Results
One patient was hyperthyroid and presented initially with total serum triiodothyronine and thyroxine above the assays’ normal limits (16.1 ng/dL and 2.45 ng/mL respectively, with thyrotropin at 15.2 µIU/mL), remaining so after anti-TB treatment began (with serum thyronine at 16.0 ng/dL, triiodothyronine at 2.74 ng/mL and serum thyrotropin at 2.20 µIU/mL). His free triiodothyronine and sIL-2Rα remained normal in both samplings.

Overall hormone and sIL-2Rα measurements results are presented in table 1. Mean thyrotropin and sIL-2Rα remained well within normal limits at the first and at the second sampling. Mean total thyroxine and sIL-2Rα did not show any statistically significant differences between measurements. The observed elevation in total triiodothyronine levels (noted in 27/29 patients), after two weeks of anti-TB treatment, was statistically significant (Kruskal-Wallis p<0.05). Mean sIL-2Rα free triiodothyronine showed an increase after the initiation of anti-TB treatment, however these mean values were within normal limits and differences were not statistically significant. Mean sIL-2Rα levels were higher before treatment compared to mean values after treatment began, but not up to statistical significance and within normal limits. With the exception of the hyperthyroid patient, sIL-2Rα levels were inversely correlated with total triiodothyronine levels before treatment (Spearman’s rank correlation R=-0.62, p< 0.01), while no correlation was found at the second sampling, after two weeks of anti-TB therapy (Spearman’s R=0.11, p=0.70). Serum thyronine, total free triiodothyronine and free thyroxine were not correlated with sIL-2Rα neither before nor after the initiation of anti-TB therapy.

Table 1: Overall hormone and soluble interleukin-2 receptor measurements results of the patients (n=29) included in the study

| Measured parameter | 1st sampling mean(SE) | 2nd sampling mean(SE) | p-value |
|---------------------|------------------------|------------------------|---------|
| Thyrotropin (mIU/mL) | 10.70±0.15 | 10.50±0.16 | 0.9021 |
| Total thyroxine (ng/dL) | 9.9±0.45 | 9.8±0.45 | 0.9120 |
| Total triiodothyronine (pg/mL) | 2.98±0.25 | 3.00±0.25 | 0.8515 |
| Free thyroxine (µg/dL) | 1.1±0.05 | 1.0±0.05 | 0.4957 |
| Soluble interleukin-2 receptor (µg/mL) | 8.32±1.24 | 8.05±1.29 | 0.8331 |

* comparison of parameters’ results between samplings significant at the p<0.05 level (Kruskal-Wallis nonparametric ANOVA).

Discussion
This study’s patients initially presented with low to normal serum total triiodothyronine levels, which, following anti-TB treatment, showed a small but statistically significant elevation. This is a finding compatible with the low T3 syndrome and hypothyroidism (8). A significant negative correlation was observed between serum total triiodothyronine and sIL-2Rα in patients with TB, an anti-thyroid disease, before administration of anti-TB treatment. Consistently high levels of sIL-2Rα have been found in patients with untreated Graves’ disease and toxic adenoma (4), while low levels of sIL-2Rα have been consistently measured in hypothyroid post-thyroidectomy patients (4) and reported in cases of autoimmune thyroiditis (10). Levels of sIL-2Rα have been shown to be affected essentially in severe cases of TB and in immunocompromised patients (9). The patients of this study were not immunocompromised and made an uneventful recovery, so in this setting, we also speculate (given the small overall variations), a relation between thyroid hormones and sIL-2Rα in the low-T3 syndrome. Since the measurement of sIL-2Rα has already been proposed as an indicator of disease activity in Graves’ disease (11) and an early response marker in thyradoxicosis’ treatment (5), further relevant studies can be envisaged, in order to assess the behavior and clinical utility of sIL-2Rα levels versus thyroid function parameters in non-thyroidal disease.

