Clin Exp Med
DOI 10.1007/s10238-017-0477-y

ORIGINAL ARTICLE

Cardiac involvement in undifferentiated connective tissue disease at risk for systemic sclerosis (otherwise referred to as very early–early systemic sclerosis): a TDI study

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Received: 2 August 2017 / Accepted: 27 September 2017

Abstract Undifferentiated connective tissue disease at risk for systemic sclerosis (UCTD-risk-SSc), otherwise referred to as very early–early SSc, is a condition characterized by Raynaud's phenomenon with serum SSc marker autoantibodies and/or typical capillaroscopic findings and unsatisfying classification criteria for the disease. The aim of the present study was to assess the prevalence of right (RV) or left ventricular (LV) systolic and/or diastolic dysfunction by standard echocardiography and tissue Doppler imaging (TDI). Thirty patients with UCTD-risk-SSc (28 female, mean age 47 ± 13 years, range 21–70) and 30 age- and sex-matched controls underwent cardiac assessment by standard echocardiography and TDI. UCTD-risk-SSc patients and controls did not show any difference at standard echocardiography. Despite results falling within the respective normal ranges, TDI pointed out a mild impairment of LV and RV diastolic (E_m 15 ± 4 vs. 19 ± 5, $p = 0.0004$; E/E_m 6.1 ± 1.7 vs. 4.8 ± 1.2, $p = 0.001$; E_t 14 ± 3 vs. 16 ± 2, $p = 0.02$; E_t/A_t 0.9 ± 0.4 vs. 1.3 ± 0.3, $p = 0.002$; E/E_t 3.5 ± 1.2 vs. 4.2 ± 0.9, $p = 0.02$) and systolic function (S_m 13 ± 3 vs. 15 ± 2 cm/s, $p < 0.0003$; S_t 14 ± 2 vs. 16 ± 3 cm/s, $p < 0.0001$) and increased estimated pulmonary artery wedge pressure (9 ± 2 vs. 8 ± 1, $p = 0.001$) in UCTD-risk-SSc patients as compared to controls. Notably, a statistically significant difference also emerged in the prevalence of TDI detected E′/A′$_t$, (71% of UCTD-risk-SSc patients vs. 19% of controls; $p < 0.0001$). Our study shows that UCTD-risk-SSc patients show a previously unrecognized, mild biventricular systolic and diastolic dysfunction as compared to controls. The pathophysiologic meaning as well the predictive value of developing overt SSc await to be elucidated.

Keywords Undifferentiated connective tissue disease at risk for systemic sclerosis · Very early–early systemic sclerosis · Heart in UCTD-risk-SSc · Cardiac involvement in SSc

Introduction

The label "undifferentiated connective tissue disease at risk for systemic sclerosis" (UCTD-risk-SSc) refers to a group of conditions characterized by Raynaud's phenomenon (RP) with SSc marker autoantibodies and/or typical capillaroscopic findings and unsatisfying 2013 ACR/EULAR classification criteria for SSc as well as criteria for SSc sine scleroderma [1]. These conditions are otherwise referred to as very early/early SSc [2–10]. The previously undefined boundaries with respect to other SSc stages [3, 7, 8] and the absence of a certain evolution into overt SSc [2, 8] induced us to first underline classification criteria [9] and then propose the change in the label [10].

Patients with UCTD-risk-SSc/early SSc have been reported to present, in about 40% of the patients, a preclinical, vascular, internal organ disease as detected by a diffusing lung capacity for CO (DLCO) < 80% of the predicted value (lung involvement) and/or a low oesophageal sphincter

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Published online: 09 October 2017

(LES) pressure < 15 mmHg (oesophageal involvement) and/or a mitral *E/A* ratio < 1 (heart involvement) [2, 6, 8]. However, the prevalence of the latter finding did not result to differ between patients and controls.

Pulsed tissue Doppler imaging (TDI) is a non-invasive technique introduced after standard echocardiography and widely available at present. It allows to detect early right and left heart functional abnormalities with higher sensitivity and specificity than standard echocardiography [11, 12]. Actually, investigating 74 definite SSc patients by both standard echocardiography and pulsed TDI, we could detect a greater prevalence of systolic and diastolic dysfunction by the latter technique and a further deterioration of both at 3 years of follow-up [13].

