Assessment of cardiac autonomic dysregulation and ventricular repolarization in patients with asymptomatic systemic sclerosis

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Systemic sclerosis (SSc) is a multisystem disorder characterized by extensive vascular damage, by early generalized microangiopathy and fibrosis of the skin and internal organs. SSc is characterized parasympathetic impairment and marked sympathetic over activity. The aim of our study was to investigate the cardiac autonomic dysregulation in patients with asymptomatic systemic sclerosis. Thirty (28 females, mean age 41.7±11.5 yrs.) patients with scleroderma and age-matched thirty (28 females mean age 40.52±10.2 yrs.) healthy subjects as control group were enrolled to this study. Controls that had no cardiovascular risk factors were included in this study. All patients and the controls underwent a 24-hour EKG holter recording. Clinical and laboratory parameters of all subjects were assessed. Among time domain HRV parameters SDANN index, rMSSD and pNN50% were significantly lower in patients with SSc. Minimum and maximum heart rate (beats/min) were significantly higher in patients with SSc when compared with controls. QT interval durations and corrected QT interval durations were significantly increased in patients with SSc compared to controls (p=0.036, p=0.044 respectively). In addition, SSc patients had significantly higher systolic pulmonary arterial pressure (p=0.032). The assessment of HRV and QT interval durations in patients with SSc may represent a useful tool in monitoring the cardiovascular risks. Reduced heart rate variability and QT interval durations are evidence of sympathetic over activity, which is contributed to the clinical consequences in patients with SSc.

Key Words: 24-hour holter monitoring, Systemic sclerosis, Heart rate variability

INTRODUCTION

Scleroderma is a multisystem disorder whose course can vary from being a relatively benign condition involving the skin and peripheral vasculature to a rapidly progressive disease affecting internal organs (Black and Stephens, 1993). Involvement of major organs, such as heart, lungs and kidneys, was found to be an independent adverse predictor of mortality (Ioannidis et al., 2005). Cardiac involvement is a poor prognostic sign. The early detection of cardiopulmonary involvement in scleroderma is important for optimal treatment and for preventive measures in the early stages of the disease and it may be underdiagnosed particularly in the asymptomatic population (Hüral et al., 2009). 24 hours rhythm Holter monitor have been shown to reflect separates the heart rate spectrum into various components such as QT dynamicity, heart rate variability analysis and quantifies sympathetic and vagal influences on the heart.

The aim of our study was to assess sympathetic/parasympathetic autonomic function and ventricular repolarization in patients with systemic sclerosis.
MATERIALS AND METHODS

Study population

The current study was carried out in the Department of Cardiology, Faculty of Medicine, Dicle University between Marc 2009 and April 2010. The local ethics committee approved the study and all the subjects gave written informed consent. We prospectively studied 30 patients with SSc (28 females and 2 men, mean age 41.7±11.5). SSc patients as defined by the according to the criteria of the American College of Rheumatology (4) Patients were classified as having diffuse or limited scleroderma according to the extent of cutaneous Involvement and 30 controls (28 females and 2 men, mean age 40.52±10.2) that had no cardiovascular risk factors were included in this study. All patients received nifedipine 60 mg/day drug therapy.

Patients with evidence of moderate to severe valvular disease; ischemic heart disease potentially influence QT duration administration of drugs atrial fibrillation, heart failure, hypertension, diabetes mellitus, hypercholesterolemia abnormal serum levels of electrolytes (Potassium: 3.5-5.5 mEq/L; Calcium: 8.6-10.2 mg/dl) or any other cardiac or systemic disease were excluded. All subjects underwent ambulatory 24-hour rhythm Holter monitoring recording and standard echocardiography.

Ambulatory 24-hour electrocardiograms and time domain Heart rate variability (HRV) analysis

A 24-hour ECG monitoring was performed. All the tapes were subsequently analyzed measuring time domain HRV in the time and frequency domain, using a commercially available program (ELA medical Multichannel-Multiday Version 3.10, Italy). The normal and aberrant complexes were discriminated, and all adjacent intervals between normal beats (NN) were collected over a period of 24 hour. All of the normal intervals were analyzed employing the time domain method. The time domain analysis of HRV included the mean of all normal R-R intervals (N-N), the standard deviation of N-Ns (SDNN), the standard deviation of 5 min mean values of N-Ns (SDANN), the root mean square successive difference of N-Ns (rMSSD), and the percentage of successive N-N differences of 50 ms for each 5-min interval (pNN50%). The recordings, and the collection and elaboration of the results, were done in accordance with guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

