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Subclinical cardiac involvement in patients with facioscapulohumeral muscular dystrophy

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Abstract

Myocardial involvement is a common finding in certain myopathies, while it has not been extensively investigated in facioscapulohumeral muscular dystrophy (FSHD1A). Aim of this study was to assess in FSHD1A patients the electrical and functional properties of the myocardium. Twenty-four patients with FSHD1A (mean age 41.2 ± 14.5 years) and 24 matched healthy subjects were studied. Standard- and signal-averaged electrocardiography were recorded to determine QT dispersion and the presence of ventricular late potentials (VLPs). Standard echocardiography with systo-diastolic variations of integrated backscatter signal (CV-IBS) were performed to assess functional properties of the myocardium. Compared with control subjects, patients with FSHD1A had significantly lower CV-IBS and higher QT dispersion. Nine patients had positive VLPs. QT and QTc dispersion were inversely related to CV-IBS at both septum and posterior wall levels. Moreover, septal CV-IBS was inversely related to the KpnI-BinI4q fragment size. These results suggest a subclinical cardiac involvement in FSHD1A patients, which can represent a substrate for ventricular arrhythmias and heart failure.

Keywords: Facio-scapulo-humeral muscular dystrophy; Integrated backscatter; Ventricular late potentials; QT dispersion

1. Introduction

Facio-scapulo-humeral muscular dystrophy type 1A (FSHD1A) is an autosomal dominantly inherited disorder presenting with early involvement of facial and scapular muscles but a high degree of variability with respect to age at onset, severity and pattern of muscle involvement, both between and within families.

Myocardial involvement is a common finding in Duchenne-type muscular dystrophy, in which heart failure and dysrhythmias are the leading causes of death following respiratory failure [1,2]. Although previous studies showed electrophysiologic abnormalities in FSHD1A, represented by a high susceptibility to inducible atrial arrhythmias and relatively common sinus node dysfunction [3], lack of evidence exists on the presence of cardiac involvement in these patients.

Integrated backscatter signal (IBS) analysis is a recent echocardiographic technique which enables to assess textural and functional properties of the myocardium [4–7]. In addition, QT interval dispersion and ventricular late potentials (VLPs), measured with signal-averaged electrocardiography analysis, reflect the electrical properties of the myocardium and represent indices of electrical instability [8–10].

Thus, the aim of this study was to assess non-invasively the functional properties of the myocardium in FSHD1A patients by IBS analysis, and to investigate a potential substrate for ventricular arrhythmias by the analysis of QT dispersion and VLPs.

2. Materials and methods

2.1. Subjects

Twenty-four patients with FSHD1A and without known left ventricular dysfunction (mean age 41.2 ± 14.5 years)

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who were attending the neuromuscular clinic of the local institution were invited to participate in the study. Criteria for the diagnosis of FSHD1A included autosomal dominant inheritance, characteristic facial involvement, scapular/deltoid muscle weakness greater than biceps/triceps weakness and myopathic changes on skeletal muscle biopsy and electromyogram. The severity of skeletal muscle involvement was scored as 1–5 as previously published [11].

At enrollment, patients underwent a full history, physical examination, standard 12-lead ECG, 24-h ambulatory ECG monitoring, signal-averaged ECG and echocardiography with IBS analysis.

Additionally, we selected 24 matched healthy volunteers to form the control group. The protocol was approved by the Ethics Committee of the University of Pisa, and all the participants gave written consent to the study.

2.2. Genetic analysis

Molecular analysis to detect the presence of EcoRI-4q35 polymorphic fragments ranging between 10 and 38 kb in size has been used to confirm the diagnosis of FSHD1A. DNA has been extracted from lymphocytes derived from freshly collected or from Epstein-Barr virus-transformed lymphoblasts, according to the salting-out procedure. For Southern blot analysis with 4q35 markers restriction of genomic DNA, 32P-labeling, and hybridization with L1LA5 (D4S163), pH30 (D4S139), and p13E-11 (D4F104S1) have been performed, as described in previous studies [11–13]. Pulsed field gel electrophoresis (PFGE) analysis of p13E-11 alleles has been performed as described [13].

2.3. Echocardiography

The study was performed using an *HP Sonos 5500* (Hewlett-Packard, Co., Andover, Mass) phased-array echocardiograph with M-mode, two-dimensional, equipped with pulsed, continuous and color-flow Doppler capabilities. The echocardiograms were evaluated according to the recommendations suggested by the American Society of Echocardiography [14]. IBS analysis was performed using a special software package, available as an option of the *HP Sonos 5500*, as previously described [15]. Briefly, this system is capable of providing either conventional two-dimensional envelope-detected echocardiographic images or IBS images in which the grey level is displayed proportional to the integrated backscattered power. The backscatter can be measured in dB from an operator-defined region of interest (ROI). A maximum of 60 frames displayed at a real-time frame rate of 30 Hz (30 frames/s) are captured into cine-loop memory and subsequently stored on optical disk in a digital format with the same resolution as the scan converter memory (512×512, 8 bits). This system has the possibility to display the transmit power, log compression and time-gain compensation values on a screen; this permits to adjust the system to the same values at every examination. Conventional B-mode images of parasternal long-axis view were obtained in each subject. The IBS was measured by placing an elliptic ROI at the center of the mid-anterior septum and of the mid-posterior wall, and time–intensity curves of backscatter were derived. The average power of the IBS contained within the ROI was measured and displayed in dB for a total of 60 time frames. The magnitude of the cyclic variations of IBS (CV-IBS) was calculated as the average in three consecutive cardiac cycles of the difference between the end-diastolic IBS value, coinciding with the peak of the R wave at ECG, and the value at end-systole, typically corresponding to the end of the T wave.

The intra-observer and inter-observer variability of IBS cyclic variations were determined in 20 randomly selected recordings twice by the same observer and once each by 2 independent observers. Intra-observer and inter-observer variability of IBS cyclic variations were 3.9 ± 2.3 and $4.2\pm3.3\%$, respectively.

2.4. Electrocardiography

ECGs of 10 s were recorded with a Cardiovit CS-100 (Schiller-AG, Baar, Switzerland), using 25 mm/s paper speed and standardized at 0.1 mV/mm. QT intervals were measured manually in all the 12 leads in blinded fashion from the onset of the QRS complex to the end of the T wave, defined as a return to the isoelectric line. If the end of the T wave could not be identified, the lead was not included. A minimum of nine leads in which the QT interval could be measured was required for QT dispersion to be determined. Three consecutive QT intervals were measured and averaged for each lead. QT dispersion was defined as the difference between the longest and shortest QT intervals. Using Bazett's formula, QT dispersion was corrected (QTc) for heart rate. All ECGs were analyzed twice by two observers. Intraobserver and interobserver variability for QT dispersion measurements were <7 and $<8\%$, respectively. Differences were resolved by consensus.

Signal-averaged ECG was recorded according to recent recommendations [16], using a special software package of the Cardiovit CS-100. Signal-averaging was filtered with the use of a continued bidirectional filter with a bandpass of 40–250 Hz. A technician interactively confirmed the measurement points from the filtered QRS complex. The noise level was 0.4 μV in all cases. Three signal-averaged ECG parameters were examined and compared between groups. These parameters included the filtered QRS duration, the duration of the terminal QRS of low amplitude signal <40 μV (LAS), the root-mean-square of the terminal 40 ms (RMS40). VLPs were considered to be positive if all the three following parameters were present: (a) filtered QRS complex >114 ms, (b) LAS >38 ms, and (c) RMS40 <20 μV.