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Trans-thoracic Echocardiography assessment of pulmonary hypertension in children with connective tissue disorders attending Cairo University Egypt Children Hospital Rheumatology Clinic

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To study the prevalence of pulmonary artery hypertension (PAH) in children with connective tissue disease (CTD). A cross-sectional study done on 50 Egyptian children aged 6 years and above who followed up at the Rheumatology Clinic at Specialized Hospital - Cairo University. Patients were diagnosed clinically and by laboratory tests to have CTD. Doppler echocardiography was done for all the enrolled patients to detect the prevalence of PAH. A Pulmonary artery mean pressure (PASP) of 25 mmHg was taken as a cut off level for diagnosis of PAH. Thirty-one (62%) patients were diagnosed as having PAH, while 19 (38%) patients were not associated with increase in PASP. Evaluation for PAH in newly diagnosed patient with CTD is important because early diagnosis of PAH in association with CTD is crucial for successful management of these patients.

Keywords: Systemic lupus erythematosus, Juvenile idiopathic arthritis, Connective tissue diseases, Pulmonary hypertension, Transthoracic echocardiography, Tissue Doppler.

INTRODUCTION

Pulmonary hypertension (PH) is a pathophysiological condition defined by an increased mean pulmonary arterial pressure (mPAP) >25 mmHg at rest. PAH can be idiopathic or associated with other conditions such as congenital heart defects and CTD (Simonneau et at., 2009). PAH is due to chronic obstruction of small pulmonary arteries resulting from sustained pulmonary vasoconstriction and lumen obliteration of small- and medium-sized arteries and arterioles with the formation of plexiform lesions and insituthrombosis, and concentric thickening of pulmonary arteries resulting from excessive proliferation of endothelial and smooth-muscle cells (Yuan and Rubin, 2005). Symptoms of PAH are non-specific and include breathlessness, fatigue, weakness, angina, syncope, and abdominal distension; symptoms at rest are reported in very advanced cases. Physical signs include left parasternal lift, accentuated pulmonary component of second sound, pansystolic murmur of tricuspid regurgitation, and diastolic murmur of pulmonary insufficiency. In advanced states, jugular vein distension, hepatomegaly, peripheral edema, ascites, and cool extremities (Gaine and Rubi, 1998). Pulmonary hypertension had been reported as the most frequent disease-associated cause of death in patients with mixed CTDs (MCTD) (Burdt et al., 1999). Trans-thoracic echocardiography (TTE) is the most useful screening tool for PH, and repeated echocardiography in high-risk CTD patients, such as those with limited disease, has been suggested

on an annual basis, to detect early manifestations of PH. Right heart catheterization (RHC) remains necessary to confirm the diagnosis, and to exclude other causes of PH such as left-sided heart disease or congenital shunts (Barst et al., 2004).

This study aimed to detect the prevalence of PH in children with CTD using TTE to estimate pulmonary artery systolic pressure (PASP) by the systolic regurgitant tricuspid flow velocity and it provided additional information about the causes and consequences of PH. We also used Tissue Doppler assessment at the level of mitral and tricuspid valve levels.

MATERIALS AND METHODS

This cross sectional study included 50 children aged ≥6 years with CTD who attended Pediatric Rheumatology Outpatient Clinic - Cairo University for follow-up. CTD included: SLE, scleroderma, Sjogren syndrome, dermatomyositis, and rheumatoid arthritis. Patients <6 years-old, on medications that might affect the cardiac function, had congenital heart disease or had chronic lung disease (other than CTD) that could be the cause of PH, and those with other known causes for PH (e.g. skeletal deformities, arteriovenous malformation, chronic anemia) were excluded.

All patients were reviewed for; demographic data, CTDs (onset, course, duration, severity, and type), manifestations of PH, manifestations of other system involvement, history of hospital admissions. Patients were subjected to thorough clinical examination.

Laboratory investigations were collected from patients' files; complete blood count (CBC), ESR, confirmatory tests for CTD (i.e. ANA (pattern and titer), rheumatoid factor, C_3, C_4, LAC, aCL, IGg, CK-MB, Anti ds DNA), renal function tests and biopsy results (if done). Findings were compared with normal values of same age and sex references.

