Implications of turbulence slope variations in different approaches

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Abstract

Both heart rate variability (HRV) and heart rate turbulence (HRT) are established tools to study cardiac autonomic activity. Short-term studies of HRV had been reported to be stable for autonomic function assessment. However, there is little information on whether short-term HRT assessment is comparable to 24 h assessment. The aim of the study is to identify the relationship of HRT values between the 24 h and isolated tachogram measurements. We collected 24 h Holter recordings from 116 patients attending the outpatient department. HRT parameters were assessed for 24 h. Using the conventional method, HRT parameters were calculated using the average of tachograms over long-term recordings. In an alternative method, HRT parameters were obtained from each tachogram. We calculated a mean value for each subject by averaging the whole HRT data of every tachogram. Correlation analysis between the two groups of HRT values was performed. The results showed a high correlation between the two methods in turbulence slope (TS) ($P<0.001$; $r=0.84$) and an extremely significant correlation in turbulence onset (TO) ($P<0.001$; $r=0.99$). The values of TS were increased when assessed by separate tachogram. The variations became prominent when TS values calculated by the conventional method were low. HRT is as useful by separate tachogram assessment as by the standard Holter recordings. However, the TS values should be redefined. In subjects with abnormal turbulence slope (<2.5) calculated by averaging long-term recordings, the possibility of TS values blunted by diverse regression slope sequences in separate tachograms should be taken into consideration.

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Introduction

Blunting the autonomic reflex modulation of the heart rate predicts poor prognosis in patients with myocardial infarction (MI) and congestive heart failure. Heart rate turbulence (HRT) has recently been introduced as a parameter for post-MI risk assessment.[1] It indicates physiological response in the sinus cycle that follows a ventricular premature complex. Variations are composed of an initial acceleration and a subsequent deceleration. This phenomenon is believed to be mainly mediated by the autonomic nervous system and is reported to reflect impaired baroreflex sensitivity.[2,3] A continuous electrocardiogram (ECG) record for 24 h is a standard method of evaluating heart rate turbulence. A previous report also demonstrated that the ratio of heart rate response to blood pressure over a few minutes can be a useful prognostic marker in congestive heart failure.[4] However, the use of HRT measurement in a short-term period was limited and previous studies presented some controversy.[5] There is little literature available on the variation between the HRT analysis derived from short-term analysis and standard 24 h Holter monitoring. The aim of this study is to evaluate the relationship between HRT indices obtained from short-term analysis and standard 24 h Holter monitoring.

Materials and Methods

The Holter recordings from a two year period from outpatient department data were retrospectively reviewed. To filter other non-autonomic-tone related physiological variations, in contrast to a previous study, those with more than 20 ventricular beats over a 24 h period were enrolled. All 24 h ambulatory electrocardiography (ECG) Holter monitoring (Medilog FD4, Oxford Instruments, sampling rate 2048 Hz) was recorded while the subjects went about their daily routine. All of them received echocardiography for evaluation. To avoid the effects of cardiac disease, those with significant valve heart disease, heart chamber dilatation, and impaired left ventricular function by echocardiography were excluded from the study. Subjects with abnormal 12-lead ECG findings (except ventricular premature beats) such as ST segment and T wave changes suspicious of ischemic heart disease and left ventricular hypertrophy were also excluded. Exercise treadmill test had been performed in individuals with more than 3 coronary artery disease risk factors, and those resulting positive were excluded from the study. Only the 116 subjects who fulfilled the criteria were included. Simultaneous three-channel 24 h Holter recorded by a digitized Holter analyzer (Medilog FD4, Oxford Instruments) and analyzed by Medilog Excel-3 (Medilog Cardiology information system V2.3, Oxford Instruments) identified ventricular premature beats. The R-R interval duration measurement and QRS morphology were automatically performed by a digitized Holter analyzer and obtained after review and manual editing by experienced staff. After identification of ventricular premature contraction (VPC) morphology, the data of R-R intervals were obtained and prepared for HRT calculation. HRT indices, turbulence onset (TO), and turbulence slope (TS) were calculated using the guideline standards of the International Society for Holter and Non-invasive Electrocardiology (ISHNE) Consensus.[6] Turbulence onset (%) was defined as a percentage difference between the mean of the first 2 R-R intervals after a ventricular premature beat and the 2 last sinus R-R intervals before ventricular premature beat. TS was calculated as the maximum slope of the regression line over any sequence of 5 R-R intervals within the first 20 sinus beats after an ectopic beat. To exclude interpolated VPCs, only those with prematurity over 20% and compensatory pause exceeding 120% of the mean of the last 5 sinus rhythm intervals preceding the VPC were accepted. The VPC had to be embedded into 5 preceding and

