

Normal and abnormal circadian profiles of heart autonomic balance, evaluated by time-related common indicator of heart rate variability

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ABSTRACT

Objective: Heart rate variability (HRV) is an universally accepted method for assessing the heart autonomic balance (HAB). At the same time HRV is a highly specific method, but with a low sensitivity to the cardiovascular diseases (CVD). We found that HRV indices may be applied to obtain differentiated characteristics of the HAB for individual CVD.

Methods: We assessed the changes taking place in the circadian characteristic of the autonomic balance, which has a definite profile with and without the principal CVD. We proposed adequate time-related autonomic balance indicator (TRABI) for evaluating the changes in the circadian nature of HAB by comparing the values of the HRV indices during rest and upon vegetative nervous system stimulation during two intervals in the 24-hour period in which there is a physiologically determined difference in the balance.

Results: The normal circadian characteristic of HAB is distinguished by a slight prevalence of the circadian nature of the parasympathetic component. The mean value of the assessments of the HRV indices using TRABI in healthy individuals, according to data from the study during rest and with the handgrip test is 0.100, according to data from the study during rest and with the Valsalva maneuver is 0.141. The mean values of the scores of the indices for HRV using TRABI in the comparative studies during rest and with the two stimulation tests are accordingly: with hypertension- 0.132 and 0.047; with morning myocardial infarction incidents- 0.177 and 0.107; with non-morning myocardial infarction incidents- 0.082 and 0.053. The patients with unstable angina in the population studied have a good long-term prognosis and the mean values in this case in the two comparative studies are 0.180 and 0.211.

Conclusions: Cardiovascular diseases have a characteristic abnormal circadian nature of the autonomic balance. In our opinion, the proposed time-related autonomic balance indicator broadens the opportunities for using HRV for HAB assessment. The method for evaluating the circadian changes in HAB through the HRV indices during rest and with stimulation during different time intervals is convenient and accessible for clinical use. (*Anadolu Kardiyol Derg 2007; 7 Suppl 1; 125-9*)

Key words: heart rate variability, time-related (circadian) changes in heart autonomic balance

Introduction

The results of our previous studies in healthy subjects (1, 2) showed: (i) no significant differences between morning and afternoon values of heart rate variability (HRV) indices from electrocardiographic (ECG) recordings in resting state (RS) and by sympathetic (handgrip test – HT) and parasympathetic (Valsalva maneuver - VM) parts of the heart autonomic balance (HAB) stimulation; (ii) statistically significant differences between resting state and stimulation values, but in different indices constellations for the morning and afternoon measurements. Therefore, it was justified to look for relative changes in time-related HAB indices. First, the indices values during resting state and with stimulation in morning measurements were compared. Next, the same comparison was done for afternoon measurements. The power of the HRV indices to detect the time-related differences between these two comparisons was evaluated by the time-related autonomic balance changes indicator (TRABI).

Methods

Let two measurements be made at two different moments of time in order to detect the influence of a factor in two tests. In each measurement i ($i=1,2$) we obtain values of an index V for N objects in two tests. For each measurement, comparing the N parallel pairs of values of the index V , we have $k_i(+)$ positive, $k_i(-)$ negative and $k_i(0)$ zero differences. Then the following limitation is valid:

$$(1) \quad k_i(+) + k_i(-) + k_i(0) = N \quad (i=1,2).$$

Let us consider the indicator

$$(2) \quad I = |(k_1(+) - k_1(-)) - (k_2(+) - k_2(-))| / 2N = |dk_1 - dk_2| / 2N,$$

where, taking into account (1), the zero differences $k_i(0)$ are indirectly included through N . Obviously, the indicator introduced by (2) measures the power of the index to respond to changes in comparing results of two tests in two measurements, performed at different moments of time (for example, morning and afternoon).

Equations (1) and (2) define a range of values of $(0;1)$ for I . In

order to illustrate the conditions for obtaining the values of I, we assume for the sake of convenience (without influencing the essence of the results) that there are no zero differences in the two measurements. Hence,

$$(3) \quad k_i(0)=0 \text{ and } N = k_i(+) + k_i(-).$$

(The presence of zero differences reduces the values of the indicator (2), depending on their number.)

