Clinical Research

Determinants of Heart Rate Turbulence after Ventricular Premature Beats in Healthy Volunteers

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Introduction: A decline in the acceleration of the heart rate (HR, heart rate turbulence, HRT) after a ventricular premature capture is associated with increased mortality in patients suffering from coronary artery disease. The physiological properties of HRT have not been evaluated in a large human cohort.

Methods: In 95 healthy individuals, HRT parameters onset (TO) and slope (TS) as well as the turbulence timing (TT) were calculated from 24-hour Holter ECGs. With the help of a simple, linear, weighted regression model, gender specific differences of TO and TS were compared. A multiple linear regression model served to evaluate the influence of age and the basic HR preceding the ventricular premature contraction (VPC) on HRT.

Results: The median of TT is present in regression line #5. We discovered that, in men and women, TO is reduced as basic HR rises ($p<0.01$). In contrast, analysis of TS showed a divergence: in men, TS declines as basic HR increases. However, basic HR modifies TS in women to some extent ($p<0.01$). A multiple, linear regression model revealed a decrease of HRT with increasing age in men.

Conclusions: The acceleration of HR after a ventricular premature beat occurred within the first 11 beats in more than 75% of our healthy individuals. An increased HR prior to VPC affects HRT in men. Increasing age leads to an attenuation of HRT in men and to a reduction of TO in women. These results emphasise the significance of the physiological properties of HRT when using HRT for risk stratification, especially in elderly patients.

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The decrease in the heart rate acceleration after a premature ventricular contraction (VPC) has proven to be a potential non-invasive factor for the assessment of the risk of total mortality in patients after myocardial infarction. These changes in post VPC heart rate (HR) were identified by Schmidt and co-workers.[1] They named their observation "heart rate turbulence" (HRT) and quantified HRT with two parameters: turbulence onset (TO) and turbulence slope (TS). Both were computed by the processing of data retrieved from Holter ECGs. A reduced HRT revealed a strong predictive value for mortality in the EMIAT and the MPIP trials, both of which included patients post myocardial infarction.[2,3]

Quite a few investigations have evaluated the properties of this phenomenon.[4-6] Currently, HRT is supposed to characterise another measurement of the baroreflex.[7] Recently, a few investigators also detected alterations of HR after an atrial extrasystole.[8,9] However, only a small number of studies gave details of observations in healthy subjects.[10] For that reason, the key objective of our investigation was to assess the physiological properties of HRT in terms of their determinants, e.g. age, gender, and basic HR, in a group of healthy volunteers.

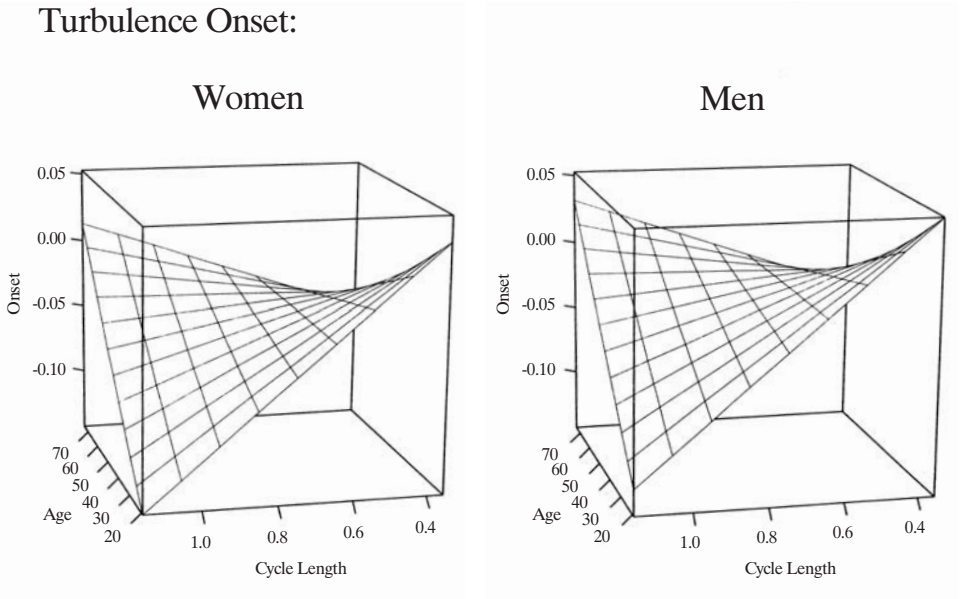

Figure 1. On the left, the three dimensional cube with the net shows turbulence onset (y-axis) with respect to age (years, z-axis) and preceding cycle length (in s, x-axis) in women. On the right, the cube with identical axes displays the relation in men. In female and male volunteers, aging causes a change in the shape of the net. It becomes more horizontal, i.e. the influence of the preceding heart rate on turbulence onset declines with age.

