Age-Dependent Response of Heart Rate Variability Parameters to Head-up Tilt Tests in Young Syncope Patients and Controls

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Abstract

This study examines the utility of heart rate variability (HRV) and repolarization parameters to predict the outcome of head-up tilt tests from early phases of the response to tilting in 44 young patients with syncope and 34 age-matched controls. Synchronized to the tilting events, we extracted minute-by-minute progression of time- and frequency domain HRV descriptors as well as mean QT interval and linear QT-RR model parameters. The Wilcoxon rank sum test revealed significant effects of age in patients. Time-courses of patients and controls exhibited a high degree of concordance in young subjects whereas after start of puberty patients exhibited more prominent and persistent responses. Controls did not change significantly. This was also confirmed by ROC analysis in three temporal regions of interest (ROI1: 0-2 min after tilt, ROI2: 2-5 min after tilt and ROI3:5-2 min before tilt back) which consistently revealed higher area under curve for older subjects with sensitivity up to 79 % and specificity up to 75% in ROI2.

1. Introduction

Syncope, a sudden loss of consciousness and postural tone owing to cerebral ischemia with spontaneous recovery, is a clinically important problem in children and adolescents, with an estimated incidence of 15-20% [1] and a recurrence rate of 35% during a three year follow-up. The most prevalent form in young patients is neurocardiogenic (vasovagal) syncope (NCS) which – although the pathophysiological mechanisms still are not fully understood – is suspected to be associated with autonomic imbalance, and is diagnosed by exposing the patient to orthostatic stress on a tilt-table (head-up tilt test, HUTT).

This study aims at finding precursors of NCS that might help to predict the outcome of the HUTT from earlier phases of the response to tilting in ECG parameters (HRV and repolarization) in order to reduce the stress for the patient and shorten the duration of the HUTT.

2. Methods

In 44 patients with history of syncope (age: 7-20, 22 ♀, 22 ♂) and 34 controls (age: 7-20, 17 ♀, 17 ♂) undergoing a HUTT in the Pediatric University Hospital Heidelberg, 12-channel ECGs were registered with a sampling rate of 500 Hz. The HUTT protocol consisted of a phase of 10 minutes of rest in supine position, after which the table was tilted to a 60 degree upright position remaining there until either the maximum of 45 min of registration time had elapsed or symptoms of syncope or presyncope occurred. All syncope patients had positive and all controls negative HUTT.

In the ECGs, QRS detection and classification was performed and carefully confirmed using self-developed software. To address possible changes in repolarization dynamics, we performed beat-to-beat QTend delineation based on a wavelet-algorithm [2]. Owing to signal quality, and to alleviate effects of postural change on Q-morphology, QT-measurements were conducted on the vector magnitude (RMS value) of the baseline-corrected ECG channels (I, II V1... V6).

The corrected series of RR-intervals and QT-intervals served as basis for HRV and repolarization parameter calculations. Intervals adjacent to ectopic beats or data gaps were labeled and interpolated employing a local phase space prediction algorithm. Parameter extraction followed a minute-by-minute grid that was aligned with the tilting events from supine to 60° and back to supine. From each epoch of one minute, we calculated the following time-domain HRV parameters [3]: Average RR-interval (meanRR), SDNN – the standard deviation of all RR-intervals between sinus-beats, and SDSD – the standard deviation of differences of successive RR-intervals. To assess changes in sympathovagal balance, we calculated the absolute and relative energy in the low-frequency band (LF, 0.05-0.15 Hz) and high-frequency band (HF, 0.15-0.4 Hz) as well as the ratio of these energies (LF/HF). We equidistantly resampled the series of RR-intervals at 3 Hz using cubic spline interpolation, and applied two 8th order Butterworth bandpass-filters (LF: 0.05-0.15 Hz and HF: 0.15-0.4 Hz) bi-directionally to this series. The variance of the filtered signals was then used as estimation of the energy in the LF and HF band.

From the QTend-interval series we calculated the mean value and fitted a linear model relating RR and QT:

$$QT = a \cdot RR + b \quad (1)$$

To compensate for inter-individual differences prior to tilting, and to pronounce the tilt-related response, all parameters were related to a baseline value that was calculated individually for each subject as average over the last five minutes prior to tilting. Changes were then expressed as relative deviations from that baseline value.

The first question of our study addressed the dependence of the time-courses on age, gender and syncope which was checked for by means of the Wilcoxon rank sum test. To assess age-related effects, we divided the sample into two subgroups with respect to the start of puberty. The threshold we chose for age was 10/11 for girls and 12/13 for boys.

