2006 to December 2007, 24-hour ambulatory electrocardiography (ECG) was performed in the outpatient department on either symptomatic or asymptomatic individuals with VPCs initially detected by 12-lead ECG. Those who fulfilled the following criteria were included in the study: (1) absence of any form of cardiovascular disease by history, 12-lead ECG and echocardiogram; (2) absence of noncardiovascular disease as diabetes mellitus, thyroid disorder, liver or kidney disease; and (3) absence of any medication affecting cardiac rate or rhythm.

Treadmill exercise test was performed to exclude ischemic heart disease in subjects with any of following criteria: (1) palpitation or chest tightness; (2) age >35 years; and (3) number of VPCs

Address for reprints: H.Y. Chen, M.D., Department of Cardiology, Heping branch, Taipei City Hospital, No. 33, Sec. 2, Zhonghua Rd., Taipei City 100, Taiwan. Fax: 886-228954666; E-mail: dae28@tpech.gov.tw; anigi426@ms24.hinet.net

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>200 beats in 24-hour period. The 24-hour ambulatory ECG was recorded while the subjects went about their normal daily routines. Only recordings with more than 80% qualified sinus beats were included.

One hundred seven subjects were included in the study. Of these, 100 underwent the exercise test and all had negative results. Ventricular premature ectopic beats were recorded and identified by simultaneously three-channel 24-h Holter recorder and a digitized Holter analyzer (Medilog FD4, Oxford Instruments, Abingdon, United Kingdom). Then the data was analyzed using Medilog Excel-3 (Medilog Cardiology Information System V2.3, Oxford Instruments).

RR interval duration measurement and QRS morphology were automatically performed by a digitized Holter analyzer and obtained after reviewing and manual editing by experienced staff.

After careful identification of VPC morphology, the data of RR intervals were extracted and prepared for HRT calculation. Only isolated ventricular ectopic beats with a distinct postectopic pause were included into HRT analysis. HRT was calculated as previously described and measured by standards of the International Society for Holter and Noninvasive Electrophysiology Consensus.^{1,7} VPCs were accepted in the study if they had following criteria: a coupling interval of less than 80% of the average of the preceding five sinus intervals; a compensatory pause exceeding 120% of the preceding sinus intervals; and if they were embedded into five preceding and 20 succeeding RR intervals. The RR intervals had to fulfill the following criteria: cycle length of more than 300 ms but less than 2000 ms; beat-to-beat difference but less than 200 ms; and difference to the reference interval of less than 20%. Thus, a single tachogram consisted of a sequence of RR intervals with 5 preceding and 20 succeeding to a VPC.

When a sequence of RR intervals was accepted as an available tachogram, another tachogram was searched from the next RR interval of the last accepted VPC tachogram. There were no two adjacent overlapping VPC tachograms in the data. Unlike the conventional manner, after filtering with the above criteria, each acceptable VPC tachogram was calculated for HRT values. To understand the possible influence of VPCs frequency on HRT parameters, the numbers of VPCs in 2- and 5-minute durations preceding each accepted VPC tachogram were calculated. The method produced values of

HRT onset and slope, and the numbers of VPCs in 2- and 5-minute durations for each VPC tachogram. All of the data, including HRT parameters and the numbers of VPCs were computed and obtained by a program written in MatLab software (version 6.1).

Statistical analyses were conducted with a commercially available software package (SPSS, version 13.0; SPSS Inc., Chicago, IL). All continuous variables are expressed as mean $\pm$ standard deviation. Mean HRT values were calculated for each correlated number of premature beats. Comparisons of the quantitative values between the number of premature beats and HRT parameters were made with *t*-test for paired samples. *P* values < 0.05 were considered statistically significant.