Methods

Ninety-five healthy persons (43 women) in our department, mainly medical students, contributed to the survey. A resting ECG, echocardiography, and a bicycle exercise test (modified Bruce protocol) were performed in order to rule out subclinical heart disease. Holter recordings of each person (Oxford Medical™ FD3-system, sampling rate 1024 Hz) were made during a day of usual physical activity. Two skilled cardiologists studied the Holter tapes in order to detect VPCs and additional premature beats. The analysis comprised a manually performed beat to beat process. Subsequently, the cycle lengths and the annotations of each beat were exported as an ASCII-file and transmitted to the Mathematical Institute (G.E.) for additional analysis. HRT and turbulence timing were calculated as previously described.[11] Abnormal findings for HRT were defined as turbulence onset ≥0% and turbulence slope ≤2.5 ms/RRI.[1]

A simple linear regression model determined the impact of age and gender. Their relation was presented in a cube, where a carpet-like net displayed the results of a single individual's HRT parameters. All statistical computations and programming were performed with S-Plus, Version 3.4 (Insightful Corp., Seattle, WA, USA).

Results

The mean age of all participants was 35 ± 14 years and their mean ejection fraction was 68 ± 6%, which did not differ between women and men. Throughout the bicycle test, men sustained a higher workload than women: 287 ± 72 vs. 176 ± 54 W ($p<0.001$). During maximal exercise, men achieved a higher systolic blood pressure (196 ± 27 vs. 181 ± 18 mmHg, $p<0.01$), but the maximum heart rate did not differ (167 /min for women and men).

Holter data

Men demonstrated a lower heart rate: 817 ± 98 ms vs. 745 ± 57 ms in women ($p<0.001$). Notably, a total of five episodes of non-sustained ventricular tachycardia were traced. The HRT computation resulted in a median TO of 3% (range from -23% to 42%) and a median TS of 16 ms/RRI (range from 0 to 98 ms/RRI). No gender specific discrepancies were identified.

The three-dimensional cubic plots (Figures 1,2) present the results of the complex analysis of the influence of age on HRT. The HRT parameters, TO or TS, are indicated on the y-axis. The other two axes display age and mean cycle length preceding the VPC. Figure 1 demonstrates the shifting of TO with regard to age and basic heart rate. It is clear that as age increases TO also rises. A similar relationship was discovered in women. Another aspect, clarified by this diagram, reflects the influence of the preceding heart rate. In both sexes, a reduction in cycle length leads to an increase in TO ($p<0.01$). Hence, increasing age as well as elevated basic heart rate attenuate the velocity of the heart rate within the first