Conclusion
Soluble serum interleukin-2 receptor alpha levels were found to be inversely correlated with total triiodothyronine levels in 29 otherwise healthy patients with pulmonary tuberculosis and the low-T3 syndrome before the administration of antituberculosis therapy. Further studies can be envisaged, in order to assess the behavior and clinical utility of this receptor’s levels versus thyroid function parameters in non-thyroidal disease.

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ORIGINAL ARTICLE

CHANGES OF SIGNAL-AVERAGED ECG IN NORMAL SUBJECTS AFTER ONE YEAR

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Summary: Repeated signal-averaged electrocardiograms (SA ECG) were recorded twice with a mean interval of 13 months in 11 healthy volunteers in order to acquire basic information on long-term changes of SA ECG. After one year the duration of filtered QRS remains the most stable parameter of SA ECG on the contrary to parameters describing end of QRS - i.e. both HFLA and RMS. Moreover iQRS seems to have better specificity in comparison to HFLA and RMS. An estimation of significant long-term changes in individual parameters of SA ECG was obtained. According to our results, only changes in QRS >13 ms, iQRS <8 ms, HFLA ≥22 ms and RMS ≥17 µV should be considered significant when found in a long-term follow-up of patients with a heart disease.

Key words: Signal-averaged electrocardiography (SA ECG), Late potentials, Long-term changes, Healthy volunteers

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Introduction
Late potentials appear to be a hallmark for sustained ventricular arrhythmias (1). Signal-averaged electrocardiography (SA ECG) helps in stratifying the risk of developing a sustained ventricular arrhythmia in patients who are recovering from myocardial infarction (2). With the present knowledge, it appears that late potentials seem to be more closely related to the underlying morphological substrate for arrhythmias than the clinically occurring arrhythmia per se. Abnormal signal-averaged ECG reflects abnormalities in ventricular activation caused by separation of myocardial bundles and the distortion of their parallel orientation by fibrosis (3).

There are several studies on the long-term changes in SA ECG in patients after myocardial infarction (4,5) and one study of patients with right ventricular dysplasia (6). But assessment of changes of SA ECG was not based on a comparison with a control group. Moreover there has been no study of the long-term changes in SA ECG in normal subjects. In order to acquire such basic information we performed a prospective study of signal-averaged ECG in 11 normal subjects. Such a study should be, in our opinion, the first step in evaluating long-term changes of SA ECG in different group of patients.

Materials and methods
11 men of relatively young age 32±5 years were studied. For inclusion into the study, each subject had to feel healthy and be active. All patients had to have a history and a physical examination neither of which was suggestive of cardiac disease, and a normal surface standard electrocardiogram. Repeated signal-averaged surface electrocardiograms were recorded with a mean interval of 13±1 months.

The recording and signal averaging and processing was performed with a system from Arrhythmia Research Technology, model 1200 EPx, based on the method previously described by Simon (1). Standard orthogonal bipolar X, Y, and Z leads were used to manalyse 250 cycles with a noise 0,4 µV. The recorded signals were amplified, averaged and filtered with a Butterworth bidirectional filter (range 40 to 250 Hz). The signal obtained from the 3 leads were then combined to form a vector magnitude (V= √X2+Y2+Z2), a measure that sums the high-frequency content from all three leads, termed ‘the filtered QRS complex’. Three indices were measured: 1. the duration of the filtered QRS (iQRS), 2. the root mean square of the terminal 40 ms of the filtered QRS (RMS) and 3. the period for which the filtered QRS remains <40 µV (HFLA). Abnormal values for these three parameters were defined according to current recommendations as iQRS >14 ms, RMS <20 µV, and HFLA ≥38 ms (2). Abnormal late potentials were defined by presence of two criteria out of the three.