RESULTS

There were 107 patients included (46 male and 61 female; age range: 18–78 years; mean age: 50.8 ± 17.2 years). All showed normal left ventricular contractility (LVEF: 64.4 ± 4.8) and normal left ventricular chamber size (LVEDD: 46.6 ± 5.2 mm) by two-dimensional echocardiogram. After Holter recording, there was a wide variation in numbers of VPCs in different individuals, ranging from 10 to 12,802 with mean 1839 ± 3663 in 24 hours. After screening, using the exclusion criteria, 23,122 VPC tachograms were available. After calculating HRT parameters, TO ranged from -8.94 to 3.31 , with mean of -2.26 ± 2.95 (%), and TS from 4.7 to 45.3 , with mean of 18.9 ± 10.0 (ms/N). The relationship between age and number of total VPCs was shown in Figure 1A, while Figure 1B showed the distribution of the total number of available VPCs with respect to age.

Comparing the numbers of VPCs preceding the tachograms with the HRT parameters, both turbulence onset and slope showed significant difference with the number of VPCs ($P < 0.001$). The results showed that TO increased as VPC's frequency increased, while TS decreased as VPC's frequency increased. Changes of turbulence onset and slope are horizontal while the number of VPCs is low (Figs. 2A and B). However, there were rapid increases in TO values when the number of VPCs was >15 (beats/2 minutes) and prominent decreases in TS values when the number of VPCs reaches 14 (beats/2 minutes).

In addition, increased TO and decreased TS slowed down when the number of preceding VPCs

Figure 1. (A) The relationship between age and the number of VPCs in a 24-hour period (left panel). The numbers of VPCs decreased with increasing age. (B) Right panel shows the distribution of the number of available VPCs with respect to age (right panel).

Figure 2. Relation between the numbers of preceding VPCs in 2-minute duration (x-axis) and the values of HRT onset (A) (upper left), and HRT slope (B) (upper right) (mean $\pm$ Std Err) (y-axis). (C) The amount of available HRT tachograms (y-axis) with respect to the numbers of preceding VPCs (x-axis) (lower panel).

Figure 3. Relation between the numbers of preceding VPCs in 5-minute duration (x-axis) and the values of HRT onset (A) (upper left), and HRT slope (B) (upper right) (mean $\pm$ Std Err) (y-axis). (C) The amount of available HRT tachogram (y-axis) with respect to the number of preceding VPCs (x-axis) (lower panel).

was >30 (beats/2 minutes). The correlation curve between the VPC's number and HRT parameters appeared as a sigmoid-shaped curve. Figure 2C displayed the detailed distribution of the amounts of available VPC tachograms with respect to the numbers of preceding VPCs in 2 minutes. When the relations between the number of VPCs in 5-minutes preceding a VPC tachogram and the HRT values were analyzed, there were similar results (Figs. 3A and B). There were rapid increases in TO values when the number of VPCs was >35 (beats/5 minutes) and rapid decreases in TS values when the number of VPCs was >30 (beats/5 minutes). The correlation curves also appeared as sigmoid shaped.

To avoid the influence of sex and age on HRT values, the number of VPCs, and their relationships, the tachograms and data by sex were di-

vided into two subgroups. The data were also dichotomized by age (separate by 51 years) into two subgroups. There were 15,208 available VPC tachograms in 52 subjects with age <51 years, and 7914 available VPC tachograms in 55 subjects with age >51 years. Results of analysis of the relations between the number of VPCs in 2-minutes preceding VPC tachogram and the HRT values in the two age groups, were showed in Figure 4. In previous studies, the TO values decreased and TS values increased with increasing age.⁵ In the current study, there were lower TO and higher TS values in the upper panel (subjects aged <51 year old) than in lower panel (subjects aged >51 years). Comparing the two groups, changes in both TO and TS values by increased preceding VPC numbers were more prominent in group 1 (upper panel) than in group 2 (lower panel).

Figure 4. Relation between the numbers of preceding VPCs in 2-minute duration (x-axis) and the values of HRT onset (A) (upper left) and HRT slope (B) (upper right) (mean $\pm$ Std Err) (y-axis) in subjects with age ≤ 51 years. Relation between the numbers of preceding VPCs in 2-minute duration (x-axis) and the values of HRT onset (C) (lower left) and HRT slope (D) (lower right) (mean $\pm$ Std Err) (y-axis) in subjects with age > 51 years.