Obviously, the indicator is zero if $dk_1 = dk_2$. Considering (3), this is possible only if both equalities $k_1(+)=k_2(+)$ and $k_1(-)=k_2(-)$ are satisfied. In other words, the indicator value is zero (no time-related changes) only in case there is no change in the number of positive and negative differences of the index V values obtained from two tests in the two measurements.

The maximum value $I = 1$ is defined from $|dk_1 - dk_2| = 2N$ and considering (3), it is necessary that $dk_1 = -dk_2$, or that one of the two conditions be satisfied: $\{k_1(+)=N, k_1(-)=0; k_2(+)=0, k_2(-)=N\}$, or $\{k_1(+)=0, k_1(-)=N; k_2(-)=N, k_2(+)=0\}$. There is a case of full change in the number of positive and negative differences of the index V values from the two measurements and the two tests.

Results

Time-related autonomic balance profile in healthy subjects

The evaluation results for the morning and afternoon measurements during RS and with the HT are shown in Figure 1. The respective results for RS and VM are shown in Figure 2.

The comparison of morning results during RS versus the HT and during RS versus the VM showed different sensitivity of the time-domain and frequency-domain indices. We explain the small number of indices reacting to the HT with respect to RS with the morning background parasympatheticotonia which suppresses the effect of additional sympathetic stimulation. A considerably larger set of significantly differing indices ($p < 0.05$) in the VM with respect to RS can be explained with low morning parasympathetic tone, thus allowing stimulation.

The relatively low afternoon sympathetic tone results in the opposite tendency of the time-domain indices. All six indices showed significant differences during RS versus the HT, which we relate to possible additional sympathetic stimulation. The fact they are parameters derived from the dRR-tachogram is due to their higher sensitivity to HRV, reduced by the sympathetic stimulation. The afternoon relative hypersympatheticotonia limits the possibility to provoke considerable change in HAB by the VM. Hence, the number of significantly differing time-domain indices was reduced.

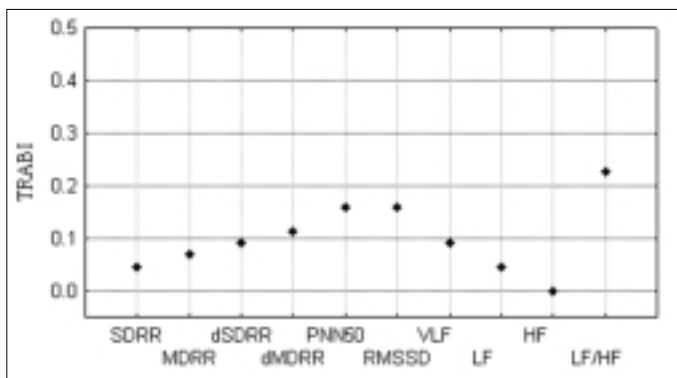


Figure 1. Values of TRABI for the HRV indices in healthy subjects: a comparison of morning and afternoon measurements in the resting state and during handgrip test

HRV- heart rate variability, TRABI- time-related autonomic balance changes indicator

The results of morning and afternoon measurements reveal the possibilities of HRV indices to respond to changes in HAB. The time-domain and frequency-domain indices have different sensitivity to the changes. On the other hand, the two sets of time-domain indices (from RR and dRR tachograms respectively) have different power to represent HAB changes. The frequency-domain indices (Table 1) (VLF, LF and HF in the HT and LF and HF in the VM) show high sensitivity to HAB changes, even considering its relative stability in healthy subjects. This is demonstrated by the unilateral changes of these indices for all or most subjects in morning and afternoon measurements. Therefore, the specific time-related balance changes are masked in the prevailing tendency to changes in the frequency-domain indices in stimulation compared to RS. In other words, the frequency-domain indices are insensitive to time-related changes in the HAB. Only LF/HF ratio shows a different response to morning versus afternoon changes, due to its inherent elasticity as the ratio of the values of two indices. Its power for assessment of the autonomic balance during RS and in stimulation is limited by its high variability.

The heart autonomic balance in healthy subjects is characterized by relative stability. In spite of this relative stability, HRV indices can reveal time-related HAB changes during the different time intervals of the 24-hour period.