Evaluation of cardiac status was done by chest X-ray, ECG, M-mode, 2-dimensional and Doppler [pulsed-wave, continuous-wave, Color Doppler and Tissue Doppler imaging (TDI)] echocardiography were performed at rest, using two machines: Siemens accuSon CV70 and GE Vivid 7 ultrasound machines with a 3-5 MHz transducer according to guidelines of the American Society of Echocardiography (ASE) (Valente et al., 2014). Left ventricular (LV) percentage of fractional shortening and subsequently LV ejection fraction, stroke volume (SV), and cardiac output (CO) were estimated according to the recommendation ASE and using apical 2- and 4-channel views. Assessment of pulmonary artery flow was performed using Doppler recording of the systolic pulmonary flow, pulmonary acceleration time (PAT), right ventricular ejection time (RVET). Pulmonary artery systolic pressure (PASP) was measured using tricuspid regurgitation, which was carefully assessed by color and continuous-wave Doppler tracing to measure peak systolic right ventricular to right atrial pressure gradient. A tricuspid regurgitation (TRV) of 2.5 m/s was taken as the cutoff level for diagnosis of pulmonary hypertension. The maximal transtricuspid gradient was calculated according to the simplified Bernoulli equation, using an apical 4-chamber and parasternal short-axis and long-axis views. If a holosystolic flow was still not observed, the regurgitation will not be considered being measurable.

TDI velocity analysis measurements were performed at the tricuspid valve level of the RV free wall (the lateral tricuspid annulus), the mitral level of the LV free wall (the lateral mitral annulus), and the level of the interventricular septal crest to assess early diastolic dysfunction in right ventricle and left ventricle.

TDI measurements from each of these myocardial wall segments included peak systolic annular velocity (S), peak early diastolic annular velocity (E), and peak late diastolic annular velocity (A) waves.

The lowest wall filter settings were used to record flow velocities. Diastolic LV function were evaluated by Doppler parameters, including peak early diastolic filling velocity (E), peak late diastolic filling velocity (A), E/A ratio (a measure of relative blood volume, filling the left ventricle in early versus late diastole), LV isovolumic contraction time (IVCT) and LV isovolumic relaxation time (IVRT).

And then the following equations were calculated:

-PAT/RVET: the ratio between pulmonary acceleration time and right ejection fraction time.

-E/A: the ratio between peak early tricuspid inflow velocity (E) and peak atrial velocity (A)

-E/E': peak early tricuspid inflow velocity /early diastolic velocity by TDI at septal and lateral annular sites; $E' = E / ((Es+E_L)/2)$.where E_L is eitherE_m: peak early diastolic lateral mitral annular velocity wave or E_t: peak early diastolic lateral tricuspid annular velocity wave.

-LA/AO: ratio between LA diameter and Aortic diameter.

-LV mass index= LV mass/ BSA, where BSA (m^2) = ([Height (cm) x weight (kg)]/ 3600)$^{1/2}$.

We compared all echocardiographic and TDI findings by normal values according to age and sex (Reference values: Qasim AN and Raina A. Echo normal lab values echocardiographer.org).

Consents were obtained from every parent/surrogate of patients. The Scientific Research Committee of the Pediatrics Department, Cairo University approved the study protocol. Data confidentiality was preserved. Data were statistically described in terms of mean±SD, median and range, or frequencies and percentages when appropriate. Comparison of numerical variables was done using Mann Whitney *U* test for independent samples. For comparing categorical data, Chi square test was performed. Exact test was used instead when the expected frequency <5. Yates correction equation was used instead when the expected frequency <5. Correlation between various variables was done using Pearson moment correlation equation for linear relation in normally distributed variables and Spearman rank correlation equation for non-normal variables. *P*-values <0.05 were considered statistically significant, <0.001 highly significant. Correlation between different parameters was stratified according to r value: r ≤0.25 = weak correlation; r >0.25 ≤0.5 = mild correlation; r >0.5 <0.75 = moderate correlation; r ≥0.75 = strong correlation. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

RESULTS

Fifty patients with age ranged 6-16 years (mean±SD 12.36±2.926; median 12.5 years) were included. Age of CTD onset ranged from one to 14 years (mean±SD 7.45±3.420; median 8 years), 34/50 (68%) were females and 16/50 (32%) were males (F:M=2.125/1). According to body mass index (BMI), patients were classified to average-weight 26 (52%), underweight 7 (14%), overweight 8 (16%), and obese 9 (18%). Systolic blood pressure (SBP) centile ranged from 0-100% (mean±SD 73.1%±32.33%, median 89%), and diastolic blood pressure (DBP) centile ranged from 1-100% (mean±SD 78.8%±24.08%, median 86%).

