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Detection of right ventricular dysfunction by tissue Doppler imaging in asymptomatic patients with pulmonary sarcoidosis

To the Editors:

Tissue Doppler imaging (TDI) is a relatively new ultrasound modality in echocardiography, which is used to detect left and right ventricular functional abnormalities early and accurately by recording systolic and diastolic velocities of the mitral and tricuspidal annulus, respectively. The value of this method has been corroborated on numerous studies describing right ventricular (RV) dysfunction in a variety of systemic diseases with pulmonary and/or cardiovascular involvement [1].

Sarcoidosis is a multisystem granulomatous disease of unknown aetiology characterised by cardiorespiratory manifestations, among others. RV dysfunction is often apparent but not clinically recognised until pulmonary hypertension has been developed [2]. The purpose of this study was to evaluate RV function in patients with sarcoidosis by the use of ultrasound, including the TDI modality, and correlate it with clinical, respiratory and cardiac parameters.

We conducted an observational case–control study. Consecutive sarcoidosis patients were recruited from the outpatient Sarcoidosis Clinic of the General Hospital of Chest Diseases of Athens, Athens, Greece between October 2007 and June 2008. The primary criterion for enrolment was the presence of biopsy-proven pulmonary sarcoidosis without the presence of cardiac involvement, according to the modified criteria of the Japanese Ministry of Health and Welfare [3]. The exclusion criterion was the presence of any associated disease that could influence systolic and/or diastolic properties of the heart. Subgroup analyses were performed with the patients divided in two groups based on the therapy administered: a subgroup with patients who did not receive any therapy and a subgroup with patients who received any kind of therapy (cortisone, *etc.*). Those who did not receive any medication were further classified into groups according to the disease stage at which the patients originally presented. All patients were compared to healthy volunteers. The two groups (patients and healthy controls) were age-, sex- and body mass index-matched. None of the patients or control subjects was receiving any cardiac medication. Data regarding the clinical evaluation of disease severity, including symptoms (including functional ability according to the New York Heart Association (NYHA) scale), chest radiograph, high-resolution computed tomography imaging and lung function tests (including forced expiratory volume in 1 s (FEV_1), forced expiratory vital capacity (FVC), FEV_1/FVC, total lung capacity and diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$)) were collected. Radiographic staging was estimated using conventional chest radiography [4]. Echocardiography was performed with a commercially available ultrasonic device (Sonos 5500; Hewlett-Packard, Andover, MA, USA). Two-dimensional measurements, and conventional Doppler and TDI recordings of both the free-wall side of the mitral and tricuspid annulus were acquired [5]. This study was approved by the Institutional Ethical Committee (General Hospital of Chest Diseases ''Sotiria'', Athens, Greece) and informed consent was obtained from all participants.

Distribution normality of the continuous variables was assessed by the Kolmogorov–Smirnov test. Differences among different subgroups were evaluated by one-way ANOVA, with Scheffe *post hoc* analysis for multiple comparisons. Bivariate

correlations were evaluated by Pearson's product–moment method. Stepwise multivariate linear regression analysis was performed to estimate independent predictors/determinants of TDI indices. p-values of <0.05 were assumed to represent statistical significance.

Among 56 consecutive patients who were referred for possible enrolment into the study, 50 met the study criteria, and six were excluded due to arterial hypertension (four patients) and cardiac arrhythmias (two patients). The remaining 50 patients (35 males and 15 females, mean±SD age 42±8 yrs) were classified into two groups based on their therapy. 20 (40%) patients did not receive any medication and 30 (60%) patients received medical therapy. As far as those who did not receive any therapy are concerned, 14 patients presented at stage I, four patients at stage II and two patients at stage III. None presented at stage IV. The mean±SD duration of the disease was 5±4.57 yrs. All patients were classified in NYHA class II. All consecutive patients were compared to 45 healthy volunteers (30 males and 15 females, mean±SD age 38±12 yrs).