To quantify the extent of differences between subjects with positive (patients) and negative HUTT (controls), we defined three temporal regions of interest (ROIs, see Fig. 2): the first, ROI1, two minutes immediately after tilt, ROI2 3-5 min after tilt and ROI3 5-3 min before tilt-back. In each of the ROIs, we averaged values and performed a receiver operating characteristics (ROC) analysis yielding sensitivity and specificity for HUTT outcome prediction as well as the area under the ROC curve (AUC).

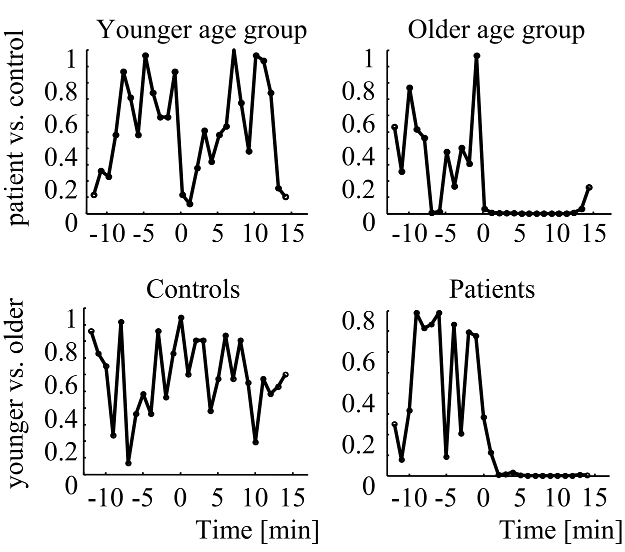

Figure 1. Results of Wilcoxon rank sum test for parameter meanRR. Upper diagrams show p-values for patients vs. controls in dependency of age (left: younger group, right: older group). Lower diagrams show p-values for age-difference in dependency of syncope (left: controls, right: patients). Age threshold is <11 (♀) and <13 (♂) Time axis is relative to tilting (at 0 min).

3. Results

Average tilting duration in young patients was 1112±658 min compared to 1284±564 min in older. Figure 1 shows results of the Wilcoxon rank sum tests for differences in relative change of mean RR-interval with respect to disease status (Fig. 1 upper) and age (Fig. 1 lower). Obviously, differences between patients and controls are significant only in the older group i.e. after start of puberty. There was no evidence for gender-specific differences in our HRV data. Therefore, for further analysis we kept separate groups with respect to age but not with respect to gender. Interestingly, the influence of age is confined to patients, and is not found in controls (Fig. 1 lower diagrams). In Figure 2, the corresponding average time-courses of the relative change of mean RR-interval for the age-related subgroups are depicted. Both exhibit a tilt-induced decrease of meanRR that is most prominent within the first two minutes after tilt and comparable in magnitude in this time-interval. Whereas, however, for the older group, the difference between patients and controls persists and even tends to increase with time, the curves in younger patients remerge 5-6 min after tilt. The apparent increase of meanRR in patients observed at this time is due to early syncope in two subjects.

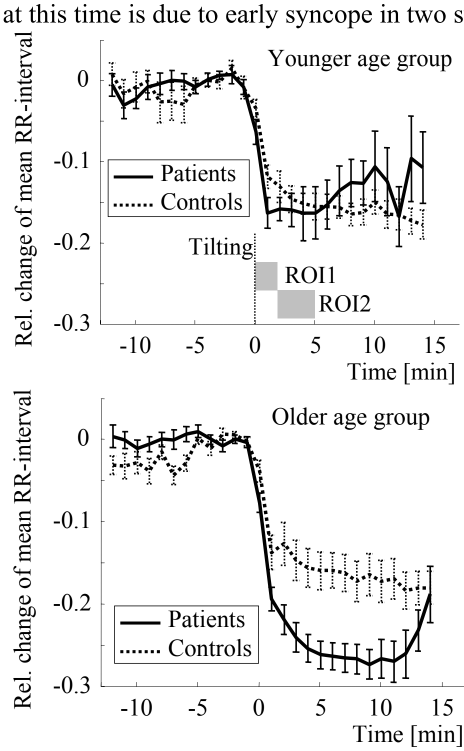

Figure 2. Average relative change of mean RR-interval during HUTT for younger (upper) and older (lower) age group in patients (solid) and controls (dotted). Error bars indicate standard error of mean (SEM). Time axis is relative to the moment of tilting (at 0 min).