The aim of the present study is to assess the prevalence of right (RV) or left ventricular (LV) diastolic and/or systolic dysfunction by both standard echocardiography and TDI in UCTD-risk-SSc patients.

Materials and methods

Thirty patients with UCTD-SSc-risk, consecutively admitted from 1 June 2015 to 31 May 2016 at the Rheumatology Unit of the University of Campania "Luigi Vanvitelli" (28 female, aged 21–70 years, mean 47 ± 13 years, median 47.5 years), were enrolled in the study after giving written informed consent.

Classification

UCTD-SSc-risk was diagnosed in patients with RP and either SSc marker autoantibodies or distinct capillaroscopic alterations, who at admission neither satisfied the 2013 ACR/EULAR criteria for SSc [14] nor presented any manifestation suggestive of SSc sine scleroderma [15].

Assessment at admission

Patients underwent a detailed history, an accurate physical examination, routine laboratory investigations, nailfold capillaroscopy, autoantibody detection and investigation of preclinical organ involvement, as previously described [4]. Patients were investigated for typical microvascular alterations (megacapillaries and/or avascular areas) by wide-field nailfold capillary microscopy, ANA and SSc marker autoantibodies (i.e. anti-DNA topoisomerase I-anti-Scl70; anticentromere-ACA; anti-RNA polymerase III; anti-fibrillarin; anti-Pm-Scl; and anti-Th/To), as previously described [4–6, 9].

Medications

All the 30 patients were being treated with acetylsalicylic acid and dihydropyridine calcium channel blockers. Two out of them had arterial hypertension: one was also being treated with ACE-inhibitors, the other one with angiotensin receptor blockers.

Controls Thirty age- and sex-matched controls (28 female, aged 18–68 years; mean 46 ± 12 years, median 46.5 years) admitted to the Outpatient Clinic of the Cardiology Unit, who presented no relevant findings at clinical examination, ECG and chest radiography and denied any acrovascular symptoms, were enrolled in the study after giving written informed consent. Six out them had arterial hypertension: three were being treated with dihydropyridine calcium channel blockers, two with ACE-inhibitors and one with a combination of the two drugs.

Preclinical internal organ involvement

Lung and oesophagus

All the patients underwent lung function study according to established guidelines [16] to investigate DLCO, whereas only patients who consented were investigated by oesophageal manometry [17] devoted to assess basal LES pressure.

Echocardiography

Echocardiographic examinations were performed by two independent highly trained cardiologists (PA and ER), blinded to the clinical characteristics of the study population, using commercially available equipment with a phased array system (Vivid E9, GE Healthcare, Milwaukee, Wisconsin, USA) and a 2.5- or 3.5-MHz transducer.

The procedure was performed following international recommendations [18].

Specific views included the parasternal long- and short-axis views (at the mitral valve and papillary muscle level), apical four-, two- and three-chamber views and subcostal views, including respiratory motion of the inferior cava vein. Pulsed, continuous wave and colour-Doppler interrogation was performed on all four cardiac valves. TDI analysis was performed for analysing diastolic and systolic function of both left and right ventricles from the four-chamber view. Specific measurements were made by the average of 3–5 cardiac cycles.

M- and B-mode measurements LV diastolic and systolic diameters, interventricular septum and posterior wall thickness were assessed in parasternal long-axis view with the patient in the left lateral position. LV ejection frac-

tion was calculated by the biplane Simpson's rule in the apical four- and two-chamber views. Left atrial maximal volume was measured at the point of mitral valve opening using the biplane area–length method and corrected for body surface area [18]. RV end-diastolic chamber size was accurately assessed using five linear dimensions according to the American Society of Echocardiography guidelines for the echocardiographic assessment of the right heart in adults [18]. In particular, three of the five parameters included the measurement of the basal, mid-cavity and longitudinal diameters from the apical four-chamber view at end-diastole. The echotransducer was adjusted to the level of the RV chamber, with the goal of optimizing RV chamber size. The remaining two parameters included the measurement of the RV outflow tract at the proximal or subpulmonary region and at the distal or pulmonic valve from the basal parasternal short axis and the parasternal short axis of pulmonary bifurcation views, respectively. Right atrial (RA) measurements were assessed in the apical four-chamber view. RA area was estimated by planimetry at the end of ventricular systole (largest volume), tracing from the lateral aspect of the tricuspid annulus to the septal aspect, excluding the area between the leaflets and annulus, following the RA endocardium, excluding the inferior and superior cava vein and RA appendage [18]. Tricuspid annular plane systolic excursion (TAPSE) was calculated as index of RV longitudinal systolic function by placing an M-mode cursor through the tricuspid annulus in a standard apical four-chamber window, and measuring the difference between the end-diastolic and end-systolic amount of longitudinal motion of the annulus.