All data were expressed as mean ± standard deviation (SD). In order to gain criteria for significant changes for all measured parameters we doubled and rounded up standard deviation of mean change of each of the parameters. Any change in case of QRS, RMS, HFLA higher by 1 ms and in case of RMS higher by 1 µV was considered to be significant (table 1).
Results

On the basis of the previously defined criteria, late potentials were found in 2 out of 11 volunteers (18%) in the first measurement. After 1 year the signal averaged ECG of both previously positive volunteers were found to be within normal limits, but one subject (9%) whose SA ECG was originally normal was classified as late potentials positive.

Interestingly, in all cases of positive SA ECG, late potentials were present due to coincident abnormal values of HFLA and RMS. IQRS was well within normal limits in all measurements. Both RMS and HFLA were in all 22 measurements 4 times abnormal.

Mean changes of measured parameters, and calculation of final values of changes considered abnormal are shown in table 1.

Table 1:

| Parameters | Mean change ± SD | 2 SD | Borderline values | Abnormal values |
|------------|----------------|------|------------------|----------------|
| IQRS (ms)  | 1.985±6.112    | ±11  | ±13              |                |
| fQRS (ms)  | 2.3±1.1       | ±0.6 | ±1.7            |
| HFLA (ms)  | 0.51±0.204    | ±0.0 | ±0.22           |
| RMS (µV)   | 0.7±0.37      | ±0.3 | ±0.6            |

Changes of measured parameters of SA ECG after one year in healthy volunteers (n=11) and calculation of changes considered to be abnormal.

According to our results we consider as significant a change of the standard QRS duration ≥13 ms, a change of IQRS ≥8 ms, a change of HFLA ≥2±2 ms and a change of RMS ≥17 V.

Discussion

Using the currently recommended method in 11 healthy volunteers, we found the abnormal late potentials in 2/11 (18%), which is slightly higher than reported in previous studies (7,8). This difference may be caused by the different method of detection of late potentials, but also by the small size of our group of volunteers. Interestingly, the abnormal late potentials in our group did not remain stable over the longer period, they either appeared or disappeared without any apparent changes in the health status of the study participants. An important finding is that the abnormal late potentials were always diagnosed by simultaneous different methods of late potentials, but also by the abnormal late potentials in our group did not remain stable.

To our knowledge the estimation of the significance of long-term changes of the SA ECG parameters is the first attempt to obtain such criteria. In previous research just the occurrence of abnormal late potentials was used to describe changes in SA ECG. Such studies were done in patients after myocardial infarction (4,5). But by this simple way of evaluation changes in late potentials may be underestimated. For example prolongation of IQRS from 95 ms to 113 ms is definitely a significant change without meeting defined criteria for late potentials. But a change as small as 1 ms may be sufficient to meet recommended criteria e.g. prolongation IQRS from 114 to 115 ms.

Blomström-Lundqvist et al. (6) have arbitrarily defined the changes in late potentials as 10 µV or more for RMS and 10 ms or more for HFLA under 25 µV to be significant. Our results clearly show their suggested criteria to be unacceptable. The most important limitation of our study is the limited size of the group of volunteers. At the beginning of the study we considered the size to be sufficient as we expected only a small variability in the studied parameters in time. Although limited by the size of the group, the findings demonstrate that in the long-term follow-up, only rather large differences in individual parameters of SA ECG are significant changes of SA ECG in different groups of patients. We consider IQRS to be the most useful parameter of SA ECG for assessment of long-term changes of SA ECG.

Conclusion

The duration of IQRS appears to be the most stable parameter of SA ECG on analysis of the long-term changes of SA ECG parameters. The fQRS is clearly superior to both RMS and HFLA. We obtained an estimate of significant long-term changes of parameters of signal-averaged ECG which might be useful in evaluating changes of SA ECG in different groups of patients. We consider IQRS to be the most useful parameter of SA ECG for assessment of long-term changes of SA ECG.

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Results

On the basis of the previously defined criteria, late potentials were found in 2 out of 11 volunteers (18%) in the first measurement. After 1 year the signal averaged ECG of both previously positive volunteers were found to be within normal limits, but one subject (9%) whose SA ECG was initially normal was classified as late potentials positive.