Time-related autonomic balance profile in mildly hypertensive subjects

The mean value of TRABI and the evaluations for the HRV indices in the comparative study between the reaction during the HT and during rest in the morning and in the afternoon in mild hypertensive patients does not differ significantly from the mean value in healthy individuals (Fig. 3). Nevertheless, for some of the time - domain HRV (Table 1) indices - SDRR, MDRR, dSDRR, RMSSD - the values of TRABI are higher for the hypertensive patients. It can be considered that the sympatheticus in the mild hypertensive patients has a more pronounced circadian nature compared to normotensive individuals. The index PNN50 has lower values for TRABI in the hypertensive patients, which is probably due to the disordered circadian nature of the parasympathetic part of the balance, manifested even during the sympathetic test. The frequency indices have almost identical low values for the index in hypertensive patients and in normotensive individuals. The evaluation for LF/HF ratio is higher in the normotensive individuals as a reflection of the preserved higher elasticity of the ratio between the sympathetic and the

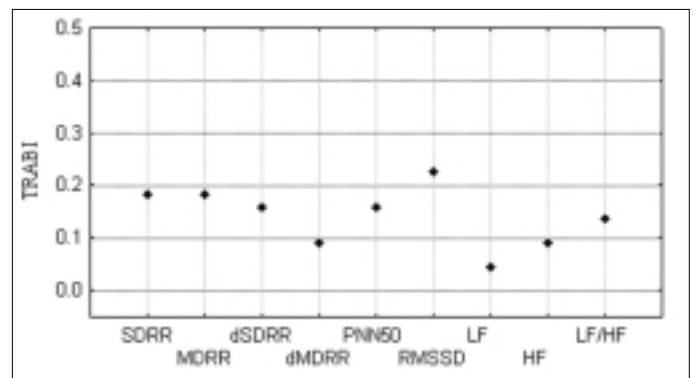


Figure 2. Values of TRABI for the HRV indices in healthy subjects: a comparison of morning and afternoon measurements in the resting state and during Valsalva maneuver

HRV- heart rate variability, TRABI- time-related autonomic balance changes indicator

vagal component in the autonomic balance. In the mild hypertensive patients, due to the elevated sympathetic tone in the morning, the stimulation cannot induce changes to the same degree as in normotensive individuals, and the elasticity of the ratio is limited.

The mean value of TRABI and the evaluations for the HRV indices in the comparative study between the reaction during the Valsalva maneuver and during rest in healthy individuals is significantly higher than the mean value in the hypertensive patients (Fig. 4). It can be claimed that the hypertensive patients have a reduced circadian nature of the parasympathetic part of the autonomic balance. All values of TRABI for the different indices are lower for the hypertensive patients. Only the evaluation for the LF index in the hypertensive patients has a higher value. This result is in support of the tendency in the sympathicotonia in hypertensive patients towards a more pronounced circadian nature, which was mentioned earlier.

Several conclusions can be formulated as a summary of the above results. The values of the HRV indices in the mild hypertensive patients are significantly lower than the values in healthy subjects. In the mild hypertensive patients there is a more pronounced circadian nature in the sympathetic component of the autonomic balance; the parasympathetic tone is suppressed; there is no circadian nature in the parasympathetic part of the autonomic balance.

Time-related autonomic balance profile in unstable angina pectoris

The mean value of TRABI for the HRV indices from the comparative study of the response to the HT with respect to rest in the morning and in the afternoon in the patients with unstable angina (UA) is higher, although insignificantly, than the respective value in healthy individuals. For certain indices, the values of the index in the patients considerably exceeded the values in the healthy individuals. Such are the assessments for SDRR, dSDRR, dMDRR, PNN50 and the LF/HF ratio (Fig. 5). These results indicate that in

Table 1. Definitions of time and frequency domain heart rate variability indices

Time-domain indices

A. Indices from the RR-interval tachogram (t1,t2,...,tn) in ms represent time intervals between successive R-waves of the electrocardiogram):

- SDRR (standard deviation)= $\sqrt{((t_1 - RRA)^2 + (t_2 - RRA)^2 + \dots + (t_n - RRA)^2) / (n-1)}$
- MDRR (mean deviation)=1/n*(|t1-RRA|+|t2-RRA|+...+|tn-RRA|).
(where RRA (mean value)=1/n*(t1+t2+...+tn)).