20 succeeding R-R intervals, which had to fulfill the following criteria: cycle length greater than 300 ms but less than 2000 ms; beat-to-beat difference less than 200 ms; and difference to the reference interval less than 20%. Thus, a single tachogram consisted of a sequence of sinus R-R intervals with 5 preceding and 20 succeeding to a VPC. When a sequence of R-R intervals was accepted as an available tachogram, another tachogram was searched from the next R-R interval of the last accepted VPC tachogram. There were no 2 adjacent overlapping VPC tachograms in the data. Two different methods were used to compute the HRT parameters. According to the conventional method, as previously described, HRT parameters were calculated using tachograms averaged over long-term recordings.[1] According to a second method, the HRT parameters were calculated for each tachogram separately (separated method). After averaging the whole data obtained from every tachogram, the mean TO and TS values were used as 24 h HRT values for each subject. Two groups of continuous variables obtained by different methods were compared to determine their relationship. We used Bland-Altman plots to examine the error in assessment by separated tachogram compared with the conventional method for each subject.[7] The aim was to evaluate whether one technique could be substituted for another. When constructing Bland-Altman plots in the present study, the x-axis is the mean of the values determined by the appropriate conventional and separated methods, and the y-axis is the difference between the values for these two methods. Perfect agreement would have been a difference of ±0 SD, and the limits of agreement are defined as the mean difference plus and minus 1.96 times the standard deviation of the differences. All continuous variables were expressed as mean±SD. Comparisons of the quantitative values were calculated using the t-test for paired samples. Pearson's correlation analysis was performed to show the correlation between two groups of continuous variables. A P value less than 0.05 was considered statistically significant.

Results

One hundred and sixteen (116) subjects, 46 males and 70 females, mean age 37.1±12.5 years (range 15-63 years), were included in the study. The mean available VPCs for every subject were 295.2±323.4 (range 12-1486). There was a broad spectrum of HRT parameters: TO ranging from 3.08% to -6.95% by 24 h tachograms averaged (conventional method) and 3.09% to -6.76% assessed by averaging available separated tachograms; and TS ranging from 1.11 to 26.17 (ms/beat) by 24 h tachograms averaged and 4.27 to 41.76 (ms/beat) assessed by averaging available separated tachograms. The baseline characteristics/demographics of subjects, heart rate turbulence and heart rate variability included in this study are shown in Table 1. Values of TO was ≧0 and TS less than 2.5 ms/beat were defined as abnormal. Only the conventional method showed that 5% (6 of 116) of subjects had abnormal TS. When TS values were measured by averaging all separated tachograms, all the subjects had normal TS values. As for TO, 8% (9 of 116) of subjects had abnormal values by both conventional and separated methods.

In each subject, the values of HRT indices as calculated by the conventional method were compared with the values measured by the separated tachograms. The results showed a high correlation between the two methods in TS ($P<0.001$; $r=0.84$) and an extremely significant correlation in TO ($P<0.001$; $r=0.99$). Moreover, TO values measured by the separated method were approximately the same as the values obtained by the conventional method. However, the TS values calculated by the separated method were higher than those values obtained by the conventional method. The correlations between different values by the two methods for every subject are shown in Figure 1.

