International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

The relationship between left ventricular deformation and heart rate variability in patients with systemic sclerosis: Two- and three-dimensional strain analysis

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ARTICLE INFO

Article history:
Received 4 December 2016
Received in revised form 26 January 2017
Accepted 10 February 2017
Available online xxxx

Keywords:
Systemic sclerosis
Left ventricle
Strain
Heart rate variability

ABSTRACT

Objective: We sought to investigate left ventricular (LV) function and deformation, as well as heart rate variability (HRV), and their relationship, in patients with systemic sclerosis (SSc).
Methods: The study included 49 SSc patients and 38 age-matched healthy subjects. All patients underwent clinical examination, serological tests, 24-h Holter monitoring, and comprehensive two- and three-dimensional echocardiography (2DE and 3DE).
Results: 2DE and 3DE LV global longitudinal and circumferential strain, as well as 3DE area strains are significantly reduced in SSc patients comparing with controls. 2DE and 3DE LV radial strains are similar between the observed groups. 2DE LV layer-specific longitudinal and circumferential strains are also significantly affected by SSc. Parameters of cardiac autonomic nervous system, assessed by HRV indices, SDNN, SDANN, rMMSD, p50NN, 24-h HF, LF and TP are significantly lower in SSc group. HRV indices (24-h HF and LF) are associated with 2DE LV global, 2DE LV layer-specific and 3DE LV mechanics independently of main demographic, clinical and echocardiographic parameters of the study population. Additionally, Modified Rodnan Skin Score, clinical parameter of skin involvement in SSc, is significantly associated with HRV (24-h HF and LF), 2DE and 3DE LV deformation.
Conclusion: SSc significantly impacts LV deformation, all myocardial layers, and cardiac autonomic nervous function. A significant association between cardiac autonomic nervous system function, skin involvement and LV mechanics is revealed in SSc patients. These findings should encourage detailed cardiac assessment and further cardiac follow-up of the SSc patients with higher skin involvement, even when traditional echocardiographic parameters are within normal range.

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1. Introduction

Systemic sclerosis (SSc) is chronic systemic disease characterized with vascular damage and fibrosis of practically all organs. Autopsy studies showed that heart is involved in >80%, but clinical manifestations appear in only 15–20% [1–3]. Echocardiography represents a well-established method in detection of subtle changes in myocardial structure and function. Using conventional echocardiographic methods investigations confirmed that left ventricular (LV) systolic and diastolic functions are impaired in SSc patients [4,5]. The introduction of two-dimensional speckle tracking imaging provided the insight in LV mechanics in SSc subjects [6–8]. However, data regarding layer-specific strain and three-dimensional strain are still unavailable.

Cardiac autonomic nervous system is affected in SSc patients [9,10]. There are several possible reasons, but the widely accepted mechanism is the involvement of cardiac conduction system. In previous studies heart rate variability (HRV)-derived indices showed significant impairment of sympathetic and parasympathetic cardiac nervous system [9,10]. Furthermore, researches demonstrated the association between LV diastolic function an HRV parameters in SSc patients [11]. The relationship between 2DE and 3DE LV mechanical parameters with HRV indices was not investigated so far.

Considering the fact that arrhythmias and especially atrial fibrillation are more prevalent in SSc patients [12,13], and the fact that HRV could predict atrial fibrillation [14], we were interested to investigate 2DE and 3DE mechanics, including multilayer LV strain, and correlate

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http://dx.doi.org/10.1016/j.ijcard.2017.02.043
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Please cite this article as: M. Tadic, et al., The relationship between left ventricular deformation and heart rate variability in patients with systemic sclerosis: Two- and thr..., Int J Cardiol (2017), http://dx.doi.org/10.1016/j.ijcard.2017.02.043

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these parameters with HRV indices in patients with SSc and potentially show that determination of LV mechanics and/or autonomic nervous function could be good predictors of dysrhythmias in SSc patients.

2. Methodology

In this cross-sectional study was involved 49 consecutive SSc patients with no cardiovascular symptoms and 38 healthy subjects with similar age and sex distribution, but without cardiovascular risk factors. Exclusion criteria were heart failure, coronary artery disease, previous cerebrovascular events, atrial fibrillation, congenital heart disease, valvular heart disease more than mild, asthma or obstructive pulmonary disease, neoplastic disease, cirrhosis of the liver, kidney failure, or endocrinological diseases including type 2 diabetes mellitus. Patients with non-sinusal rhythms and artificially paced were excluded.

Blood pressure was measured by sphygmomanometer in the morning hours by taking the average value of two consecutive measurements in the sitting position 10 min apart. Blood pressure was calculated as average values between all the measurements.

All patients underwent a physical examination, including anthropometric measures (height, weight), estimation of skin thickness by the modified Rodnan Skin Score (mRSS), laboratory testing (antinuclear [ANA], anticentromere [ACA], and antitopoisomerase I antibody [Scl-70] levels), echocardiography and 24-hour Holter monitoring. Body mass index (BMI) and body surface area (BSA) were calculated for each patient.

The study was approved by the local Ethics Committee, and informed consent was obtained from all the participants.