ECG Interval Measurements

Standard 12-lead ECGs (Hewlett-Packard digital recorder model 4745A) were performed daily at a paper speed of 25 mm/sec in all patients. ECG interval measurements were performed by an observer. The RR, QT, and JT intervals were measured during sinus rhythm in each of the standard V, through V6 precordial leads. For the latter two measurements, the point of T wave offset was defined as return of the terminal T wave to the TP baseline. When a U wave was present and interrupted the T wave, the terminal portion of the visible T wave was extrapolated to the TP baseline to identify the point of T wave offset. Each interval measurement recorded was the average of those intervals available on the patient's 12-lead ECG. Each QT interval and QTC were corrected for the patient's heart rate using Bazett's formula \[QTc = QT / \sqrt{RR}\] where QTC is corrected QT interval (Day et al., 1990).

Echo-cardiography

All echocardiographic examinations were performed by an experienced echo-cardiographer blinded to clinical data with the use of a commercially available ultrasound system (Vivid S 5, GE). Standard echocardiography was performed with the participants in the partial left decubitus position and measurements were done according to the guidelines of the American Society of Echocardiography (American Society of Echocardiography Committee on Standards, 1989). Two-dimensional (2D) images were obtained from standard windows (parasternal long axis, apical four- and two-chamber, and long-axis views). Left ventricular ejection fraction was estimated by Simpson's method. The estimated pulmonary arterial systolic pressure was calculated as the sum of the trans tricuspid gradient and the estimated right atrial pressure. From the apical four-chamber view, right ventricular inflow, parasternal short axis or subcostal view, continuous wave Doppler echocardiography was used to assess the peak tricuspid regurgitate velocity. Using the simplified Bernoulli equation, the right atrial pressure was estimated using the diameter of the inferior vena cava and the response to changes in respiration. Pulmonary hypertension was defined as a systolic pulmonary artery pressure value ≥40 mmHg.

Statistical analysis

Statistical analyses were performed with the SPSS 15.0 program for Windows. Genders of the subjects were analyzed among groups by Pearson's Chi-square test. Data were compared with the nonparametric Mann–Whitney (unpaired data) and Wilcoxon (paired data) tests. \(P < 0.05\) was considered significant. All quantitative data are expressed as means ± SD. Measures of heart
rate variability were transformed by natural logarithm because their distributions were skewed. Their correlations were assessed with Pearson’s correlation coefficients.

RESULTS

A total of 56 women and 4 men, mean aged 41.11±5.6 years (range 18–65 years) were enrolled. 30 patients with SSc (28 females mean age 41.7±11.5 yrs.) and 30 controls (28 females, mean age 40.52±10.2) were enrolled. There were 28 diffuse scleroderma and 2 limited scleroderma patients. The mean duration of the disease was 8.5±5.2 years. All patients were receiving calcium channel blocker therapy (nifedipine) for SSc-related digital vasculopathy. Twenty-six patients were receiving steroids, twenty-for patients Cyclophosphamide and nine patients’ azathioprine. The two groups of patients were similar with regard to age, sex, blood and biochemical parameters (table 1). SSc patients had significantly higher systolic Pulmonary arterial pressure compared to controls (p=0.032) (table 1). The echocardiographic and cardiac Doppler examination showed normal findings in all patients.

Ambulatory 24-hour electrocardiograms findings of the subjects demonstration; Minimum heart rate and maximum heart rate significantly higher in patients with SSc (p=0.047, p=0.002 respectively) (table 2). QT durations and corrected QT interval durations were significantly increased in patients with SSc (p=0.036, p=0.044 respectively) (table 2). The analysis of 24 h recordings evidenced significant cardiac arrhythmias in 25 patients. In particular significant supraventricular arrhythmias (number of supraventricular ectopic beats >30 h and or runs of ≥3 consecutive ectopic beats) were present in 25, ventricular arrhythmias in 13 patients No significant bradarrhythmias or ischaemic like transient electrocardiographic changes were found (table 2).

The time domain analysis of time domain HRV results, included the mean of SDNN, SDANNindex patients and control groups were not different, but other time domain HRV parameters; SDNNindex, rMSSD and pNN50% of SSc significantly lower than controls (p=0.001, p=0.014, p=0.046 respectively) (table 3).