Colour-Doppler analysis Valve regurgitation was quantified from colour-Doppler imaging. Intermediate vena contracta values (3–7 mm) were confirmed by the proximal isovelocity surface area method [18].

Pulsed wave Doppler-derived LV and RV diastolic inflow was recorded in the apical four-chamber view by placing the sample volume at the tip level of the mitral and tricuspid valves. *E* and *A* peak velocities (m/s) and their ratio were measured for both ventricles [18].

Tissue Doppler imaging In order to obtain a measure of LV and RV myocardial function by TDI, LV and RV peak systolic velocity (S'_m and S'_t, respectively) and LV and RV early and late diastolic velocity (E'_m, A'_m, E'_t, A'_t, respectively) were assessed from the apical four-chamber view by placing the sample volume at the mitral and tricuspid annulus. The E'_m considered was the mean value from the lateral and medial position. Because this technique uses Doppler, special care is required to ensure optimal image orientation and avoid underestimation of velocities.

Non-invasive pulmonary artery systolic pressure Peak tricuspid regurgitant velocity was measured from the spectral profile of the tricuspid regurgitant jet in the RV inflow projection of the parasternal long-axis view, the parasternal short-axis view or the apical four-chamber view. The highest transvalvular velocity was used for calculation of right ventricular systolic pressure. Pulmonary artery systolic pressure (sPAP) was assumed to equate right ventricular systolic pressure in the absence of pulmonic stenosis and/or RV outflow tract obstruction. sPAP was then calculated as $4 \times V^2$ + estimated RA pressure by inferior vena cava dimension and collapsibility [18] (where *V* is the maximal velocity of the tricuspid regurgitant jet). Mean pulmonary artery pressure was calculated as $0.6 \times \text{sPAP} + 2$ [18]. Capillary wedge pressure (CWP) was estimated from the ratio of mitral *E* flow velocity wave and tissue Doppler mitral annulus E' early diastolic velocity, with $\text{CWP} = 1.9 + 1.24\ E/E'_m$ [19].

All data were analysed offline by two observers blinded to the patient conditions (MD and AD). Intra- and inter-observer variability was less than 1% and less than 4.0%, respectively.

Statistical analysis

Continuous variables were analysed by paired and unpaired *t* test. Chi-square test or Fisher exact test was applied for contingency tables. Spearman's rank order correlation test was used to investigate associations between distinct continuous variables. Covariate-adjusted analysis of outcome was performed by Cox proportional hazards model.

A p value < 0.05 was considered statistically significant. Data are expressed as mean ± SD. Statistical analysis was performed using SPSS software on PC (version 12.0.1; SPSS Inc., Chicago, Illinois, USA).

Results

Table 1 lists demographic, serological, capillaroscopic, subsetting and therapeutic data of the 30 UCTD-risk-SSc patients enrolled in the study. A preclinical lung involvement was detected in 12 patients, a preclinical oesophageal involvement was observed in six patients, out of whom three had a DLCO < 80%. Therefore, 15 patients (50%) showed either lung or oesophageal preclinical internal organ involvement, or both.

Table 2 shows the main standard echocardiographic and TDI parameters recorded in the study population. No difference was detected between UCTD-risk-SSc patients and controls in any standard mono- and 2D echocardiography-detected parameter. TDI revealed a significantly reduced E_m wave suggestive of impaired LV diastolic function;

Table 1 Demographic, serological, capillaroscopic and physiological features of the 30 UCTD-risk-SSc/early SSc patients enrolled in the study

Sex (F/M)	28/2
Age (years)	Median 47.5; range 21–70
Disease duration from RP onset (years)	Median 7; range 0–24
Antinuclear antibodies	27 (90%)
Marker SSc antibody	20 (66%)
Anticentromere	13 (43%)
Anti-DNA topoisomerase I	6 (20%)
Anti-RNA polymerase III	0
Anti-fibrillarin	0
Anti-Th/To	0
Anti-Pm-Scl	1 (3%)
Capillaroscopic findings	
Avascularar areas ± megacapillaries	0
Megacapillaries only	22 (73%)
Preclinical internal organ involvement (lung and oesophagus)	
Basal LES pressure < 15 mmHg	6/20 (30%)
DLCO < 80% of the predicted value	12/30 (40%)
Any of them	15/30 (50%)