B. Indices from the tachogram of the differences between RR-intervals (dRR-tachogram) for each two successive R-waves: dt1=t1-t2; dt2=t2-t3;...;dtn-1=tn-1-tn:

- dSDRR (standard deviation)= $\sqrt{((dt_1 - DRRA)^2 + (dt_2 - DRRA)^2 + \dots + (dt_{n-1} - DRRA)^2) / (n-2)}$
- dMDRR (mean deviation)=1/n-1*(|dt1-DRRA|+|dt2-DRRA|+...+|dtn-1-DRRA|);
(where DRRA (mean value)=1/n-1*(t1+t2+...+tn-1))
- PNN50- number of R-waves for 1 min, where the corresponding difference dti exceeds 50 ms;
- RMSSD- root mean square deviation of the differences between adjacent RR-intervals.

Frequency-domain indices

From the frequency spectrum, as integral (or area) in the range of

- VLF - very low frequencies, 0.016 – 0.05 Hz;
- LF - low frequencies, 0.05 – 0.15 Hz;
- HF - high frequencies, 0.15 – 0.35 Hz;

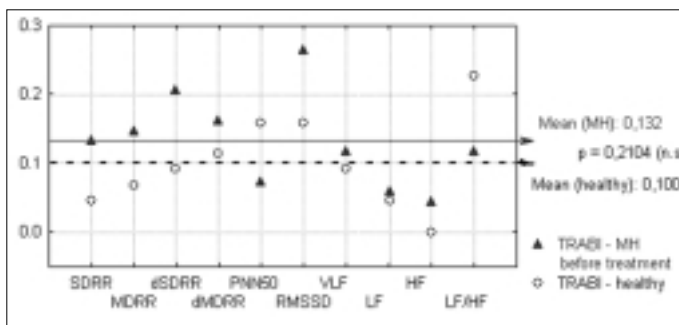


Figure 3. Values of TRABI for the HRV indices in healthy subjects and in mild hypertensive individuals: comparison between morning and afternoon measurements during rest and handgrip test

HRV- heart rate variability, TRABI- time-related autonomic balance changes indicator

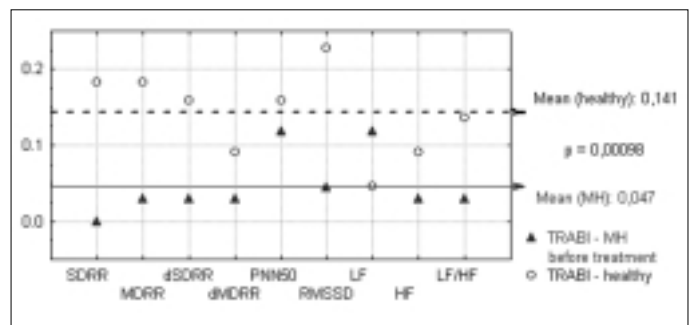


Figure 4. Values of TRABI for the HRV indices in healthy subjects and in mild hypertensive individuals: comparison between morning and afternoon measurements during rest and Valsalva maneuver

HRV- heart rate variability, TRABI- time-related autonomic balance changes indicator

patients with UA the sympathetic component in autonomic balance is more time-dependent than in healthy individuals.

The mean value of TRABI for the HRV indices from the comparative study of the response to the VM and rest in the morning and in the afternoon in the patients with UA does not differ significantly from the value in healthy individuals (Fig. 6). For most indices from the time area the values of TRABI in patients with UA and in healthy individuals are close. This result is in support of the conclusion that the circadian characteristic of the parasympathetic tone in persons with UA is analogous to the normal one. However, the values of the index for the indices LF and LF/HF ratio are higher in patients with UA than in healthy individuals, being 0.4 for LF and reaching 0.6 for LF/HF. Probably in the sample in which there is a sympathetic component as well, the stimulation of the sympathetic is suppressed due to its blocking described above. As a result, the frequency indices respond in a range in which there was no saturation of the values, and the time changes in the autonomic control can be reflected.

Time-related autonomic balance profile in the incidents from myocardial infarction

Results in the patients with morning myocardial infarction (MMI)

The mean value of TRABI for the HRV indices from the comparative study in the morning and in the afternoon of the response to the HT compared to rest for the patients with MMI is significantly higher than for healthy individuals (Fig. 7). It can be claimed that the patients with MMI have a marked circadian characteristic of the sympathetic. For all indices, with the exception of LF/HF, the values of TRABI are higher in the patients with MI. The lower value of the index for LF/HF is explained with hypersympatheticotony and blocked response to stress, on the one hand, and decreased circadian nature of the parasympathicus

– on the other, which does not allow this index to reflect the time changes in autonomic balance.

