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Short-Term Heart Rate Variability Response to Head-Up Tilt in Young Syncope Patients and Controls with Respect to Age

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Abstract—**This study aims at characterizing the short-term time-courses of time- and frequency-domain heart rate variability (HRV) parameters during head-up tilt test (HUTT). Data from 44 young patients with a history of syncope and 34 age-matched controls was analysed in two age-groups related to puberty (≤13 and ≥ 14 years), and separately for gender, by extracting minute-by-minute progression of mean RR-interval, standard deviation of RR-intervals (SDNN) and their first difference (SDSD) as well as low-frequency (LF, 0.05-0.15 Hz) energy, high-frequency (HF, 0.15-0.4 Hz) energy and the LF/HF-ratio. Time-courses were individually normalized and averaged after synchronization to the events of tilt and tilt-back/syncope. We observed remarkable age-related differences not only with respect to response to tilting but also regarding the differentiation of patients with positive HUTT from controls with negative HUTT. ROC-analysis in three regions of interest (0-2 min after tilt, 2-5 min after tilt, 5-2 min before tilt-back) revealed generally much weaker and less persistent differences in younger subjects whereas in elders the differences were clearer and often most pronounced immediately before syncope. For both age-groups, the relative change of mean RR provided best separation, however in elders in the ROI just before syncope (sensitivity: 74%, specificity 80%) in young immediately after tilt (sens.: 71%, spec.: 74%). In elder subjects, the relative reduction of SDNN 2-5 minute after tilt achieved almost the same performance (sens.: 74%, spec. 80%) as in the ROI before syncope (sens. 78%, spec. 73%), indicating the existence of rather early precursors of syncope that might help to predict the outcome of the HUTT in subjects in or after puberty.**

I. Introduction

WITH an estimated incidence of 15-20% [1], syncope represents a clinically important problem in children and adolescents. The main symptom is sudden loss of consciousness and postural tone with spontaneous recovery. In young patients, the most commonly found form is neurocardiogenic syncope (NCS), usually diagnosed or confirmed by head-up tilt testing (HUTT). Although the patho-physiological mechanisms yet are not fully understood, an association between NCS and autonomic imbalance is assumed.

This study analyses short-term heart rate variability (HRV), known to reflect changes in the autonomous nervous system (ANS) [2], during HUTT to assess to which extent differences in the ANS might contribute to the development of syncope and whether there are effects related to age or gender.

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II. Material and Methods

Starting with a 10 min phase of rest in supine position, 12-channel ECGs (sampling rate 500 Hz) were obtained during HUTT in 44 patients (22 male, 22 female, age 7- 20 yrs) with a history of syncope and positive HUTT, and 34 healthy control subjects (17 female, 17 male, age 7- 19 yrs) with a negative history of syncope and negative HUTT. After 10 min, the table was tilted to a 60 degree upright position that was maintained until either symptoms of syncope or pre-syncope occurred, or 45 min of registration time had elapsed.

Using self-developed software, QRS complexes were detected and classified according to morphology and timing. Consistency was confirmed manually accessing the raw ECG data. From the classified beats, the series of RR-intervals was constructed with intervals adjacent to ectopic beats or data gaps being interpolated using a local phase-space prediction algorithm. The suchlike corrected RR-series served as basis for all further calculations.

Analysis was performed in non-overlapping segments of 1 minute duration that were synchronized to the events of tilting and tilt-back/syncope. From each segment, we calculated the following time-domain HRV parameters: Mean RR interval, SDNN, the standard deviation of all intervals delineated by sinus beats, and SDSD, the standard deviation of differences of successive RR-intervals. To assess changes in sympathovagal balance, we estimated the energy in the low-frequency (0.05-0.15 Hz) and high-frequency (0.15-0.4 Hz) band as well as the LF/HF energy ratio. Frequency-domain parameters were calculated as energy (variance) of bi-directionally bandpass-filtered time-series (Butterworth filters of order 8 with cutoff-frequencies according to the definitions of LF and HF band). Prior to filtering, the series of RR-intervals was equidistantly re-sampled with 3 Hz using cubic spline interpolation.