DLCO diffusing lung capacity for CO, *LES* low oesophageal sphincter, *RP* Raynaud's phenomenon, *SSc* systemic sclerosis, *UCTD-risk-SSc* undifferentiated connective tissue disease at risk for systemic sclerosis

Table 2 Echocardiographic features in the study population

	UCTD-risk-SSc ($n = 30$)	Controls ($n = 30$)	p
Mono and 2D			
LVEDd (mm)	46 ± 5	46 ± 2	0.55
LVESd (mm)	28 ± 4	29 ± 2	0.14
IVS (mm)	10 ± 3	10 ± 2	0.59
PW (mm)	9 ± 3	8 ± 3	0.20
LVEF (%)	61 ± 4	63 ± 4	0.11
TAPSE (mm)	23 ± 3	22 ± 4	0.13
ICV (mm)	13 ± 4	14 ± 3	0.38
LA area index (ml/m^2)	23 ± 5	22 ± 4	0.67
Doppler left heart			
E_m (cm/s)	85 ± 17	88 ± 11	0.41
A_m (cm/s)	73 ± 17	70 ± 13	0.49
E_m/A_m	1.2 ± 0.4	1.3 ± 0.3	0.22
E'_m (cm/s)	15 ± 4	19 ± 5	0.0004
A'_m (cm/s)	12 ± 4	13 ± 4	0.21
E'/A'_m	1.5 ± 0.7	1.6 ± 0.5	0.42
E/E'm	6.1 ± 1.7	4.2 ± 1.2	0.002
S_m (cm/s)	13 ± 3	15 ± 2	0.0003
Doppler right heart			
E_t (cm/s)	59 ± 12	56 ± 14	0.45
A_t (cm/s)	47 ± 15	42 ± 8	0.08
E/A_t	1.3 ± 0.4	1.3 ± 0.2	0.73
E/E't	4.2 ± 0.9	3.5 ± 1.2	<0.02
E'_t (cm/s)	14 ± 3	16 ± 2	0.02
A'_t (cm/s)	17 ± 5	13 ± 3	0.001
E'/A'_t	0.9 ± 0.4	1.3 ± 0.3	0.002
S_t (cm/s)	14 ± 2	16 ± 3	<0.0001

UCTD-risk-SSc undifferentiated connective tissue disease at risk for systemic sclerosis, *LVEDd* left ventricular end-diastolic diameter, *LVESd* left ventricular end-systolic diameter, *IVS* interventricular septum, *PW* posterior wall, *LVEF* left ventricular ejection fraction, *TAPSE* tricuspid annulus plane systolic excursion, *ICV* inferior cava vein, *LA* left atrium, *E E* wave, *A A* wave, S_m *S* wave at mitral annulus, E_m *E* wave at mitral annulus, A_m *A* wave at mitral annulus, S_t *S* wave at tricuspid annulus, E_t *E* wave at tricuspid annulus, A_t *A* wave at tricuspid annulus

significantly reduced E_t, increased A_t and reduced E_t/A_t ratio, each suggestive of impaired RV diastolic function; and significantly reduced S_m and S_t suggestive of LV and RV involvement, respectively. In addition, pulmonary artery wedge pressure (PAWP), generically indicative of left heart disease, was found to be increased (9 ± 2 vs. 8 ± 1, $p = 0.001$). Nevertheless, no difference was detected in estimated sPAP (29 ± 3 vs. 27 ± 3, $p = 0.13$), nor in SV (data not shown). In this regard, it is worth noting that neither SSc patients nor any controls showed any significant mitral or aortic valve regurgitation or stenosis, and neither UCTD-risk-SSc patients nor controls had pericardial effusion.

Table 3 lists the prevalence of definitely altered systolic and diastolic function of right and left ventricles by conventional Doppler echocardiography and TDI. We detected a greater prevalence of mitral $E/A < 1$ (33 vs. 23%), $E'/A'_m < 1$ (42 vs. 29%) and $E_t/A_t < 1$ (20 vs. 10%). Nevertheless, a statistically significant difference only emerged in TDI detected E'/A'_t, which was found to be < 1 in 71% of UCTD-risk-SSc patients versus 19% of controls ($p < 0.0001$).

