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Low-T3 Syndrome and Signal-Averaged ECG in Hemodialyzed Patients

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Summary

The study was designed to evaluate the potential link between low-T_3 syndrome and signal-averaged ECG parameters (SAECG) in a group of hemodialyzed patients (HD-pts). 52 selected HD-pts (without relevant thyroid and cardiac diseases) were included. SAECGs were performed postdialysis together with evaluating free triiodothyronine (fT_3), free thyroxine (fT_4), reverse triiodothyronine (rT_3), thyroid stimulating hormone levels and echocardiography. For each SAECG, QRS duration (QRSd), root-mean-square voltage of the terminal 40 ms of the QRS (RMS40), and low-amplitude signal duration (LAS40) were measured. Abnormal SAECGs were found in 30.8 % of HD-pt. HD-pts with decreased fT_3 and increased rT_3 values (low-T_3 positive) revealed higher QRSd and LAS40 values in comparison with low-T_3 negative HD-pts ($p=0.019$, $p<0.001$ respectively). Low-T_3 positive HD-pts had lower RMS40 values than low-T_3 negative patients ($p<0.001$). The Pearson test showed significant correlations between QRSd and fT_3 ($r=-0.592$, $p<0.001$); QRSd and rT_3 ($r=0.562$, $p<0.001$); RMS40 and fT_3 ($r=0.432$, $p=0.009$); RMS40 and rT_3 ($r=-0.325$, $p=0.025$). On multivariate analysis, both fT_3 and rT_3 levels were found to be independent predictors of QRSd and RMS40 values. Our study showed that decreased fT_3 and increased rT_3 concentrations due to low-T_3 syndrome influence SAECG parameters in HD-pt.

Key words

Haemodialysis • Late ventricular potentials • SAECG • Low-T_3 syndrome • Reverse triiodothyronine

Introduction

Signal-averaged electrocardiograms (SAECGs), a non-invasive technique for the detection of high-frequency, microvolt-level cardiac electrical activity in the terminal portion of QRS complexes, has been widely used to record ventricular late potentials. Ventricular late potentials are thought to result from fragmentation of electromotive forces in abnormal areas of ventricular myocardium where activation is delayed by slow conduction. Many reports have demonstrated that the presence of an abnormal SAECG reflects delayed ventricular depolarization and identifies the structural substrate for the ventricular tachycardia in the re-entry mechanism. Recent studies have demonstrated that functional abnormalities are also capable of transforming

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a stable substrate into an unstable one (Kjellgren and Gomes 1993, Steinberg 1996, Meier *et al.* 2001*)*. An abnormal SAECG can identify those patients at increased risk of malignant ventricular arrhythmias, and sudden cardiac death *(*Kjellgren and Gomes 1993, Steiberg 1996, Morales *et al.* 1998, Antzelevitch and Fish 2001*)*.

The cardiovascular system is one of the most important targets on which thyroid hormones act. Clinical and experimental studies have shown that triiodothyronine increases the heart rate, cardiac output, heart contractility and consumption of oxygen and nutrients. It also decreases systemic vascular resistance and improves diastolic relaxation, leading to a more efficient use of energy and nutrients by cardiomyocytes *(*Gomberg-Maitland and Frishman 1998, Klein and Ojamaa 2001*)*. In severe non-thyroidal diseases, including chronic renal failure, sepsis, trauma, starvation, chronic heart failure, myocardial infarction, unstable angina and some other diseases, a typical pattern of altered thyroid hormone metabolism may occur. This condition, which has been called "low-T_3 syndrome", is characterized by decreased serum concentrations of free iodothyronine (fT_3) and increased concentrations of reverse triiodothyronine (rT_3), without a compensatory increase in thyroid stimulating hormone (TSH) *(*Chopra 1997, Camacho and Dwarkanathan 1999*)*. The precise mechanisms responsible for the low-T_3 syndrome are not well understood, however recent studies have documented that the low-T_3 syndrome correlates with poor cardiac prognosis and that the low-T_3 syndrome is a strong predictor of death in cardiac patients (Friberg *et al.* 2001, Iervasi *et al.* 2003), but the pathophysiological mechanisms of these relations remain unclear. We assumed that the low-T_3 syndrome might be associated with measurable conduction abnormalities due to supposed discrete myocardial changes. According to our knowledge, no studies have focused on documenting the possible link between low-T_3 syndrome and SAECG parameters.

The purpose of this study was thus to evaluate the potential link between the low-T_3 syndrome and SAECG parameters in a group of selected HD-pts.