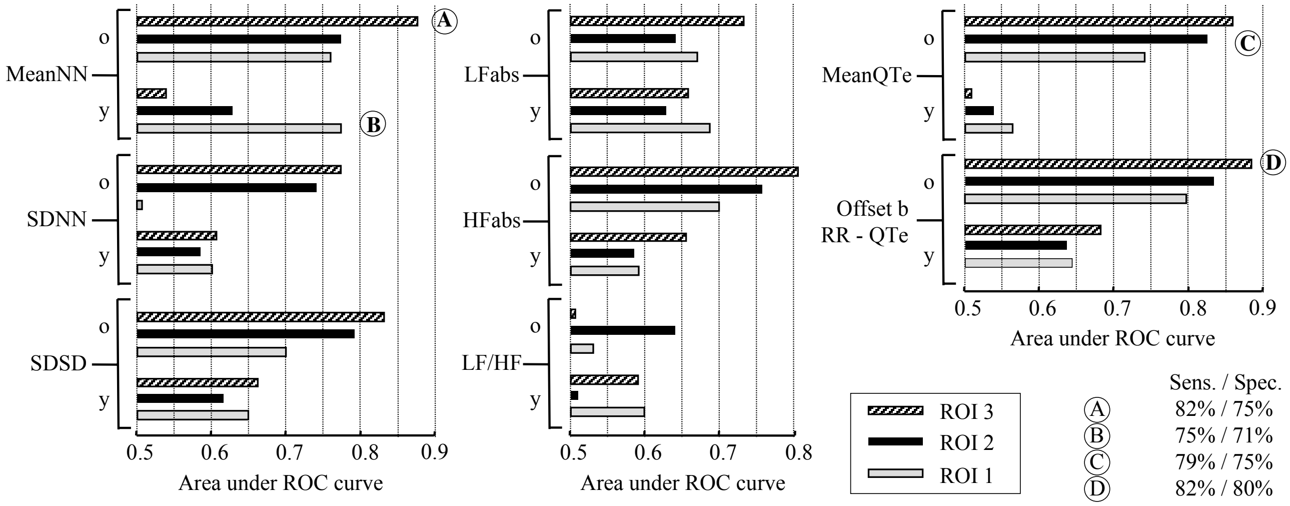

Figure 3. Results of ROC-Analysis for time-domain (left), frequency domain (middle) and repolarization (right) parameters. For each parameter, two groups of three bars are shown which correspond with age groups ‘younger’ (letter ‘y’, age <11 for ♀, <13 for ♂) and ‘older’ (letter ‘o’, age ≥11 for ♀, ≥13 for ♂). Within the groups each bar represents one ROI (see legend). Sensitivity and specificity for selected bars as marked by letters A-D, are given. Please note that time- and frequency-domain results refer to baseline-normalized data whereas AUC for QT refers to absolute values.

The median time-courses are concordant with the average control response later than six minutes after tilt.

Maximal average RR-decrease is much stronger in older patients (ca. -25%) than in younger (ca. -15%) whereas controls exhibit an average decrease of about -15% regardless of age. The average baseline RR-interval before tilt was 810 ms in older and 750 ms in younger subjects, and there was no significant difference in absolute heart rate between patients and controls.

Dependence of the degree of separation between patients and controls on age, as seen in meanRR (Fig. 2), is typical for most parameters considered in this study. The overall variance SDNN as well as SDSD and HFabs are reduced upon tilting. Controls and younger patients exhibit largely comparable reactions which are consistently weaker than those of the older patients. The relative response of LFabs is less uniform and reflects together with LF/HF a high degree of inter-individual variability. Generally, LF/HF increases upon tilting. The relative increase is slightly greater in older patients than in others, which seems to be owing to a reduced ‘absolute’ LF/HF level at baseline. This reduction is significant ($p<0.02$) in five out of 12 minutes of baseline data and also in the first minute after tilting.

The time-courses and the AUC of the relative changes in QTend closely resemble those of meanRR (Fig. 1 and 3), however on a smaller scale of approx. 6-7% reduction in controls and young patients, and 10% in older. Absolute QT values yielded better results in terms of separation between patients and controls in ROI2 and ROI3 since older patients had significantly shorter QT after tilting. Significance was lost after correction for heart rate (QTc) according to Fridericia. Moreover, an effect of gender was observed with significantly shorter QTc in male patients (not controls) during baseline and tilt.