As far as the relationships between distinct TDI parameters, LV and RV diastolic and systolic function resulted to be nearly significantly related each other: rho between E'/A'_t and E'/A'_m being 0.35 ($p = 0.006$) and that between S_t and S_m 0.47 ($p = 0.008$). These results are consistent with SSc myocardial disease where small intramyocardial coronary vessels and fibrosis involve both ventricles.

No significant association emerged between any TDI parameter and either autoantibody profile or the presence of lung and/or oesophageal preclinical involvement.

Discussion

Preclinical internal organ involvement in patients with UCTD-risk-SSc/very early–early SSc was first reported by us in 2011, demonstrating the presence of a DLCO < 80%

Table 3 Prevalence of parameters suggestive of altered left and right ventricular diastolic and systolic function by standard Doppler echocardiography and tissue Doppler imaging in the study population

	UCTD-risk-SSc ($n = 30$)	Controls ($n = 30$)	p
$E/A_m < 1$ (%)	10 (33)	7 (23)	0.56
$E'/A'_m < 1$ (%)	13 (42)	9 (29)	0.42
$E/A_t < 1$ (%)	6 (20)	3 (10)	0.47
$E'/A'_t < 1$ (%)	22 (71)	6 (19)	<0.0001
$S_m < 7.5$ cm/s (%)	0 (0)	0 (0)	1
$S_t < 11.5$ cm/s (%)	2 (6)	1 (3)	1

Values are expressed as number (%)

UCTD-risk-SSc undifferentiated connective tissue disease at risk for systemic sclerosis, *E E* wave, *A A* wave, E'_m *E* wave at mitral annulus, A'_m *A* wave at mitral annulus, E'_t *E* wave at tricuspid annulus, A'_t *A* wave at tricuspid annulus, S_m *S* wave at mitral annulus, S_t *S* wave at tricuspid annulus

of the predicted value, a basal LES pressure < 15 mmHg and an inverted *E*/*A* ratio in seven, four and one patients, respectively, accounting for a cumulative prevalence of 8/19 patients (42%) [4]. Subsequently, we confirmed these results on a larger series [6, 9]. Moreover, Lepri et al. [8], while confirming the occurrence of a low basal LES pressure, pointed out the presence of impaired anorectal function in a separate single-centre study.

Out of the distinct findings of preclinical internal organ involvement, the impaired LV filling as detected by an inverted mitral *E*/*A* ratio was the only parameter, the prevalence of which did not result to be statistically different from that of controls [4, 6, 9].

A number of studies have been devoted to investigate cardiac disease in patients with definite SSc by TDI [13, 20–25], and all have ensued in the detection of a higher prevalence of both RV and LV diastolic and systolic alterations.

To the best of our knowledge, this is the first study that investigated cardiac disease in patients with UCTD-risk-SSc/early SSc by pulsed TDI. We found significantly lower E_m, E_t, E/A_t and E/E'_t and significantly higher A_t, all indicative of diastolic impairment of both ventricles, and significantly lower S_m and S_t indicative of systolic impairment as well. Moreover, a statistically significant difference emerged in the prevalence of TDI inverted E'/A'_t, (71% of UCTD-risk-SSc patients vs. 19% of controls; $p < 0.0001$).

Taken together, these results demonstrate the presence of preclinical heart disease in UCTD-risk-SSc patients, which could depend on small intramyocardial coronary involvement and/or patchy myocardial fibrosis, which are the distinctive features of SSc heart disease [20, 21]. Preclinical heart disease was not found to be related either to autoantibody profile or preclinical lung or oesophageal involvement, mirroring definite SSc in which no distinct autoantibody profile is associated with heart disease and the involvement of different organ vascular trees are not associated each other.

From a pathophysiologic point of view, the contribution of each of the two mentioned alterations to the impaired diastolic and systolic function awaits to be investigated by a cardiac magnetic resonance [22] and/or an endomyocardial biopsy study [23].