The mean value of TRABI for the HRV indices from the comparative study in the morning and in the afternoon of the response to Valsalva maneuver compared to rest in the patients with MMI does not differ significantly from the value in healthy individuals (Fig. 8). The patients preserve the normal circadian nature of the parasympathetic component in autonomic balance. The evaluations of TRABI for the indices SDRR, RMSSD and LF/HF are lower in patients with MMI. The result can be explained with the relatively decreased circadian nature of the parasympathetic part of the autonomic balance compared to the marked circadian nature of the sympathetic part in this group of patients.

Results in the patients with myocardial infarction in the non-morning hours (NMMI)

The mean value of TRABI for the HRV indices from the comparative study in the morning and in the afternoon of the response to HT compared to rest in the patients with NMMI almost coincided with the value in healthy individuals (Fig. 9). This result means that in the patients with NMMI there was no substantial impairment in the circadian nature of the sympathetic part of the balance. Only for the indices SDRR and MDRR the values of the index are higher in patients with NMMI compared to the evaluations in healthy individuals. Obviously, the circadian nature of the parasympathicus is impaired and hence also partial manifestation of the circadian nature of the sympathetic part of the balance is possible.

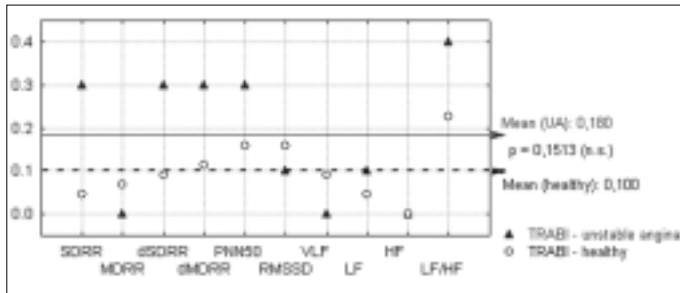


Figure 5. Values of TRABI for the HRV indices in healthy individuals and in patients with unstable angina: comparison between morning and afternoon measurements during rest and handgrip test

HRV- heart rate variability, TRABI- time-related autonomic balance changes indicator

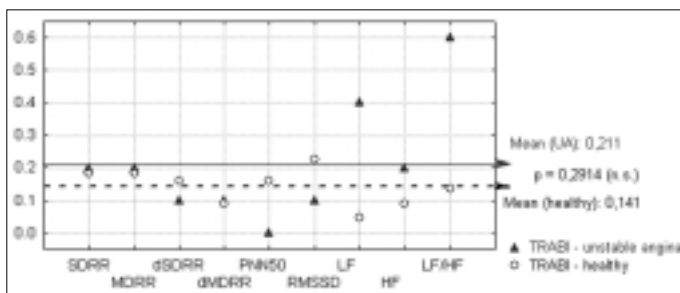


Figure 6. Values of TRABI for the HRV indices in healthy individuals and in patients with unstable angina: comparison between morning and afternoon measurements during rest and Valsalva maneuver

HRV- heart rate variability, TRABI- time-related autonomic balance changes indicator

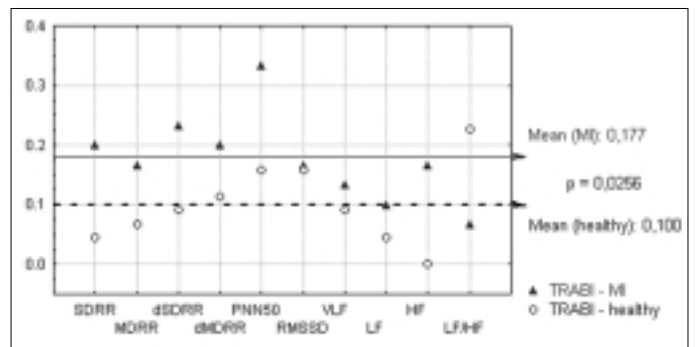


Figure 7. Values of TRABI for the HRV indices in healthy individuals and in patients with morning myocardial infarction: comparison between morning and afternoon measurements during rest and handgrip test