To alleviate the influence of inter-individual differences, all parameters were related to a baseline value that was calculated individually in each subject as average over the last five minutes prior to tilting. Changes were then expressed as *relative deviations* (in %) from these individual

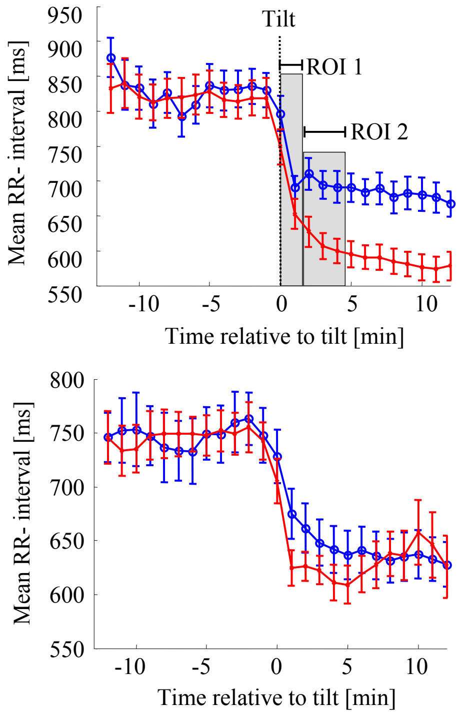

Figure 1: Average minute-by-minute values of mean RR (upper diagrams) for patients (red) and controls (blue) around time of tilting (t=0). Error-bars indicate ±SEM. The upper diagram shows values for the group of age ≥14 years, the lower for the group ≤13 years.

levels. We plotted minute-by-minute time-courses of each HRV-parameter as mean and standard error of means (SEM) over the groups of patients and controls. Age- and gender-dependency was checked for by comparing plots averaged in subgroups of age less than 14 (13-) and 14 or older (14+) separately for females and males.

In search of potential differences between patients and controls, we defined three regions of interest (ROIs): The first two minutes immediately following tilting, minutes 3-5 after tilt and minutes 5-3 before tilting back. In each ROI we performed a receiver operating characteristics (ROC) analysis on the intra-individual average values over the ROI. Group-separation was assessed as sensitivity, specificity and area under the ROC curve (AUC).

III. Results

Figure 1 shows the time-courses of the mean RR-interval (absolute) averaged for the age-related subgroups 13- and 14+. In both, we find a tilt-induced decrease which is stronger in patients than in controls, and most accentuated during the first two minutes after tilt, however emanating from different baseline levels (14+: 830ms, 13-: 750ms) and with remarkably contrasting behavior starting two minutes after tilt: whereas, for the elder group, the deviation persists and even slightly increases with time, the curves in younger patients remerge about 6-7 min after tilt.

The age-dependence of the difference between patients and controls appears even more pronounced in SDNN (Fig. 2), which reflects a reduced overall variability as reaction to tilting in all subjects, however with identical behavior for patients and controls in young. The 14+ group instead, exhibits a persistent reduction below - 40% for patients whereas in controls values stabilize at -20% with the greatest difference 3-5 min after tilt. Consequently, the distinction between patients and controls is higher in ROI2 (AUC=83.5, sens.=74%, spec.=80%) than in ROI1 (AUC=54.8) for group 14+ (Figure 3B) whereas in younger patients, SDNN completely fails (AUC<55.8). Figure 3A-F gives the age-dependent group separations for all HRV features considered in this study. Obviously, for the group 13-, only mean RR in ROI1 – the first 2 min after tilt (Figure 1) - achieves moderate separation (Figure 3 A AUC=78.6, sens.=71.4, spec.=73.7) whereas in all other parameters and ROIs, the distinction is much more pronounced in elder subjects.

The time-course of LFabs (Fig. 4) documents this issue, where tilting seems to have virtually no effect in the younger group whereas in elders, we find a transient decrease for patients and an increase on average in controls, however with a rather high SEM and therefore only moderate specificity (Fig. 3D, ROI2: AUC=76.7, sens.=87%, spec.=66.7%).

The courses of absolute HF energy and SDSD are strongly correlated. As a reaction to tilt, the energy of the HF-fluctuations is reduced. Consequently, the LF/HF-ratio rises after tilt, again more pronounced for 14+ than for 13- but without significant contribution to separation between