Detecting patchy myocardial fibrosis in UCTD-risk-SSc/early SSc patients, who, by definition, do not satisfy the 2013 ACR/EULAR classification criteria for SSc [14], might pave the way to the need for an earlier detection of internal organ involvement in these patients. Unravelling this aspect might be instrumental in choosing the appropriate drugs to be administered to the individual UCTD-risk-SSc/early SSc patient in order to contrast the evolution of his/her heart disease.

At present, no study has definitely pointed out a role of any drug in the treatment of scleroderma heart disease. Allanore et al. [24] detected a lower prevalence of LV ejection fraction < 55% in SSc patients who were given calcium channel blockers. Lee et al. [25] reported a lower prevalence of LV diastolic impairment in SSc patients who had been treated with ACE-inhibitors. These drugs and recently available antifibrotic agents [26] might have a role in this scenario.

Out of the parameters of diastolic and systolic function, the distribution of which resulted to be statistically different between UCTD-risk-SSc/early SSc patients and controls, an $E'/A'_t < 1$ only was found to be more prevalent in the former (71 vs. 19%; $p < 0.0001$). Although the topic is debated [27], our data appear to identify in an impaired, right ventricular diastolic filling the first, defined, altered physiologic parameter in UCTD-risk-SSc/early SSc.

Our team was the first to show the presence of RV diastolic dysfunction in SSc patients, as assessed by standard echocardiography, which was associated with LV dysfunction and pulmonary artery pressure [28]. This finding was then confirmed by TDI examination [29]. Recently, RV diastolic dysfunction was observed in 25% out of 212 SSc patients and was found to be associated with pulmonary artery pressure [30]. In our series, RV and LV diastolic and systolic function was found to be related with each other as it would be expected by the known distribution of vascular and interstitial involvement in the SSc heart. However, an additive effect of increased pulmonary artery pressure is likely to occur.

Preclinical lung or heart involvement as evidenced by a DLCO < 80% of the predicted value and/or a mitral *E*/*A* ratio < 1 was found by us to be associated with a significantly increased incidence of defined SSc during follow-up in 60 well-characterized early SSc patients (who were subsequently labelled as UCTD-risk-SSc) [9]. A prospective

study is needed to ascertain whether alterations detected by TDI have an additive prognostic value.

The detection of preclinical lung and/or oesophageal and/or cardiac involvement could induce to consider UCTD-risk-SSc patients or at least those with such physiologic alterations, as SSc patients unsatisfying classification criteria [14, 15]. Nonetheless, the same, putatively vascular, lung, oesophageal and standard echocardiography alterations are also detectable in patients with strictly defined UCTD [4, 5], including, as far as lung involvement is concerned, patients without Raynaud's phenomenon [31]. These considerations, along with the lack of a certain evolution into defined SSc, underlie the view that what really separates SSc from UCTD-risk-SSc (or early SSc) is the presence of skin or organ fibrosis [1] and support the use of the current terminology, i.e. UCTD-risk-SSc or early SSc.

Our study has two main limitations: we did not perform 2D strain imaging, which represents an additional and novel tool for an early identification of systolic and diastolic dysfunction; the present study is a single-centre study with a small number of patients. Further larger and multicentre studies are warranted to confirm our data.

In conclusion, despite echoparameters fall in the normal range, our data raise interesting question marks regarding the heart function suggesting the presence of a subtle diastolic and systolic alterations of RV and LV function in patients with UCTD-risk-SSc/early SSc.

From a nosographic point of view, our results widen the boundaries of the preclinical, internal organ involvement in these conditions.

From a pathophysiologic point of view, our results suggest the presence of an early heart involvement in patients who have a 50% risk of developing overt SSc, but do not yet satisfy the classification criteria for SSc. Unravelling the cause of these alterations (i.e. whether they depend on small intramyocardial coronary artery disease or patchy fibrosis, or any of them) is likely to contribute to the understanding of the pathogenesis of SSc heart disease.

From a clinical point of view, TDI emerges as the technique to be used in the approach to the patient with UCTD-risk-SSc/early SSc in order to highlight the presence of alterations that would be missed by using standard echocardiography only.

From a therapeutic perspective, the characterization of the anatomical alterations underlying these physiologic alterations is likely to assist in preventing the evolution of heart disease in these patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The study was approved by Ethical Committee of University of Campania "Luigi Vanvitelli" (protocol number 709).

Informed consent Informed consent was obtained from all individual participants included in the study.

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