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Original Article

Subclinical myocardial dysfunction by tissue Doppler echocardiography in primary antiphospholipid syndrome: Preliminary results

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ABSTRACT

Aim of the work: To preliminary evaluate the myocardiac function in asymptomatic primary antiphospholipid syndrome (PAPS) patients using conventional and tissue Doppler echocardiogram.
Patients and methods: Nine female PAPS patients asymptomatic for cardiac manifestations and 7 matched controls were enrolled. Myocardial function was determined by echocardiogram (conventional and tissue Doppler imaging 'TDI' techniques).
Results: The median age of the patients was 43 (26–55 years) and disease duration 10 (3–19) years. Traditional cardiovascular risk factors were similar in PAPS and controls. Venous and arterial events were present in 55.6%, 22.2% showed obstetric features, 33.3% had stroke, 44.4% deep venous thrombosis and 66.7% had livedo reticularis. All patients were under oral anticoagulants with international normalization ratio within therapeutic range (2–3). 88.9% were positive for IgG and/or IgM anticardiolipin antibodies and 66.7% were positive for lupus anticoagulant. Conventional echocardiographic data were not altered in all evaluated parameters comparing patients and controls. Regarding TDI, a lower S' (systolic wave which is related to systolic function in the analysed segment) of lateral wall of left ventricle was observed in PAPS in comparison to controls [0.085 (0.007–0.12) vs. 0.12 (0.09–0.13), p = 0.004] as well as A′ wave of the septum (related to late diastolic function in the analysed segment) [0.07 (0.06–0.08) vs. 0.09 (0.07–0.11), p = 0.02].
Conclusion: The present study demonstrated subclinical myocardial dysfunction using TDI in asymptomatic PAPS patients. TDI is non-invasive and cost effective. Prospective studies including a large number of participants in order to confirm these preliminary data are needed.

1. Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder mainly characterized by a combination of venous and/or arterial thrombosis and/or recurrent fetal wastage [1]. Often, these are also accompanied by thrombocytopenia associated with the presence of moderate to high titers of antiphospholipid (APL) antibodies such as lupus anticoagulant (LA), anticardiolipin (ACL), and more recently, anti-beta2-glycoprotein (anti-β2GPI) antibodies [2].

Patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are at increased risk of atherosclerosis, and occurs much earlier compared to the general population even after accounting for traditional risk factors [3]. The increased intima-media thickness as a marker of atherosclerosis is confirmed in SLE patients with secondary APS and its link with disease activity favors the role of disease-specific potential risk factors [4]. This syndrome has been associated with the presence of early atherosclerosis and coronary events [5]. The APS is a prothrombotic state in the presence of atherosclerosis may be associated with high risk of atherothrombosis [6]. Several studies have confirmed the presence of atherosclerosis in APS patients [7–11].

The systolic and diastolic function can be assessed by Doppler echocardiography, using the 2-D evaluation plus the conventional and tissue Doppler. The conventional Doppler determines mitral and tricuspid flows (peak velocity of E and A waves, the isovolumetric relaxation time and deceleration time) [12]. In turn, the

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tissue Doppler allows further evaluation of the pattern of myocardial perfusion of both ventricles [13]. The use of conventional Doppler has limitations in patients with high heart rate, change in pre-and afterload (eg, hypovolemia or hypertension) or even pseudo-normalization of diastolic function (grade II diastolic dysfunction) [14]. In the case of tissue Doppler these aspects are not relevant because myocardial perfusion is independent of these factors and may be used with relative safety in the presence of tachycardia [15,16], presents a high spatial and temporal myocardial flow velocity, and is particularly useful in evaluating ventricular diastolic function in many segments [17]. The Doppler echocardiography has emerged as an important noninvasive diagnostic tool, providing reliable data in the stages of diastolic function preceding systolic dysfunction that may evolve to symptomatic heart failure. With tissue Doppler and color M-mode, the accuracy in identifying moderate diastolic dysfunction, the pseudonormal pattern, has significantly improved [18]. There is no data in the literature regarding the assessment of cardiac function using tissue Doppler imaging (TDI) in patients with primary APS (PAPS).

The purpose of the present study was to preliminary evaluate the presence of myocardial dysfunction in PAPS without clinical cardiac symptoms using the conventional and tissue Doppler echocardiogram.

2. Patients and methods

Nine PAPS patients fulfilling the Sapporo criteria [19] regularly followed at Rheumatology Division, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo were included. Seven age, gender and race-matched healthy controls were also added. Exclusion criteria were current history of heart failure, arrhythmia, coronary artery disease, age >70 years old, renal insufficiency, known valve abnormalities, glucocorticoid use, non-controlled hypertension ($\geq$140/100 mmHg) and inadequate echocardiographic imaging. Patients with other connective tissue diseases such as systemic lupus erythematosus were also excluded. All subjects had no cardiovascular symptoms. Clinical and laboratory data of patients were assessed by an extensive review of their medical charts and by clinical examination. All participants provided written informed consent and the study was approved by the local ethics committee.