Methods

Patients

Fifty-two HD-pts (24 F and 28 M), age 23 to 46 years (mean 36.1±7.3), who were treated by HD from 13 to 52 months (mean 31.7±13.4) were selected from a larger group of HD-pts. Informed consent was obtained in each case, and the local committees of ethics approved the studies. The causes of end-stage renal disease were chronic glomerulonephritis (N=21), pyelonephritis (N=9), obstructive nephropathy (N=7), polycystic kidney disease (N=5) and unknown/uncertain (N=10).

The inclusion/exclusion criteria were as follows: (1) HD-pts with evidence of thyroid or pituitary disorders or altered TSH levels were excluded; (2) HD-pts with evidence of organic heart disease such as old myocardial infarction, ischemic heart disease (Canadian Cardiovascular Society class > I), heart failure (New York Heart Association class > I), ejection fraction <60 %, and left ventricular mass index (LVMI) higher than 134 g/m^2 for males and 110 g/m^2 for females *(*Devereux 1993*)* were excluded from the study; (3) all included HD-pts displayed a sinus rhythm and no evidence of intraventricular conduction disturbances; (4) none of the HD-pts included in the study received medication known to alter the thyroid function or QRS duration; 5) HD-pts affected by diabetes, amyloidosis, and with C-reactive protein serum level > 5 mg/dl were excluded from the study. HD-pts were dialysed 3-times weekly with polysulphone dialysers (Fresenius) and bicarbonate containing dialysate. The mean weekly HD duration was 12.3±0.5 h.

Control Group

Thirty-eight healthy subjects, similar to the patients' gender distribution (16 F and 22 M), and age (21 to 52 years, mean 38.6±6.7), took part in the SAECG and biochemical studies as a control group.

SAECG

SAECGs were performed 2 h after the end of the HD session (to eliminate the influence of fluid overload on SAECG parameters) by using a CODAX-SAI-IK system together with blood chemistry and echocardiographic examinations. Signals received from 3 bipolar orthogonal modified Frank leads were amplified and filtered with the use of Butterworth filters between 40 and 250 Hz. Recordings were accepted for analysis if two of the following criteria were met: number of beats averaged > 250, mean noise levels < 1.0 μV. Abnormal SAECG parameters were: ventricular activation time (QRSd) >114 ms, duration of low amplitude signals lower than 40 μV (LAS40) > 38 ms, root mean square voltage of signals in the last 40 ms of the high frequency QRS intervals (RMS40) < 25 μV. An SAECG was

considered positive for LP if two of these three parameters were abnormal *(*Antzelevitch and Fish 2001, Kjellgren and Gomes 1993*)*.

Echocardiographic examination

The LVMI was calculated by using the formula obtained by Devereux *(*Devereux *et al.* 1993*)*.

Biochemical measurements

The following serum biochemical parameters were measured postdialysis by using routine methods: sodium, potassium, magnesium, phosphorus, calcium, urea, creatinine, albumin, bicarbonate, pH, C-reactive protein, and intact PTH haemoglobin. The levels of fT_4 and fT_3 were determined postdialysis using RIA, and the TSH levels using IRMA (Brahms Diagnostica). Reverse T_3 was determined using RIA (Biochem Immunosystem). The normal ranges in our laboratory are 0.4-4.9 mU/ml for TSH, 12.0-22 pmol/l for fT_4, 3.0-7.0 pmol/l for fT_3, and 0.15-0.61 nmol/l for rT_3. The dialysis adequacy was evaluated by the estimation of equilibrated Kt/V (Schneditz and Daugirdas 2001).

Statistical analysis

Statistical analysis was carried out on an IBM PC using Statistica Version 5, and the results were tested for normality. Data are expressed as mean ±S.D., except data regarding PTH – presented as median and range. The statistical significance of the differences between the group means were compared by the paired Student's t-test. Linear regression analysis was performed by using the Pearson test. Multiple stepwise regression analysis was performed to estimate the potential influence of various factors on SAECG parameters. The following independence parameters were entered into the models: (1) the age, albumin, sodium, potassium, calcium, phosphorus, magnesium, bicarbonate, PTH, Hb, urea, LVMI, and fT_3; (2) the age, albumin, sodium, potassium, calcium, phosphorus, magnesium, bicarbonate, PTH, Hb, urea, LVMI and rT_3. Significance levels < 0.05 were accepted as significant.