Patients' baseline characteristics, pulmonary function tests, and ultrasound and TDI parameters are presented in table 1. There were no significant differences regarding the heart rate, or systolic and diastolic blood pressures between the two groups (table 1). Pulmonary function tests revealed an impairment of lung function in 27 out of 50 (54%) patients, with a restrictive pattern present in 20 out of 50 (40%) patients. Isolated $D_{L,CO}$ reduction was observed at 15 out of 50 (30%) patients, while an obstructive pattern (FEV_1/FVC <70%) and mixed forms were found in 5 out of 10 (10%) patients.

Both the conventional Doppler and the TDI indices of diastolic function of the left ventricle showed no differences between the two groups. The classical Doppler indices of diastolic function (early (Et) and late (At) tricuspid inflow velocities, as well as the ratio Et/At) of the RV did not differ significantly

TABLE 1 Patients' and controls' baseline characteristics, pulmonary function tests, and ultrasound and tissue Doppler imaging (TDI) parameters

	Total patients	Without therapy	With therapy	Controls
Patients n	50	20	30	45
Males/females n	35/15	13/7	22/8	30/15
Age yrs	42±8	41.5±8.5	42.25±7.91	38±12
Disease duration yrs	5±4.57	5.1±4.65	3.5±4.37	
Heart rate beats·min^{-1}	77±12	77±13.34	76.88±9.55	76.8±10
Systolic BP mmHg	123.1±16.5	125.28±17.28	117.14±12.2	115.8±14.3
Diastolic BP mmHg	78.5±12.2	79.72±13.11	75±8.17	74.8±9.1
Pulmonary function tests % pred				
FEV_1	92.2±19	94.7±15.52	85.14±26.94	
FVC	97.3±18.5	99.8±15.76	90.14±24.71	
FEV_1/FVC	85.31±11.8	86.85±9.93	81±16.16	
TLC	87.3±12.5	88.15±11.41	84.86±16.05	
$D_{L,CO}$	84±17.2	84.65±17.54	82.14±17.27	
Ultrasound parameters				
Et/At	1.344±0.456	1.32±0.47	1.39±0.46	1.471±0.288
Stage I		1.35±0.47		
Stage II		1.26±0.57		
Stage III		1.24±0.47		
Eat cm·s^{-1}	14.46±4.31	15.16±3.77	17.00±4.15	16.5±3.84
Stage I		16.2±3.87		
Stage II		12.85±3.29		
Stage III		12.55±1.20		
Aat cm·s^{-1}	18.3±4.97*	19.02±4.81*	19,41±4.3*	13.2±3.73
Stage I		18.72±4.54		
Stage II		20.75±7.14		
Stage III		17.60±0.85		
Eat/Aat	0.79±0.41*	0.85±0.33*	0.99±0.4*	1.25±0.39
Stage I		0.91±0.29		
Stage II		0.74±0.51		
Stage III		0.72±0.10		

Data are presented as mean±SD unless otherwise stated. BP: blood pressure; % pred: % predicted; FEV_1: forced expiratory volume in 1 s; FVC: forced expiratory vital capacity; TLC: total lung capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; Et: early tricuspid diastolic wave maximal velocity using classical Doppler; At: late tricuspid diastolic wave maximal velocity using classical Doppler; Eat: early tricuspid diastolic wave maximal velocity using TDI; Aat: late tricuspid diastolic wave maximal velocity using TDI. *: $p<0.05$.

between the two groups. However, the TDI velocities of the patient group exhibited a significant increase for late tricuspid diastolic wave maximal velocity using TDI (Aat; p=0.003), while early tricuspid diastolic wave maximal velocity using TDI (Eat)/Aat (p=0.0025) was, also significantly, decreased. (table 1) Univariate analysis showed the Aat wave was correlated with the heart rate (r=0.456, p=0.033) and the $D_{L,CO}$ (r= -0.388, p=0.05). The Eat/Aat was correlated with age (r= -0.467, p=0.022), diastolic blood pressure (r= -0.425, p=0.033), interventricular septum (r= -0.432, p=0.045), diameter of the right ventricle (r=0.535, p=0.042) and the relative wall thickness (r= -0.441, p=0.028).