Bland-Altman plots were constructed between the two methods; the results are shown in Figure 2. The results in differences of TO indicate that the two methods may be used interchangeably. However, the differences in TS between the two different calculation methods vary greatly. In addition, the dif-

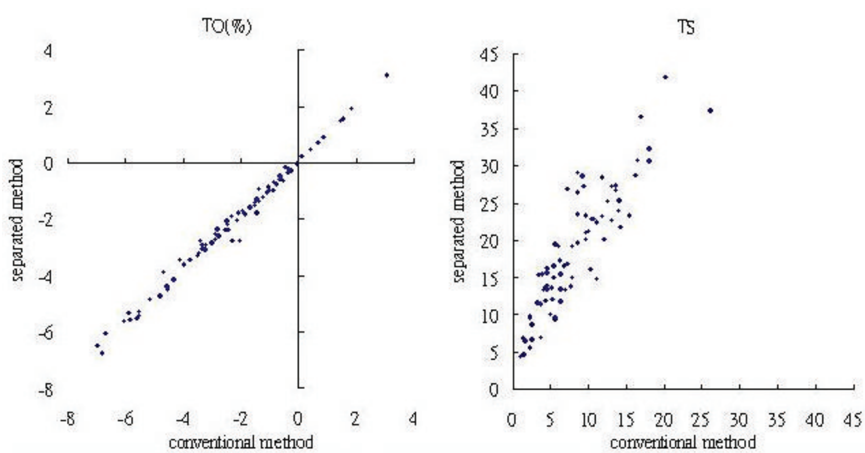

Figure 1. Scattergram and correlation of heart rate turbulence values assessed by the conventional and separated methods in TO (%) (left panel) and TS (right panel).

Table 1. Heart rate turbulence and heart rate variability parameters included in the study.

	Mean±SD	Median
Patient, n	16	
Age, y	37.1±12.5	7
Sex (M/F), n	46/70	
VPCs	295.2±323.4	99
HRT parameters		
TO(%) (conventional method)	-2.51±2.07	-2.43
TO(%) (separated tachograms)	-2.37±2.0	-2.35
TS(ms/RR) (conventional method)	8.74±4.85	7.87
TS(ms/RR) (separated tachograms)	19.27±7.66	19.28
HRV parameters: frequency-domain		
ULF (ms^2)	2388.0±1468.5	2103.5
VLF (ms^2)	1963.6±1065.8	1791.6
LF (ms^2)	570.8±433.5	466.7
HF (ms^2)	320.5±398.9	183.4
LF/HF	2.6±1.8	2.3
HRV parameters: time-domain		
RR (ms)	825.5±121.3	814.8
SDNN (ms)	122.0±38.7	125.5
SDNNI (ms)	52.1±17.0	49.8
SDANN (ms)	107.8±43.2	106.1
rMSSD (ms)	35.9±16.5	31.1
pNN50 (%)	8.5±9.3	5.7

ferences are proportional to the mean. To find the possible factors influencing variation of TS values calculated by the two different methods, TS(difference) was defined as the difference between the values by different methods divided by the conventional method: i.e.

$$TS_{(difference)}=(TS_{(separated)} - TS_{(conventional)})/TS_{(conventional)}$$

where $TS_{(separated)}$ was the TS value measured by the separated tachogram, and $TS_{(conventional)}$ was the TS value measured by the conventional method. The values of $TS_{(difference)}$ ranged from 0.06 to 4.08 (mean 1.49±0.8 and median 1.35). When comparing the $TS_{(difference)}$ values with the number of available VPCs, increased VPCs did not increase the $TS_{(difference)}$ (r=0.04). Comparing the $TS_{(difference)}$ values with the subject's age, increased subject's age also increased the $TS_{(difference)}$ values and there was a mild correlation between them (r=0.38). When comparing the $TS_{(difference)}$ with $TS_{(conventional)}$ values, there was moderate correlation (r= -0.67). Finally, there was no significant difference between sexes in $TS_{(difference)}$ (P=0.48).

Discussion

Heart rate turbulence (HRT) represents variations of heart rate after a single ventricular premature beat and indicates temporal response of baroreflex after transient hemodynamic change. HRT was initially reported in 1999 as a parameter for risk assessment after myocardial infarction.[1] Both HRT and heart rate variability are methods which can be used to assess autonomic effect on the cardiovascular system. There are reports of short-term studies of HRV which remained stable that relate to screening variations in heart rate.[8,9] However, there is little information on whether short-term HRT assessment is comparable to 24 h measurement, which is the standard for assessing HRT. This study compares the difference between calculating HRT parameters by the conventional method of using tachograms averaged over 24 h long-term recordings and the mean values of measurements by each separated tachogram. The results show approximately the same in TO values. For TS, the results demonstrate different values obtained by different methods. Nonetheless, there is a high correlation between the two different methods. Since TS is defined as the maximal positive regression slope assessed over any 5 consecutive sinus rhythm R-R intervals within the first 20 sinus rhythm R-R intervals after VPC, variable sequences of maximal positive regression slopes among different VPC tachograms may increase the values of TS by averaging the separated available tachograms. Thus, TS calculation is more complicated than TO values. As seen in the example shown in Figure 3, the