Results

Baseline characteristics of the studied patients are shown below. For the HD-pts the mean level of haemoglobin was 7.921±0.507 mmol/dm^3, creatinine 368.3±102.4 μmol/dm^3, albumin 603±40 μmol/dm^3, intact PTH 28.65 pmol/dm^3 range 0.79-105.1, bicarbonate 25.7±3.6 mmol/dm^3, potassium 3.93±0.40 mmol/dm^3, calcium 2.61±0.23 mmol/dm^3, phosphorus 1.28±0.25 mmol/dm^3 and magnesium 1.14 ± 0.29 mmol/dm^3. The equilibrated Kt/V value was 1.12±0.18.

The thyroid hormones levels are depicted in Table 1. No significant changes in TSH levels were found between HD-pts and controls. The fT_4 values had only a tendency to be lower in HD-pts than in the control group, but did not reach statistical significance (p=0.11). The fT_3 level was significantly lower, and the rT_3 level significantly higher in the group of HD-pts when compared to the controls. Eleven out of the 52 HD-pts (21.1 %) included in the study had lower fT_3 and higher rT_3 levels than referential laboratory ranges.

Table 1. Thyroid hormone levels in hemodialysis patients and controls

	HD (n=52)	**Controls (n=38)**	**HD vs. controls**
TSH (mU/ml)	2.41±0.99	2.49±1.03	NS
fT4 (pmol/l)	13.9±2.2	15.9±1.9	NS
fT3 (pmol/l)	3.42±0.51	4.18±0.53	p=0.002
rT3 (nmol/l)	0.51±0.21	0.28±0.14	p<0.001

The results of the SAECG parameters are presented in Table 2. Only one out of the 52 HD-pts included in the study matched the criteria for diagnosing LP occurrence, which constitutes 1.92 % of HD-pts. In the control group no presence of LP was observed. HD-pts had a significantly higher filtered QRS duration compared to the controls (p=0.011). RMS40 and LAS40 showed no significant differences between HD-pts and controls. One abnormal SAECG parameter was found, however, in 16 HD-pts (30.8 %) and in 3 controls (7.9 %). HD-pts with decreased fT_3 and increased rT_3 values (low-T_3 syndrome positive group) revealed significantly higher QRSd and LAS40 values in comparison with the group of HD-pts with fT_3 and rT_3 values in normal ranges (low-T_3 syndrome negative group) (p=0.019 and p<0.001 respectively). Low-T_3 syndrome positive HD-pts had significantly lower values of RMS40 than low-T_3 syndrome negative patients (p<0.001).

Table 2. Signal averaged ECG parameters in hemodialysis patients and controls

Parameter	HD-pts n=52	Controls n=38	HD-pts vs. controls	Low T3 (+) n=11	Low T3 (-) n=41	Low T3(+) vs. low T3(-)
QRSd (ms)	101±8	97±4	p=0.012	106±8	100±7	p=0.006
RMS40 (μV)	73.67±32.27	83.10±31.11	NS	49.20±34.82	80.23±31.75	p<0.001
LAS40 (ms)	23.03±10.01	18.57±8.92	NS	31.66±10.79	20.7±9.23	p<0.001

Low T3 (+) – HD patients with decreased fT3 and increased rT3 levels. Low T3 (-) – HD patients with fT3 and rT3 levels in normal ranges

Table 3. Results of Multiple Regression Analysis

Model 1

		Independent variable	B	St. error	β	p
Dependent variable	*QRSd*	rT3	1.402	0.590	0.488	0.029
		Model (R=0.488, R2=0.239)				
	RMS	rT3	217.201	87.173	0.402	0.023
		Model (R=0.735, R2=0.541)				

Model 2

		Independent variables	B	St. error	β	p
Dependent variable	*QRSd*	fT3	- 63.584	27.825	- 0.493	0.012
		Model (R=0.727, R2=0.529)				
	RMS	fT3	226.6	83.49	0.488	0.015
		Model (R=0.703, R2=0.494)				

No significant changes between the blood cell counts, levels of urea, creatinine, albumin, C-reactive protein, LVMI and Kt/V value were found in the group of low-T_3 syndrome positive HD-pts in comparison with low-T_3 syndrome negative patients. Similarly, no significant changes were noted in the plasma levels of electrolytes, or of the bicarbonate level in those two groups.

The results of the analysis performed using the Pearson test showed a significant correlations between (1) QRSd and the serum level of fT_3 ($r = -0.592$, $p<0.001$); (2) QRSd and the serum level of rT_3 ($r=0.562$, $p<0.001$); (3) RMS40 values and fT_3 serum level ($r=0.432$, $p=0.009$); (4) RMS40 values and rT_3 level ($r = -0.325$, $p=0.025$); (5) QRSd and LVMI values ($r=0.331$ $p=0.022$).