Multivariate stepwise regression analysis showed that increasing age is independently associated with lower Eat (p=0.013). Also, lower $D_{L,CO}$ levels were independently related with higher RV Aat (p=0.001). Finally, RV dimension was positively and independently associated with RV Eat/Aat (p=0.001). Subgroup analyses based on therapy status and disease activity showed no differences among the groups with respect to TDI indices.

The main finding of our study was the detection of a significant increase in Aat in patients with sarcoidosis compared to the control group, while At was unable to detect these abnormalities. Increased A-wave suggests increased stiffness of the RV with concomitant elevated ventricular filling pressures, resulting in a decreased Eat/Aat wave ratio, implying diastolic dysfunction. Cortisone treatment was unable to affect TDI indices in our study. Another important finding was the association of the increased Aat with $D_{L,CO}$ impairment, suggesting that pulmonary involvement in patients with sarcoidosis may affect myocardial function, irrespectively of clinical presence of pulmonary hypertension.

TDI has become an established component of the diagnostic ultrasound examination and allows quantitative assessment of RV systolic and diastolic function. Usually, it can identify RV dysfunction with a sensitivity and specificity of 90 and 85%, respectively [6]. Numerous studies have shown the use of TDI gives reproducible and easily obtained noninvasive parameter correlated with invasive measurements of RV referring to intrinsic contractility and its filling pressures [7].

Increased stiffness of the RV with concomitant elevated ventricular filling pressures detected with the use of TDI can be associated with vascular involvement of sarcoidosis. The presence of sarcoid granulomas may limit pulmonary perfusion and RV output and, therefore, increase the afterload of the RV, causing impaired diastolic relaxation and distensibility. Pathological surveys have documented that specific vascular lesions are extremely common in sarcoidosis, resulting in occlusive changes, perivascular fibrosis or granulomatous pulmonary angiitis [8]. Thus, direct vascular involvement or indirect vascular remodelling, augmented by vasoactive mediators and/or growth factors, may cause a shift in RV filling from the early to the later part of diastole, contributing to RV remodelling.

In our study, the increased A-wave is associated with $D_{L,CO}$ impairment observed in the pulmonary function tests of sarcoidosis patients. In parenchymal lung disease, pulmonary function tests characteristically reveal a restrictive pattern in sarcoidosis, with a reduction in $D_{L,CO}$ [9]. The presence of sarcoid granulomas preceded by an alveolitis that involves the interstitium more than the alveolar spaces and characterised by the accumulation of inflammatory cells, including monocytes, macrophages, and lymphocytes, is the primary cause of $D_{L,CO}$ reduction, in accordance with the degree of inflammation and irrespective of clinical disease severity. As a result, the presence of sarcoid granulomas in both pulmonary interstitium and vessels of any size is the possible mechanism for the association of $D_{L,CO}$ impairment and the diastolic dysfunction of the RV observed with the use of TDI.

The main limitation of our study was the absence of other diagnostic tests, such as myocardial imaging with thallium-201 and cardiac magnetic resonance imaging, that could detect subclinical cardiac involvement resulting in cardiomyopathy that causes the RV dysfunction detected. Also, no data were collected regarding RV catheterisation, which could estimate RV pressures, pulmonary arterial pressure and ventricular stiffness [10]. Finally, although patients with sarcoidosis had no differences in TDI indices based on cortisone treatment, no data were available regarding these indices from prior examinations. As a result, the clinical significance of this method cannot be estimated.

In conclusion, TDI modality was able to detect important cardiovascular abnormalities in patients with sarcoidosis, which were associated with the extent of pulmonary involvement, as expressed by $D_{L,CO}$ impairment. This finding may contribute to early and accurate detection of patients at high risk for development of pulmonary hypertension.