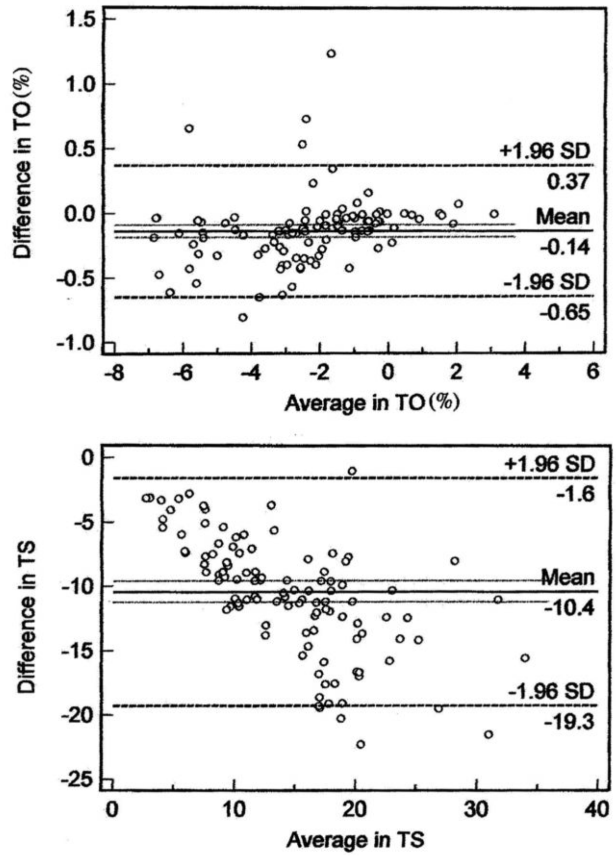

Figure 2. Scattergram of the differences plotted against the averages of the two measurements in TO (%) (upper panel) and TS (lower panel). Horizontal solid line is drawn at the mean difference in the values for the two methods and the dashed lines indicate the limits of agreement (±2 SDs).

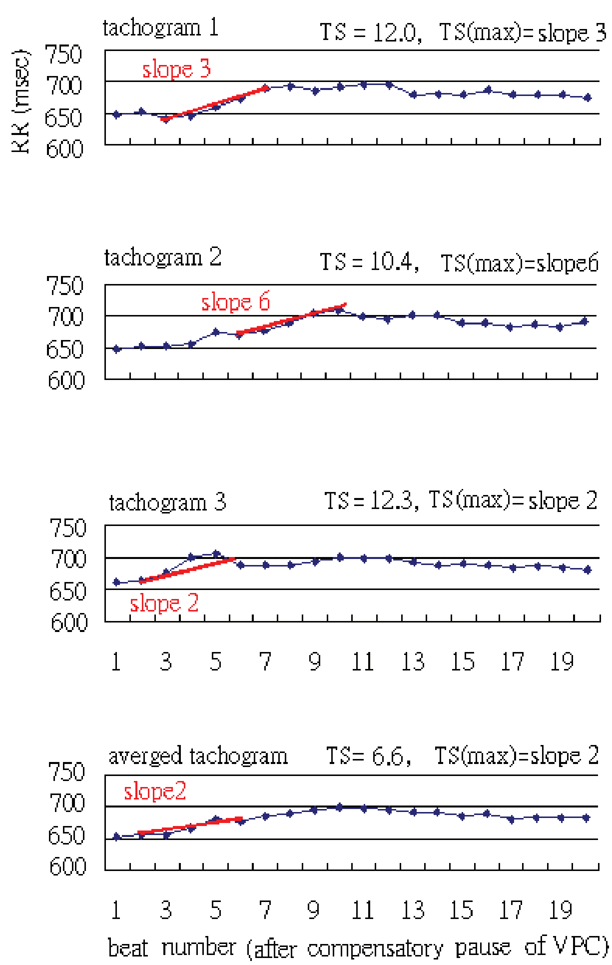

Figure 3. Three separated tachograms and their respective maximal regression slope. The number of the maximal regression slopes and their values are shown. Bottom panel: the results of the average of 3 tachograms and TS value decreased by using the average of 3 tachograms.