The ACL antibodies were tested at least twice, with an interval of 6 weeks between each measurement, using an enzyme-linked immunosorbent assay (ELISA) [20]. 50 μg/mL cardiolipin (Sigma, St Louis, MO, USA) in ethanol were used to sensitize polystyrene microtiter plates that were left to dry overnight at 4 °C. Non-specific binding sites were blocked using 30% heat-inactivated fetal calf serum in phosphate buffered saline (FCS/PBS) for 1 h. 50 mL of serum samples diluted 1:50 in FCS/PBS were added in duplicate to the plates, followed by alkaline phosphatase-be found conjugated goat anti-human IgG (Sigma, St Louis, MO, USA). Cut-off values from the manufacturer were used. Only titers of ACL >20 GPL or MPL were considered positive. The LA was measured according to international guidelines using activated partial thromboplastin time (aPTT-Diagnostica Stago, France) and diluted Russel's viper venom time (dRVVT-Trinity Biotech, Wiclow, Ireland) [21].

(NCEP): Total cholesterol (>200 mg/dl, HDL (<40 mg/dl), LDL (>130 mg/dl) and TG (>150 mg/dl) [22,23]. Systemic arterial hypertension was defined as blood pressure $\geq$140/90 mmHg or use of anti-hypertensive agents. Glucose blood level $\geq$126 mg/dl or use of hypoglycemic defined diabetes. Smoking status was categorized into current and non-smokers. Body mass index (BMI) was calculated by the formula (weight/height^2).

2.1. Echocardiography

The study was performed using a GE Vingmed System Vivid-3 Expert machine and 2.5-MHz electronic transducer. All echocardiographic evaluations were made in a supine position by the same examiner blinded to patient data. M-mode and two-dimensional imaging were performed followed by Conventional and TDI. For mitral inflow, the sample volume was placed at the mitral valve tips in the apical 4-chamber view with recording of 5–10 cardiac cycles. Using the TDI program, a 5 mm sample volume was placed at medial corner of the mitral annulus, septum and at the medial corner of the tricuspid annulus in the same view. Gains and filters were adjusted to eliminate background noise and allow for clear tissue signal; 5–10 cycles were recorded. The ejection fraction of the left ventricle was obtained using Teicholz formula. The left ventricular end-diastolic diameter, left ventricular end-systolic diameter and were measured with M-mode echocardiography using a parasternal window. Peak of early (E) and late diastolic (A) flow velocities, E/A ratio and deceleration time (DT) of flow velocity in early diastole were obtained by Doppler, as well as the isovolumetric relaxation time (IVRT). Tissue Doppler evaluates myocardial velocities, thus being more sensitive than conventional Doppler to detect early myocardial impairmen. In this method, the sample volume is placed in the lateral wall of the left ventricle, septum and lateral wall of the right ventricle. We analyse diastolic function of those segments by the velocities of the early diastolic (e′ wave) and late diastolic waves (a′ wave); we also evaluate systolic function which is analysed by the velocity of the S wave. Normal values for Doppler-derived diastolic measurements according to age were obtained from the recommendations for the evaluation of left ventricular diastolic function by echocardiography of the American Society of Echocardiography [24]. Electrocardiography was performed in all subjects in the same day of the echocardiography.

2.2. Statistical analyses

Values were expressed as median and range or percentage. Comparisons between groups were made by non-paired t-tests or X^2 tests for continuous variables. All analyses used a two-sided significance level. Statistical significance was set at $P < 0.05$.

3. Results

The 9 patients and 7 control were all females and of matched age. Traditional cardiovascular risk factors including hypertension, current and previous smoking, diabetes, dyslipidemia and familiar history of cardiovascular disease (CVD) were also comparable

Table 1
Demographic features and cardiovascular risk factors in primary antiphospholipid syndrome patients and controls.

Factor median (range) or n (%)	PAPS patients (n = 9)	Controls (n = 7)	p
Age (years)	43 (26–55)	31 (25–49)	0.053
Female sex	9 (100)	7 (100)	1
Caucasian race	8 (88.9)	7 (100)	1
Disease duration (years)	10 (3–19)	–	–
Hypertension	4 (44.4)	0 (0)	0.089
Diabetes	1 (11.1)	0 (0)	1
Dyslipidemia	3 (33.3)	0 (0)	0.21
Current smoking	0 (0)	1 (14.3)	1
Previous smoking	4 (44.4)	1 (14.3)	0.31
Familial Hx of CVD	3 (33.3)	0 (0)	0.21

PAPS: primary antiphospholipid syndrome, Hx: history, CVD: cardiovascular disease.

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