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Interferon-γ release assays in tuberculosis contacts: is there a window period?

The tuberculin skin test (TST) is the established procedure for diagnosis of latent tuberculosis infection (LTBI) among the contacts of an infectious tuberculosis (TB) case. TST may convert to positive ⩽8 weeks after *Mycobacterium tuberculosis* infection, an interval that is usually referred to as the ''window period''. A negative TST obtained <8 weeks before does not exclude infection, and a second test is recommended [1, 2]. However, TST has some limitations, such as cross-reactivity with Bacille Calmette–Guérin (BCG) and with nontubercular mycobacterial infections.

T-cell interferon-γ release assays (IGRA) are emerging as new screening tools for LTBI diagnosis. IGRAs incorporate specific antigens of *M. tuberculosis* that are absent in BCG strains and in the majority of nontubercular mycobacteria, offering enhanced specificity for detecting *M. tuberculosis* infection [3]. In addition, their use has been approved for screening of infection in contacts [1, 4]. Most TB contact studies have shown a better correlation of IGRA with the intensity of *M. tuberculosis* exposure than that obtained using TST, particularly in patients previously vaccinated with BCG [5]. Yet, to our knowledge, no study has considered carefully the window period after *M. tuberculosis* exposure while simultaneously evaluating responses for TST and IGRA. The aim of this study was to find out which of the two tests converts earlier to positive in persons with recent infection after contact with an infectious TB case.

We used a longitudinal prospective analysis to study 184 healthy adults, all having had recent contact with a microbiologically confirmed pulmonary TB index patient. The setting was a specialized TB clinic in Pontevedra, Spain, where the incidence of TB has historically been among the highest in Western Europe. In 1996, a TB control programme was established, and incidence has steadily dropped from 72.3 to 32.6 per 100,000 in 2008.

TST and a commercially available IGRA, Quantiferon®-TB Gold In-Tube (QFT; Cellestis, Carnegie, Australia), were both carried out at the first visit of the contacts to our clinic after TB exposure (time 0: TST_0 and QFT_0, respectively). The attending physician was blind to the QFT result, and medical advice was offered to the patient only on the basis of the TST result. Patients with positive TST were offered to start LTBI chemotherapy after active TB was excluded. For those contacts with a negative TST_0, a repeat TST and QFT were undertaken 2 months later (time 2: TST_2 and QFT_2, respectively), at the end of the window period. In addition, patients with a positive TST_0 but negative QFT_0 were recalled to have a second QFT 2 months later, irrespective of whether the patient was receiving treatment for LTBI.

Peripheral blood was processed for the QFT assay according to the manufacturer's instructions. Samples were frozen and stored at -70°C for analysis 3–4 weeks later. The cut-off value for a positive test was 0.35 $IU \cdot mL^{-1}$. TST was carried out according to the Mantoux method, with 2 units of tuberculin RT-23 (purified protein derivative; State Serum Institute, Copenhagen, Denmark), following the standardised protocol. A positive TST was defined as an induration of ⩾5 mm. We excluded from the study HIV-infected persons or those with other immunosuppressive conditions, pregnant females, and those with a previous documented positive TST. Institutional ethical approval was obtained from the Ethical Committee of Clinical Research (Xunta de Galicia, Spain). All participants included in the study gave their written informed consent.

Initially, 184 participants, recent contacts of microbiologically confirmed pulmonary TB patients were enrolled in the study, but 32 were excluded due to a history of a previous positive TST (28 cases) or because of incomplete data for the index TB case (four cases). The remaining 152 participants had a median age of 44 yrs (interquartile range 32–55 yrs) and were contacts of 48 different index TB patients. None had ever previously received TB or LTBI treatment. 55 (36.2%) contacts had had a previous BCG vaccination. For 137 (90.1%) contacts, the index TB case was acid-fast bacilli positive.