maximal regression slope in 3 tachograms are slope 3, slope 6 and slope 2, respectively. And the values of maximal slope (TS) in three separated tachograms are 12.0, 10.4, and 12.3. The average of TS value in 3 separated tachograms is 11.6. However, when we calculate TS values using tachograms averaged over 3 recordings, the value is 6.6. In this example, variations in R-R intervals resulting in different sequences of maximal positive regression slope among different VPC tachograms increase the TS values using the separated method, and TS value is lower using the conventional method. This phenomenon was also demonstrated in our study. When we defined TS curve for each available separated tachogram as the sequence of slope values in every 5 consecutive beats after a single VPC (Figures 4 and 5), TS curves for all available tachograms were calculated and observed in a 63-year old female with abnormal TS value (<2.5 ms/beat by the conventional method). The TS curve calculated by the conventional method was illustrated in the first curve of the x-axis. The other variable TS curves in succession were calculated for a total of 23 available separated tachograms. The number of its maximal positive regression slope and its values for every tachogram were calculated and shown in parenthesis; [ ] and { }, respectively. The results demonstrated fluctuation in every TS curve, both in sequence and the value. In this case, most of the TS values in the separated TS curve were normal (>2.5 ms/beat), but the TS value was blunted and abnormal (TS=1.3 ms/beat) when calculated by the conventional method.

The results from our study show a significant correlation in TS between the two different methods. However, in those with various TS sequences (TS curve) measured by separated tachograms, the values may be decreased when calculated by the conventional method. In fact, heart rate turbulence may be influenced by many factors such as age, gender, basal heart rate variation, and differences in individual condition.[10] Circadian oscillation and variation of autonomic tone and heart rate over a day may also influence HRT values by various hours. These different physiological conditions are reflected in diverse changes in R-R intervals and result in various TS curves. The 24 h ambulatory ECG recording included in the study was collected while the subjects went about their daily routine. This is the most influencing factor in HRT calculation and also the limitation in calculating heart rate turbulence by separated tachogram. In contrast to short-term heart rate variability, VPC is necessary in HRT assessment. Its contribution to VPC development is unpredictable and it is, therefore, difficult to collect ECG recordings for HRT measurement in a static environment. We have to collect ECG in a dynamic environment. Both human activity and motion reflected different physiological conditions, and this may affect analysis and assessments. When calculating TS, to avoid the interference, if we have the more available separated VPC tachograms, we may exclude more non-autonomic-tone related physiological variations. The more available VPC is of benefit in effective filtering. In our study, the result showed the number of VPCs had a similar effect using the 2 different methods. Increased available VPC tachograms did not significantly change the differences of TS values measured by two approaches (r=0.04). The most influential factor for the value of $TS_{(difference)}$ was initial TS value calculated by the conventional method. The main problem is presented by variables in R-R intervals resulting in different sequences of maximal positive regression slope among different VPC tachograms. It can be seen most when TS values calculated by tachograms averaged over long-term recordings are extremely low, and the difference is enhanced by age in the results. Thus, turbulence slope might be blunted by variations of TS curves in separated tachograms when using the conventional method to perform the calculation. Furthermore, the effect is more prominent when the TS value is extremely low. There