Figure 3 summarizes the results of the ROC analysis for prediction of the HUTT outcome from three ROIs in dependency of age. For virtually all parameters, AUC is lower in younger patients as compared to olders, confirming the trend already seen in Wilcoxon results (Fig. 1) and time-courses (Fig. 2). The strongest predictor in the young group is meanRR with an AUC of 0.77, 75% sens. and 71% spec. in ROI1, i.e. immediately after tilting. With comparable performance in ROI1, meanRR is also found among the best parameters in the older group. However, here we observe an increase in separation with time (i.e. closer to syncope), and the best result shortly before tilt back (AUC 0.88, sens. 82%, spec. 75%).

With respect to a practically relevant prediction, only the values in ROI1 and ROI2 are important. Here SDSD and especially the repolarization parameters exhibit best performance. Only the latter achieve an AUC > 0.8 in ROI2 with 79% sensitivity and 75% specificity for meanQTe. Closer to syncope, the differences again get clearer and reach up to 82% sens. and 80% spec. for the RR-QT model’s static offset b. It is important to note that both QT-parameters values were considered not as relative but absolute values! The results of the relative changes were comparable to meanRR.

The best performance among the generally little predictive frequency domain parameters is obtained from the relative reduction of HFabs.

4. Discussion and conclusions

A major finding of our study is the significantly clearer manifestation of differences in heart rate response to tilting between patients and controls after start of puberty as compared to before. Even more surprising appears the second important result that this is owing to altered responses alone in patients whereas controls behave largely the same before and after start of puberty (Fig. 1). It has to be noted that the latter is an effect of our approach to normalize time-courses to a baseline value, since absolute values of HRV parameters are well-known to undergo changes with age [4]. All together, this obviously makes prediction of HUTT-outcome in the younger subgroup a harder problem.

The general response pattern and the magnitude of the initial response, during the first two minutes after tilting, are often comparable for both age groups. Later, the responses of patients and controls generally remerge in young whereas the difference typically tends to increase or persist in elders. This is also obvious from Fig. 3 where AUC values of the older group exhibit an increase from ROI1 to ROI3 for most parameters which is not the case in young subjects. Although the younger subgroup contains two patients with very short tilting duration (5 min), it seems unlikely that differences in tilting times account for this result, since the average tilting duration for both groups is comparable, and median time courses confirm concordant manner in the younger subgroup. Moreover, this finding is in agreement with the clinical observation that in young patients the symptoms of syncope often (re)appear more severe during puberty. Possibly, the shorter baseline RR-interval (750 ms vs. 810 ms) limits the dynamic range for further HRV reductions in younger patients.

With respect to the symptoms of syncope, mean heart rate appears as most directly related HRV parameter. From this point of view it is plausible that for both age groups meanRR provides best separation between patients and controls, however with much better success (AUC 0.88) after start of puberty than before (AUC 0.77). Our observations on mean RR-interval and SDNN changes for the older group are in good agreement with data reported in [5].

In patients after start of puberty, the slightly lower ‘absolute’ LF/HF ratio at baseline, which points to a vagally shifted autonomic balance at rest, and the uniformly stronger and comparatively predictive decrease of HFabs and SDSD (i.e. vagal withdrawal) suggest an important role of the parasympathetic branch of the ANS in the genesis of syncope.

Although the absolute level of separation in our study is too low even in the older group for HUTT-substitution by HRV analysis, it is noteworthy that both ‘absolute’ repolarization parameters perform comparatively well, especially in ROI2 with AUC > 0.8. Whether this is due to complementary information in QT or just an effect of QT adaptation to RR, as suggested by the lack of separation in rate-corrected QTc, is hard to tell from our data since on the other hand, the quite successful static offset b of the RR-QT model also aims to eliminate dynamic influence of RR on QT, and the results are better than those of absolute meanRR. Further studies will have to assess the significance of these findings, incorporating the uncertainty of T-end determination, especially at high heart rates, the susceptibility of regression models to outliers and the influence of gender on QTc in our data.

It furthermore remains to be clarified why so little differentiation between patients and controls is seen in HRV parameters until start of puberty, and why only patients exhibit age-related changes that finally are reflected in alterations of HRV and repolarization. The most obvious changes in puberty are of humoral origin. These might - either directly or via modification of components affecting the cardiovascular regulatory system - activate mechanisms which finally enhance the contrast in HRV parameters of subjects with stable and instable circulation. Joint analysis of blood pressure, heart rate, and respiratory data should be one of the next steps to better understand the cardiovascular processes that finally discharge into syncope. Better knowledge about the nature of possible early signatures in conjunction with more sophisticated analysis and classification strategies might finally serve to predict the outcome of the HUTT at least in subjects in or after puberty.

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