In addition, when comparing with group 2, the changes of HRT values (rapid increases in TO and rapid decreases in TS values) are influenced by less preceding VPCs in group 1. These results indicated that the response of HRT values to the number of VPCs was more sensitive in younger subjects. Both the correlation curves in the two groups demonstrated as sigmoid shaped.

In two sex subgroups, there were 10,950 available VPC tachograms in 40 male subjects, and 12,172 VPC tachograms in 61 female subjects. Results of analysis of relations between the number of VPCs in 2-minutes preceding VPC tachogram and the HRT values in two groups by sex were shown

in Figure 5, which were similar between the two groups.

DISCUSSION

Heart rate changed after a ventricular premature beat had been mentioned for a long time.⁸ HRT is thought to be a measure of autonomic response to perturbations of arterial blood pressure invoked by VPC. The initial report shows that impaired parameters predict high mortality after myocardial infarction.¹ However, false positive HRT values in healthy volunteers have also been reported by a recent study.⁴ The further studies show that HRT

Figure 5. Relation between the numbers of preceding VPCs in 2-minute duration (x-axis) and the values of HRT onset (A) (upper left), and HRT slope (B) (upper right) (mean $\pm$ Std Err) (y-axis) in male subjects. Relation between the numbers of preceding VPCs in 2-minute duration (x-axis) and the values of HRT onset (C) (lower left), and HRT slope (D) (lower right) (mean $\pm$ Std Err) (y-axis) in female subjects.

values may be influenced by many factors including age and gender.⁵

In a recent study, Schwab et al. calculated the mean cycle length of 5-, 10-, and 20-preceding cycles for every VPC and demonstrated increased heart rate associated with decreased TO, and TS attenuated by basic heart rate in humans.⁶ Thus, HRT parameters represented a transient response to baroreflex. To understand any possible influence of VPC frequency on HRT parameters, the amount of the VPCs in 2- and 5-minute durations preceding each VPC tachogram were calculated.

The results demonstrate that the frequency of VPCs will change the values of HRT parameters. The relation between HRT parameters and VPC's

numbers is a sigmoid curve. While the real physiologic mechanism of HRT is not well identified, baroreflex is supposed to be the initial mechanism, followed by the sympathetic and vagal system.⁹ In the current study, in a large group of normal subjects without ischemic heart disease, the blunted HRT parameters under frequent VPCs may be caused by a relative diminished arterial blood pressure changes or other mechanisms related to baroreflex fatigue. Nonetheless, this needs further evaluation.

The threshold of VPC's number is close to 7 beats/minute in our study (Figs. 2 and 3). Moreover, this phenomenon (increased TO values and decreased TS values) is found with less frequent

VPC in younger subjects but is similar in men and women (Fig. 5). This may imply that physiologic response to baroreflex in normal subjects will be fatigued under intensive stimulation in a short duration.

LIMITATION

This study has some limitations. Data were collected from subjects who went about their daily activity. Different subjects with different physiologic condition and activities may affect the results. Second, unlike common convention, each acceptable tachogram (sequence of sinus beats with 5 preceding and 20 succeeding to a VPC) was calculated for HRT parameters. Circadian changes of daily physiologic condition and differences of autonomic tone may also influence the results. There are also less available HRT tachogram in higher frequencies preceding VPCs. Thus, a relative small sample size of available tachograms also blunts the results in high-frequency VPCs. Last, HRT is influenced by many factors such as age, gender, basic heart rate, and different physiologic condition. Further larger studies are warranted.

CONCLUSION

The study shows that increased VPC's number is associated with increased TO and decreased TS values. This illustrates that the phenomenon of physiologic baroreflex may be attenuated under intensive stimulation, which is evidenced by blunted HRT parameters by frequent VPCs. The relationship of physiologic response to VPC's frequency is demonstrated as a sigmoid curve.

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