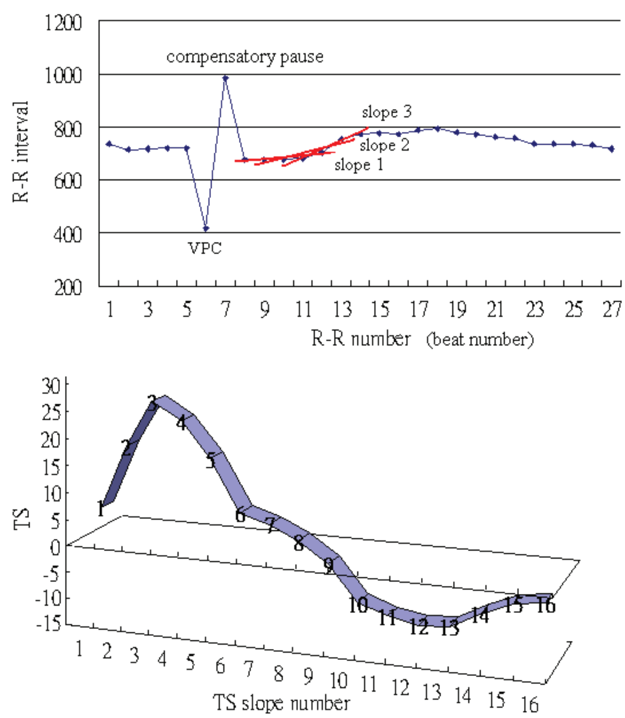

Figure 4. Upper panel: a VPC tachogram showing a sequence of R-R intervals with 5 preceding and 20 succeeding to a VPC (x-axis). y-axis shows the duration of R-R intervals. Slope 1 was defined and calculated as the slope of regression line over the first five R-R intervals after the compensatory pause beat after a VPC. Lower panel: a TS curve showing a sequence of the regression slope values over five R-R intervals assessed for each VPC tachogram.

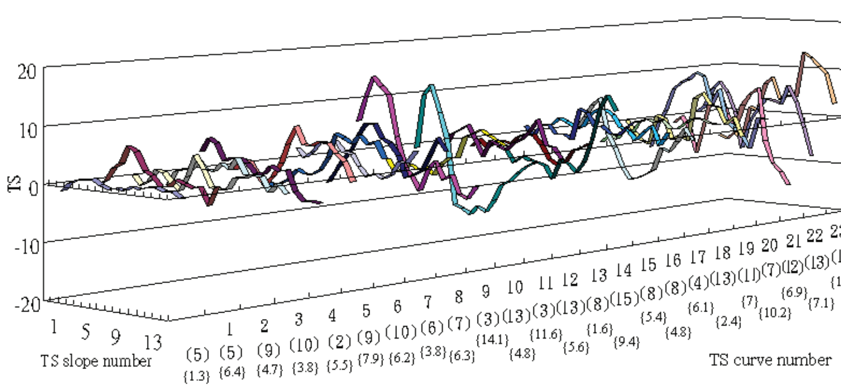

Figure 5. TS curves calculated for every available tachogram in a 63-year old female with abnormal TS value (<2.5 by conventional method). The first curve in the x-axis showed the TS curve calculated by the conventional method. The other variable TS curves in succession were calculated for a total of 23 available separated tachograms. The numbers in the brackets [ ] and { } show the number of each TS curve's maximal positive regression slope and their values, respectively. Results show variable TS curves (x-axis) and fluctuated sequences of maximal positive regression slope (TS value) in different tachograms.

have been previous reports about false positive HRT analysis in healthy subjects.[10,11] The Lancet study reported a turbulence slope which yielded a positive predictive accuracy of 27% and 25%, respectively, in Multicentre Post-Infarction Programme (MPIP) and European Myocardial Amiodarone Trial (EMIAT) data. By setting the TS threshold as 2.5, one-fourth of patients will be true positive and there will be many false positives with abnormal HRT measurement.[1] Decreased TS value may reveal either abnormal late heart rate deceleration after a single VPC or may be mainly related to variations in regression slope sequence in separated tachograms. In those with decreased TS value, both possibilities should be taken into consideration. Further large-scale evaluation is necessary to determine whether TS curve oscillation is related to autonomic dysfunction.

Conclusions

In this study, TO values are approximately the same when obtained by different methods. The TS values are a little more complicated and may be increased by the separated method. However, the two methods have high correlations. The variation in the two different approaches may become prominent when the TS value assessed by the conventional method is extremely low. In these subjects, the possibility of TS values blunted by diverse regression slope sequences in separated tachograms should be taken into consideration.

Study limitations

One limitation of our study is the retrospective nature of patient collection, which may compromise the results. Although we tried to select appropriate baseline characteristics of the patients in order to avoid the effects of cardiac disease, there may be differences in our results which cannot be controlled. In addition, variations of turbulence slope within consecutive 24 h periods had been documented.[12] Our study did not evaluate circadian effect on TS curve oscillation.

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