HRV- heart rate variability, TRABI- T-time-related autonomic balance changes indicator

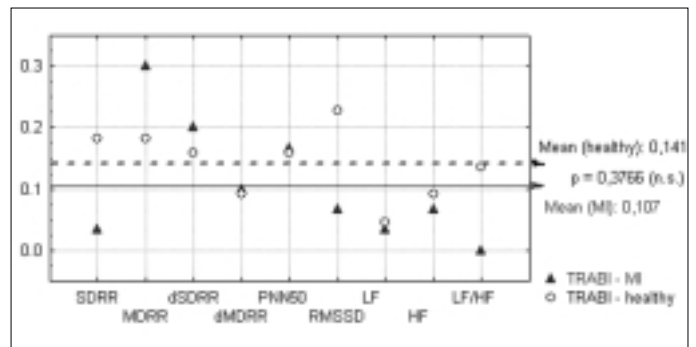


Figure 8. Values of TRABI for the HRV indices in healthy individuals and in patients with morning myocardial infarction: comparison between morning and afternoon measurements during rest and Valsalva maneuver

HRV- heart rate variability, TRABI- time-related autonomic balance changes indicator

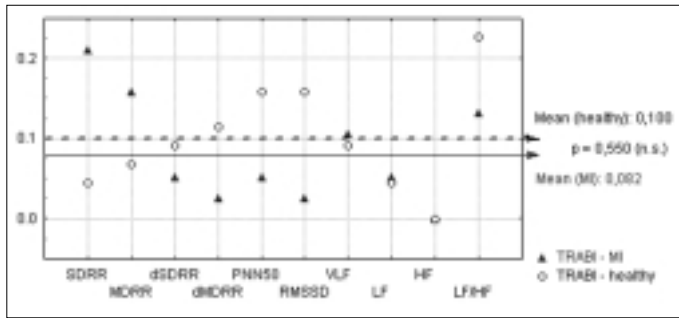


Figure 9. Values of TRABI for the HRV indices in healthy individuals and in patients with non-morning myocardial infarction: comparison between morning and afternoon measurements during rest and hand-grip test

HRV- heart rate variability, TRABI- time-related autonomic balance changes indicator

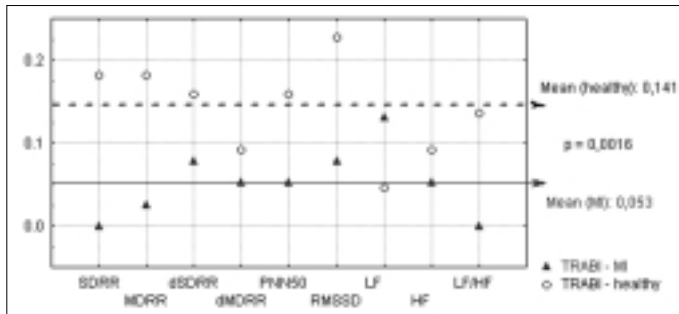


Figure 10. Values of TRABI for the HRV indices in healthy individuals and in patients with non-morning myocardial infarction: comparison between morning and afternoon measurements during rest and Valsalva maneuver

HRV- heart rate variability, TRABI- time-related autonomic balance changes indicator

The values of TRABI for the HRV indices from the comparative study in the morning and in the afternoon of the response to Valsalva maneuver and to rest in the patients with NMMI suggest that the parasympathetic sample leads to identical response in both time intervals (Fig. 10). The mean value of the index is significantly lower than that in healthy individuals. This result shows almost totally lost circadian nature of the vagal tone. Only for the index LF the value for TRABI is higher in the patients with NMMI compared to healthy individuals. The result supports the hypothesis presented above that the strongly decreased circadian nature of the vagus allows the manifestation of the circadian nature of the sympathetic.

Summarizing the results in patients with NMMI, we can assume that the circadian nature of the sympathetic part of the autonomic balance is preserved, with a strongly decreased circadian nature of the parasympathetic part of the balance.

Conclusions

The proposed method for assessment of time-related changes is an adequate quantitative measure for the individual power of the HRV indices to respond to circadian changes in the heart autonomic balance. Specific time-related changes in subjects with cardiovascular disease in initial or advanced stage can be defined by comparison with the corresponding profile of time-related changes in healthy subjects.

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