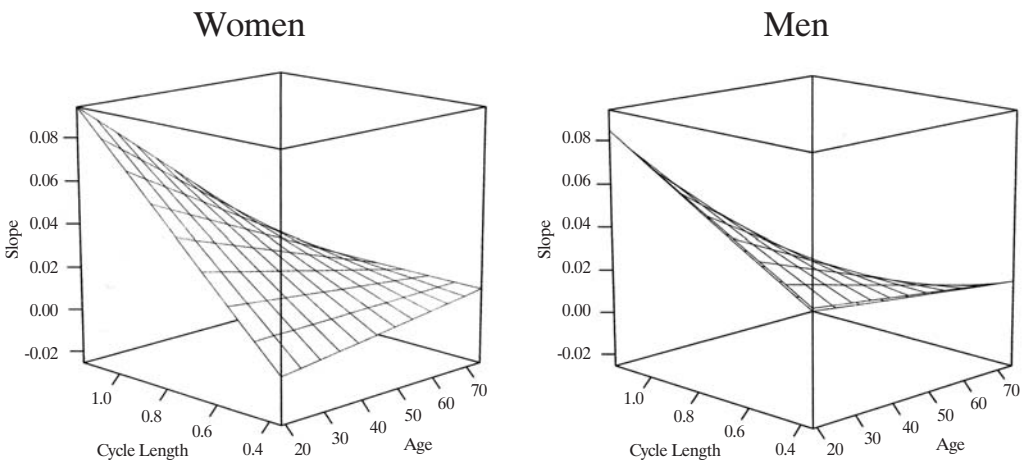

Figure 2. As figure 1 for the case of turbulence slope (in ms per RR-interval) in relation to age and preceding heart rate in women and men. Here age is displayed in the right oblique axis and basic cycle length in the left oblique axis.

two beats after a VPC. However, at the age of 50 to 70 the slope of the carpet grid decreases and the net flattens. In other words, the response to various heart rates before a VPC fades with age.

With reference to TS, the computations revealed dissimilar findings (Figure 2). The labels of the x- and z-axes were exchanged and the cube was slightly rotated to give an enhanced view of the data net. In women and men TS barely alters as age increases. Regarding the power of the preceding heart rate, all persons exhibited a similar response, which was, however, different for the two sexes ($p<0.01$ for the comparison between men and women). As with the analysis for TO, a decrease in the preceding cycle lengths moderates TS. However, the impact of the basic heart rate weakens as age increases. A more horizontal plane of the grid, beginning at the age of 40 to 50, illustrates this effect.

Discussion

The most important finding of this investigation is that age and the heart rate preceding the ventricular premature capture must not be ignored regarding their influence upon heart rate turbulence. In particular, the brief increase in heart rate after the VPC, which is quantified by the parameter turbulence onset, is governed by age as well as basic heart rate, whereas the post-extrasystolic heart rate performance, i.e. turbulence slope, is moderately influenced by age alone. An alteration in the preceding heart rate, particularly in men, has an effect on TS.

It is well known from other parameters reflecting the heart's autonomic tone that alterations occur during a person's lifetime. For instance, heart rate variability not only has a circadian appearance but also changes with age. Bonnemeier and coworkers reported on their findings in 166 healthy subjects between the ages of 20 and 70 years.[12] They perceived a continuous decay of cardiac vagal modulation during aging. Consequently, the average daily heart rate increases.

This essential observation explains our findings in 95 healthy volunteers. We were able to detect an influence of the basic heart rate, which precedes the ventricular premature beat, in such manner that alterations of the heart rate after the VPC are attenuated as the basic heart rate rises. As mean heart rate accelerates during aging, the response of the heart to a VPC weakens and, therefore, heart rate turbulence declines. In particular, this fact is visible in terms of turbulence onset.

Our results in healthy subjects are in accordance with those of Grimm et al, who studied heart rate turbulence in a total of 45 persons.[10] They discovered a decrease in turbulence slope with rising age. However, in their population the correlation coefficient R^2 was just 0.3, with a hardly significant p-value of a little less than 0.05. They detected no correlation between age and turbulence onset. In our cohort of more than twice as many volunteers we were able to discover an impact of age on both HRT parameters. It is likely that the absence of the correlation was caused by the lack of an analysis of basic heart rate.

Another valuable finding of our study consists of the high number of false positive results of turbulence onset (25%). The rate of false positive results for turbulence slope (5%) is in accordance with the results of others studying healthy persons.[10,12,13] For instance, nearly 5% of all healthy subjects in one study showed positive on T-wave alternans testing,[13] while 5% of our cohort showed a non-sustained ventricular tachycardia in their 24h Holter tracings.

Conclusions

We report on the physiological characteristics of heart rate turbulence in a large population of healthy individuals. This investigation demonstrates the important impact of preceding heart rate and age on heart rate turbulence, as well as the influence of age itself on preceding heart rate. These findings underline the importance of being aware of the alterations in autonomic cardiac tone during aging and of taking changes in the basic heart rate into account for future risk stratification investigations including heart rate turbulence.

Limitations

Although all of our participants had normal findings on ECG, echocardiogram, and exercise testing we cannot rule out the presence of any cardiovascular disease entirely.

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