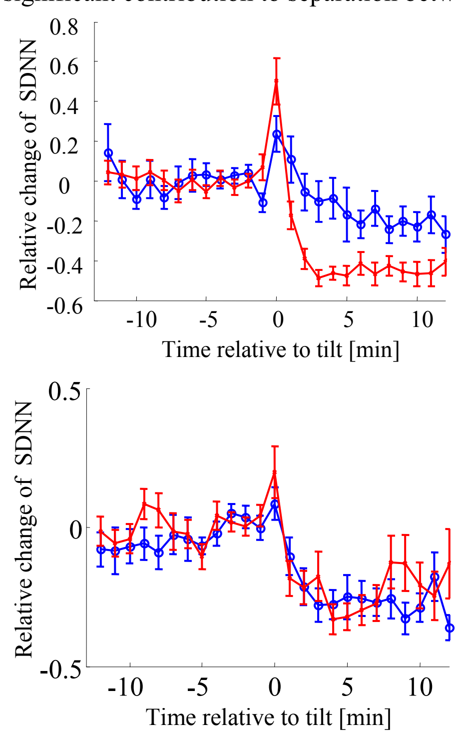

Figure 2: Relative changes of SDNN for patients (red) and controls (blue). Error-bars indicate ±SEM. Upper diagram: age ≥14 years, lower diagram: ≤13 years.

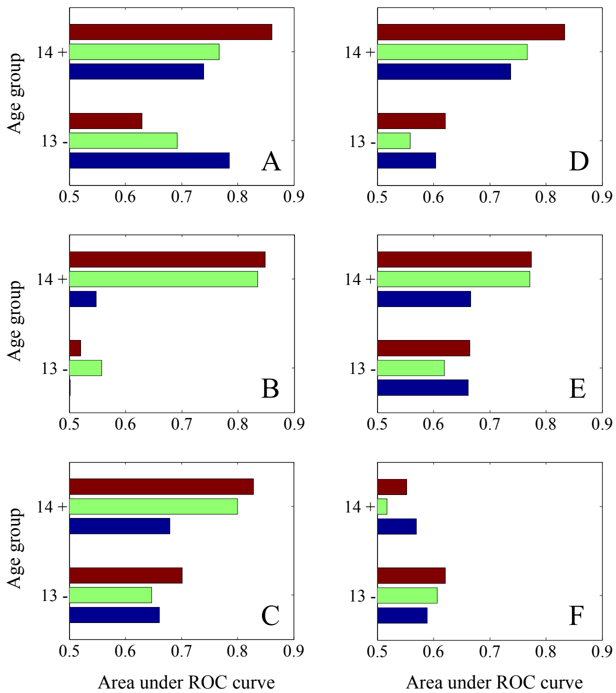

Figure 3: Area under the ROC curves in dependency of age (≤13 years, ≥14 years). Colors indicate the temporal segment used for averaging. Blue: ROI 1 (minute 1-2 after tilt); green: ROI 2 (minute 3-5 after tilt); red: ROI 3 (minute 5-3 prior end of tilt). Each diagram corresponds to relative changes to baseline of one HRV parameter. A: mean RR-interval, B: sdnn, C: SDSD, D: LFabs; E: HFabs; F: LF/HF-ratio.

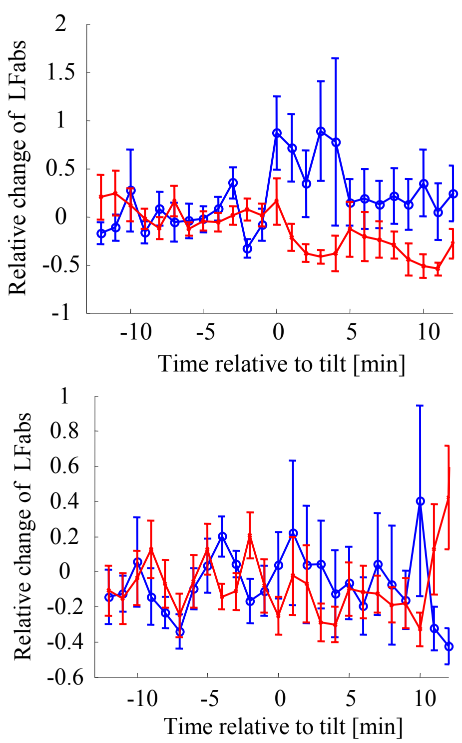

Figure 4: Relative changes of LFabs (lower diagrams) for patients (red) and controls (blue). Error-bars indicate ±SEM. Upper diagram age ≥14, lower diagram ≤13 years .