Interestingly, in all cases of positive SA ECG, late potentials were present due to coincident abnormal values of RMS and HFLA. IQRS was well within normal limits in all measurements. Both RMS and HFLA were in all 22 measurements 4 times abnormal.

Mean changes of measured parameters, and calculation of final values of changes considered abnormal are shown in table 1.

| Parameter   | Mean Change ± SD | 2 SD | Borderline Values | Abnormal Changes |
|-------------|------------------|------|-------------------|-----------------|
| IQRS (ms)   | 1.9±8.6          | 11.2 | ±12               | ±13             |
| RMS (µV)    | 0.7±13.7         | 35.4 | ±16               | ±17             |
| HFLA (ms)   | 0.5±10.3         | 20.6 | ±21               | ±22             |

Changes of measured parameters of SA ECG after one year in healthy volunteers (n=11) and calculation of changes considered to be abnormal.

According to our results we consider as significant a change of the standard QRS duration ±13 ms, a change of IQRS ±8 ms, a change of HFLA ±22 ms and a change of RMS ±17 µV.

Discussion

Using the currently recommended method in 11 healthy volunteers, we found the abnormal late potentials in 2/11 (18%), which is slightly higher than reported in previous studies (7,8). This difference may be caused by the different method of detection of late potentials, but also by the small size of our group of volunteers. Interestingly, the abnormal late potentials in our group did not remain stable over the longer period, they either appeared or disappeared without any apparent changes in the health status of the study participants. An important finding is that the abnormal late potentials were always diagnosed by simultaneous abnormalities of RMS and HFLA. In addition, we observed a low long-term stability of these parameters suggesting the poor long-term reproducibility. On contrast to RMS and HFLA no abnormal value of IQRS was observed in our study. IQRS was found to be the most stable parameter over time. In this way our work gives rise to some doubts about previously defined criteria for evaluation of SA ECG. In order to eliminate the false positive results the duration of the filtered QRS should be preferred to the other two recommended parameters of SA ECG. Our results on long-term stability of IQRS closely correspond with previous studies which found IQRS to be the most reproducible parameter of SA ECG in a short-time (6,9).

To our knowledge the estimation of the significance of long-term changes of the SA ECG parameters is the first attempt to obtain such criteria. In previous research just the occurrence of abnormal late potentials was used to describe changes in SA ECG. Such studies were done in patients after myocardial infarctions (4,5). But by this simple way of evaluation changes in late potentials may be under- or overestimated. For example prolongation of IQRS from 95 ms to 113 ms is definitely a significant change without meeting defined criteria for late potentials. But a change as small as 1 ms may be sufficient to meet recommended criteria e.g. prolongation IQRS from 114 to 115 ms. Blomstrom-Lundqvist et al. (6) have arbitrarily defined the changes in late potentials as 10 µV or more for RMS and 10 ms or more for HFLA under 25 µV to be significant. Our results clearly show their suggested criteria to be unacceptable. The most important limitation of our study is the limited size of the group of volunteers. At the beginning of the study we considered the size to be sufficient as we expected only a small variability of the studied parameters in time. Although limited by the size of the group, the findings demonstrate that in the long-term follow-up, only rather large differences in individual parameters of SA ECG (ΔQRS ±10 ms, ΔHFLA ±22 ms and ΔRMS ±17 µV) are likely to be caused by myocardial damage.

Conclusion

The duration of IQRS appears to be the most stable parameter of SA ECG on analysis of the long-term changes of SA ECG parameters. The IQRS is clearly superior to both RMS and HFLA. We obtained an estimate of significant long-term changes of parameters of signal-averaged ECG which might be useful in evaluating changes of SA ECG in different groups of patients. We consider IQRS to be the most useful parameter of SA ECG for assessment of long-term changes of SA ECG.

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