2.1. Echocardiography

Echocardiographic examinations were performed by using a commercially available Vivid 7 (GE Vingmed, Horten, Norway) ultrasound machine equipped with both a 2.5 MHz transducer.

Reported values of all 2DE parameters were obtained as the average value of 3 consecutive cardiac cycles. LV diameters, septum and relative wall thickness, were measured according to the current recommendations [15]. LV ejection fraction (EF) was calculated by using the biplane method. LV mass (LVM) was calculated by using the corrected ASE method and indexed for BSA [15]. Left atrial (LA) volume was measured by the biplane method in 4- and 2-chamber views and indexed for BSA.

Pulsed-wave Doppler assessment of transmitral LV was obtained in the apical 4-chamber view according to the guidelines [16]. Tissue Doppler imaging was used to obtain LV myocardial velocities in the apical 4-chamber view, with a sample volume placed at the septal and lateral segments of the mitral annulus during early diastole (e′). The average of the peak early diastolic relaxation velocity (e′) of the septal and lateral mitral annulus was calculated, and the E/e′ ratio was computed.

2.2. Two-dimensional (2DE) strain analysis of the left ventricle

2DE strain analysis was performed by commercially available software (EchoPAC 201, GE-Healthcare, Horten, Norway). Global longitudinal strain was calculated by averaging all the values of regional peak longitudinal strain values obtained in 3 apical views. 2DE circumferential strain and radial strain were assessed as the average of the LV six regional values measured in the parasternal short-axis view, at the level of papillary muscles [15].

Multilayer longitudinal and circumferential strains were determined by modified 2DE strain software. Multilayer longitudinal was assessed in apical 4-chamber, 2-chamber and apical long axis view, whereas multilayer circumferential strain was evaluated in short axis at the apical level. The automatic tracking of the endocardial contour was performed in end-systole. The modified 2DE strain speckle tracking allowed the investigation of 3 myocardial layers: endocardial, mid-myocardial and epicardial [17].

Automatically provided tracking by software was carefully verified and the region of interest was manually corrected to ensure optimal tracking and to cover the entire thickness of the LV myocardium including endocardial, mid-myocardial and epicardial layers in all observed echocardiographic views.

After the software automatically created a region of interest, which contained endocardial, mid-myocardial and epicardial layers, the region of interest was manually corrected to ensure optimal tracking and to cover the entire thickness of the LV myocardium. Upon delineating the region of interest, the software was used to divide the LV into 6 segments. Then the peak systolic longitudinal strain, circumferential strain of the subendocardial, middle, and subepicardial myocardial layers, and the peak systolic radial strain of the LV were calculated [17].

2.3. Three-dimensional echocardiographic (3DE) examination

A full-volume acquisition of the left ventricle required for further analyses was obtained by harmonic imaging from an apical approach. Six electrocardiogram-gated consecutive beats were acquired during end-expiratory breath-hold to generate full volume. Before storing the volume data set, the quality of acquisition was checked in each patient by using the multi-slice display, to ensure that the entire LV cavity and wall were included in the full volume and no stitching artifacts were present. The frame rate was higher than 30 frames/s.

All data sets were analyzed by a commercially available software 4D Auto LVQ software (EchoPAC 201, GE-Healthcare, Horten, Norway), which was used for the off-line analysis. The software automatically identified the LV cavity endocardial border in 3D and provided the measured LV volumes, cardiac output, stroke volume, and EF. After that, an automatic trace of the epicardial border was displayed to detect the region of interest required for 3DE myocardial deformation parameters. The 3DE deformation parameters: global longitudinal, circumferential, radial, and area strain, were calculated as weighted averages of the regional values from the 17 myocardial segments at end-systole [18]. The results of the rejected segments were excluded during the calculation of global strain values. If three or more segments were rejected, global strain values were not calculated, and these patients were excluded.

2.4. 24-hour Holter monitoring

24-hour Holter monitoring was performed with a three-channel digital Schiller Microvit MT-101 system (Schiller AG, Baar, Switzerland) and analyzed by a Schiller software (Schiller AG, Baar, Switzerland). The minimum duration of recording was 18 h (after exclusion of non-sinusal cardiac cycles). SDNN was defined as the standard deviation of all normal RR intervals. SDANN, which reflects long-term HRV and therefore mainly sympathetic activity or sympathovagal balance, was defined as the standard deviation of the averaged normal RR intervals for all 5-min segments. rMSSD was calculated as the root mean square of the difference between the coupling intervals of adjacent RR intervals. pNN50 which reflects short-term beat-to-beat HRV and consequently primarily vagal activity was calculated as the proportion of adjacent RR intervals that varied by >50 ms. After power spectral density estimation, 3 standard frequency-domain HRV measures were calculated for 24-hour [19]. Low frequency domain (LF) was defined between 0.04 and 0.15 Hz; high frequency domain (HF) was defined between 0.15 and 0.4 Hz; total spectral power (TP) for all intervals up to 0.4 Hz. Additionally, the ratio of low to high frequency power (LF/HF) is calculated. The software calculated all HRV indices in the time segments of 5 min and then provided values for each hour during the monitoring and also for 24-h.

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