The results of multiple regression analysis show independent variables influencing the estimated SAECG parameters (Table 3). In the case of the first studied model, the fT_3 level was found to be an independent predictor and influenced both the QRSd and RMS40 parameters. In the case of the second model, the rT_3 serum level was found to be an independent predictor of the QRS duration. A similar analysis performed in the control group failed to indicate any factors influencing the SA-ECG parameter values in both the Pearson test and multiple regression analysis.

Discussion

Our study confirms the results of other authors *(*Lim *et al.* 1985, Lim 2001*)* that the low-T_3 syndrome is a common finding in HD-pts, selected, adequately dialyzed, and without evident additional diseases predisposing towards the low-T_3 syndrome. Several mechanisms are responsible for the low-T_3 syndrome; the most important of which is the inhibition of the 5'-deiodinating process in peripheral conversion of T_4 to T_3 (Chopra 1997, Klein and Ojamaa 2001). The answer to the question whether the low-T_3 syndrome constitutes an adaptive, and thus beneficial response, or whether it aggravates a patient's condition, is a matter of debate. Functionally, hypothyroidism due to low-T_3 syndrome has commonly been interpreted as an adaptive response that decreases energy consumption in cardiac disease (Utiger 1995, Klein and Ojamaa 2001) and serves to defend against protein wasting in a situation in which protein/caloric intake is limited and protein/amino acid loss is significant via dialysis procedures in HD-pts (Lim *et al.* 1985, Lim 2001). However, recent studies have documented that low-T_3 syndrome correlates with poor prognosis in such diseases as chronic heart failure, acute myocardial infarction, and unstable angina (Friberg *et al.* 2001, Shanoudy *et al.* 2001, Pavlou *et al.* 2002), low serum T_3 is also a predictor of postoperative atrial fibrillation (Cerillo *et al.* 2003), and low T_3 serum level has a strong predictive value for cardiac-specific and all-cause mortality (Iervasi *et al.* 2003), but the pathophysiological mechanisms remain unclear.

In our study, abnormal SAECG parameters were found in 28.8 % of the investigated HD-pts, while in recent studies by other authors (Girgis *et al.* 1999, Meier *et al.* 2001) the prevalence of abnormal postdialysis SAECGs were higher (by about 50 %) than reported in our study. The differences may be due to: the rigorous exclusion criteria that were employed in our study, the exclusion of common confounding factors commonly seen in the dialysis population; the patient's ages; the criteria of abnormal SAECG; and the timing of SAECG measurements. The role of SAECG parameters in HD-pts is not clear. Some authors (Roithinger *et al.* 1992) reported that ventricular late potentials were not useful in identifying life threatening cardiac arrhythmias in HD-pts, while others questioned this view (Girgis *et al.* 1999, Meier *et al.* 2001). The present study shows the existence of a strong association between the low-T_3 syndrome (decreased fT_3 as well as increased rT_3 levels) and some SAECG parameters, namely filtered QRSd and RMS40, in a group of HD-pts. Within our knowledge, the association between the low-T_3 syndrome and SAECG parameters, reflecting delayed ventricular depolarization, has not been previously reported in the literature. Schippinger *et al.* (1995) found a relationship between ventricular late potentials and "subclinical" hypothyroidism, however in that study TSH levels were elevated in most patients and rT_3 levels were not evaluated. According to most authors (Friberg *et al.* 2001, Cerillo *et al.* 2003, Iervasi *et al.* 2003), thyroid abnormalities (decreased fT_3 and increased rT_3 levels) due to the low-T_3 syndrome should probably be interpreted as a marker of cardiac and cumulative mortality rather than a direct causal factor contributing to poor prognosis in cardiac patients. A particularly interesting issue, although impossible to clarify at the present stage of our study, is the question whether the relation between the low-T_3 syndrome and SAECG parameters is related to thyroid hormonal abnormalities at the tissue level, or whether it is a consequence of the underlying disease. If our results were confirmed in larger groups of patients (not only those hemodialyzed), it would suggest that low-T_3 syndrome might produce thyroid hormonal abnormalities at the tissue level (hypothyroid-like state) that contribute to deterioration or exacerbation of the existing cardiac disease.

The limitations of our study include the relatively small patient numbers and the impossibility of controlling all possible factors that might influence both the thyroid hormone metabolism and SAECG parameters. Further studies are required to confirm our results as well as to determine the possible clinical importance of the relation between low-T_3 and SAECG parameters.

In conclusion, decreased fT_3 concentrations and increased rT_3 concentrations due to the low-T_3 syndrome influence SAECG parameters in HD-pts.

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