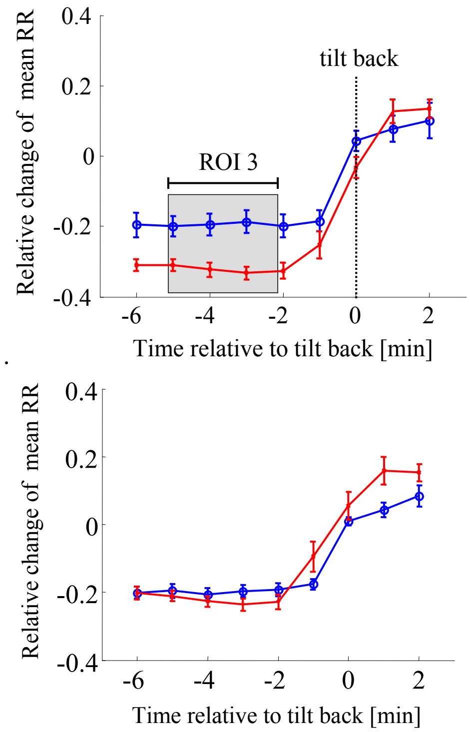

Figure 5: Average minute-by-minute values of mean RR-interval for patients (red) and controls (blue). Error-bars indicate ±SEM. Upper diagram age ≥14 years, lower diagram ≤13 years.

patients and controls (Fig. 3F). With respect to the ROIs, Figure 3 shows that the difference between patients and controls in the elder group is more pronounced in ROI2 than in ROI1, especially for SDNN (Fig. 3B). In younger subjects, the separation is generally much weaker (except mean RR in ROI1) and often better in ROI1 i.e. immediately after tilt. For both age groups, ROI 3 – shortly before tilt back – often gives the best differentiation, however especially in elders sometimes only marginally better than ROI2 (Fig. 3 BCE). In both age-subgroups, the best separation is observed in the mean RR interval (Fig. 3A), but interestingly for younger children in ROI1, whereas in elders, the difference increases closer to syncope (compare Fig. 1 and Fig. 5: ROI3: AUC 86.1, Sens. = 74%, Spec. = 80%).

Analysis with respect to gender did not reveal any nameable differences in neither age-group

IV. Discussion and Conclusion

The generally lesser pronounced reactions to tilt we found in the younger subgroup could be co-founded by the difference in absolute heart rate levels, which in younger subjects are higher than in elder (Fig. 1). This might leave less dynamic space for acceleration as reaction to tilt. But although it is known that HRV parameter levels change in the course of puberty [3], it seems remarkable that not only the response to tilt itself, although often similar in tendency, appears dependent on age. Also, the intra-age-group discrimination between patients and controls exhibits large age-related differences with respect to persistence and magnitude, generally larger and longer lasting in elder subjects and for some parameters completely lacking in young (Fig. 1, 2 and 4). Nevertheless, this finding is in concordance with the clinical observation that in patients experiencing syncope for the first time during puberty, the symptoms frequently are more severe compared to children with syncope occurring before puberty. In the latter, the symptoms often reappear more severe during puberty.

The fact that, in both age groups, mean RR achieves best separation between patients and controls is plausible considering the direct link between heart rate and the symptoms of syncope. Nevertheless, the already mentioned characteristics of increasing AUC with time from tilt for the elder subjects (Fig. 3A) and opposite behavior for the younger, suggests that the cardiovascular and humoral mechanisms leading to syncope, or at least their expression in HRV, might have different aspects before and after start of puberty. In further studies, the joint analysis of beat-to-beat blood pressure and HRV should be considered to investigate this hypothesis.

With respect to a substitution of HUTT in favor of analysis of HRV parameters, the absolute level of group-separation is too low even in group 14+ for the features examined in our study. However, it is noteworthy that SDNN in ROI2, i.e. 2-5min after tilt, achieves almost the same performance (sens.=74%, spec.=80%, AUC 83.5) than immediately before tilt back/syncope (ROI3, sens.=78%, spec.=73%, AUC=84.8).

This indicates a possible existence of changes in HRV that precede syncope, which in conjunction with more sophisticated analysis and classification strategies might serve to predict the outcome of the HUT at least in subjects in or after puberty. Our observations on mean RR-interval and SDNN changes for the 14+ group are in good agreement with data reported in [4].

Our study did not reveal differences in autonomic balance as reflected by LF/HF-ratio. Consistent with [5] we observed an increase of LF/HF with tilt that, however, in its relative magnitude did not separate patients from controls (Fig. 3F). This is in contrast to [6] who report a decrease of 11% in (adult) patients with positive HUT, and the increase found in [7], but in agreement with the results of [8]. For the 14+ group, we also observe the contrasting progression of LFabs found in [8, 6] immediately after tilt with a decrease for patients and an increase on average for controls. With respect to the small SEM found during that phase (Fig. 4), we conclude that the decrease in patients is more specific for the occurrence of syncope than the increase in controls, where the larger SEM indicates rather inhomogeneous behavior.

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