DISCUSSION

In this study showed that, noninvasive assessment of cardiac involvement with asymptomatic SSc and based on 24-hours ECG monitoring. This study demonstrates that reduced time domain HRV parameters and increased QT interval parameters in asymptomatic
diffuse scleroderma. In addition to minimum heart rate and maximum heart rate (beats/min) significantly higher in patients with SSc. Stimulation of the sympathetic nerves system may be related to increased cardiovascular diseases such as cardiomyopathy, blood pressure elevation, conduction and ventricular arrhythmias and sudden cardiac death. In addition to ventricular repolarization abnormality such as reduced time domain HRV parameters, increased QT interval parameters which is caused by sympathetic overactivity. Computerized analysis of heart rate variability has been proposed as a feasible and noninvasive tool for evaluating the autonomic control of the heart (Bigger et al., 1993).

Assessment of the presence of autonomic dysfunction in SSc patients may be of clinical and possibly prognostic relevance. In post infarction patients, reduced heart rate variability has been reported to predict risk for subsequent mortality (Bigger et al., 1993, Bigger et al., 1993, Kleiger et al., 1987). Reduced heart rate variability is a reflection of increased sympathetic activity, which is a predisposing factor for fatal arrhythmias (Ferri et al., 1997). Only a few study displayed the presence of cardiovascular autonomic dysfunction by spectral analysis of HRV in patients with scleroderma (Ciftci et al 2007, Morelli et al., 1996, Cevik et al., 2010).

Ferri and et al. reported decrease in HRV circadian rhythm associated with a decrease in parasympathetic activity and an increase in sympathetic activity in with SSc (Ciftci et al 2007). Ferri and et al demonstrated SDNN and rMSSD (ms) like HRV parameters diminish in patients with SSc.

The results of Ferri’s study generally accorded with and supported the results of our study. Orcun and et al reported in HRV analysis, autonomic balance was changed in favor of the sympathetic system in patients with diffuse scleroderma. In QT dynamicy analysis, QT/RR slopes were significantly steeper in patients with diffuse scleroderma compared to patients with limited scleroderma and controls. In addition suggest that diffuse scleroderma patients have cardiac repolarization abnormalities indicated by a steeper QT/RR regression line accompanied by sympathetic overactivity in HRV analysis. Patients with limited scleroderma did not show any significant difference compared to the controls regarding any HRV or QT dynamicy parameter (Morelli et al., 1996). However in the present study patients population was younger than those of the two study. In addition, in Ferri’s study, the number of patients were less than our study. Cevik et al. showed that minimum, maximum and mean heart rate was significantly higher while mean RR interval were significantly lower in patients with rheumatoid arthritis when compared with controls. In addition, time domain HRV parameters were significantly lower in patients with Rheumatoid Arthritis (Tsui et al., 1994).

On the other hand. Tsui and et al reported estimation of heart rate variability by ambulatory monitoring offers prognostic information beyond that provided by the evaluation of traditional risk factors in elderly people (Montanes et al., 1982). QT durations and corrected QT interval durations were significantly increased in patients with SSc. Which may explain increased incidence of ventricular arrhythmias and sudden death in this population? As far as known myocardial fibrosis is found at postmortem examination in up to 80% of patients with scleroderma (Wenzel et al., 2003). Our data indicate that underlying undetectable myocardial fibrosis is associated with prolongation of QTc. Other factors contributing to use of nifedipine. Wenzel et al reported nifedipine activates cardiac and peripheral sympathetic nerves differently depending on pharmacokinetics. These effects of nifedipine may be disadvantageous in cardiac patients with increased sympathetic activity (Sgreccia et al., 1998). Sgreccia A, and et al displayed increased QTc and QT dispersion have been reported in scleroderma patients (Pathak et al, 2005). QT dynamicy has been shown to have a prognostic value in including ventricular fibrillation ischemic cardiomyopathy, and congestive heart failure (Zareba, 2003).

CONCLUSIONS

Non-invasive parameters such as HRV may have a modest role in assessment of cardiovascular risk and prediction of sudden cardiac death risk, in addition to the traditional risk factors, in patients with SSc.
Limitations

In the present study, the number of outcomes was too small population and our results should be supported by findings of advanced studies.

REFERENCES