Systemic lupus erythematosus (SLE) was the most prevalent diagnosis among our patents 28/50 (56%), followed by JIA 18/50 (36%) and JDM 4/50 (8%).

Lupus nephritis was the most common association among SLE patients and was found in 13 patients (26%), 14% without neuropsychiatric or renal involvement, 6% with cerebritis, 4% with both cerebritis and nephritis, 4% had antiphospholipid antibodies and one case (2%) was associated with juvenile diabetes mellitus. JIA patients were classified to; pauciarticular (8%), polyarticular (8%), and systemic onset (16%), JIA associated with ankylosing spondylitis (2%) and associated with sarcoidosis (2%).

Anemia was classified according to Hb level in relation to age and sex (Chrobák, 2001); no anemia 26/50 (52%), mild 8/50 (16%), moderate 14/50 (28%) and severe anemia 6/50 (12%) patients.

Liver biopsy was done in one case and showed sarcoridosis. Pelvic X-ray in 10 cases showed articular changes in one case (2%).Hip Ultrasound in 2 cases and revealed joint effusion (4%). CT Brain for lupus cerebritis cases revealed dilated ventricles and prominent sulci in 2 cases (4%).

Doppler echocardiography was done for all patients; PASP=25 mmHg was taken as a cut-off level for diagnosis of PH. Accordingly patients were divided into two groups; group 1: CTD patients with PH (n=31, 62%), with PASP mean 33.95±13.378 mmHg (median 30.19 mmHg, range 25.04-100 mmHg) and group 2: CTD patients without PH (n=19, 38%), with PASP mean 22.58±19.17 mmHg (median 23 mmHg, range 17.22- 24.79 mmHg).

Table 1 shows descriptive data, frequency of demographic data, and the comparative analysis between groups. Significant differences were noted regarding patient's age (P=0.03) and CTD onset (P=0.019).

Group 1: Out of 31 patients, 18 (58%) had SLE (3/31 (9.7%) had no organ affection, 3/31(9.7%) had cerebritis, 9/31(29%) had nephritis, 1/31(3.2%) had both cerebritis and nephritis and 2/31(6.5%) had APL). Eleven (35.5%) patients had JIA and were classified to Pauciarticular JIA 2/31(6.5%), Polyarticular JIA 4/31(12.9%), and systemic onset JIA 4/31 (12.9%), JIA associated with sarcoidosis 1/31 (3.2%). 2/31 (6.5%) patients diagnosed JDM.

Table (1): Demographic data and comparative analysis between study groups

Variable		Total patients (n=50)				P- value
		Group 1 (n=31)		Group 2 (n=19)		
		No.	%	No.	%	
Gender	**Male**	11	35.5	5	26.3	0.549
	Female	20	64.5	14	73.7	
Consanguinity	**Positive**	15	48.4	11	57.9	0.570
	Negative	16	51.6	8	42.1	
Similar in family	**Yes**	8	25.8	6	31.6	0.750
	No	23	74.2	13	68.4	
Hospital admission	**Yes**	26	83.9	16	84.2	1.000
	No	5	16.1	3	15.8	
Course	**Stationary**	8	25.8	4	21.1	0.426
	Regressive	9	29	3	15.8	
	Progressive	14	45.2	12	63.2	
Failure to thrive	**Yes**	11	35.5	8	42.1	0.766
	No	20	64.5	11	57.9	
		Mean±SD	**Median(range)**	**Mean±SD**	**Median(range)**	**P- value**
Age (years)		13±3	13 (6-16)	11.32±2.54	10 (8-16)	0.030*
Year of CTD onset (years)		8.26±3.48	8 (1-14)	6.14±2.95	6 (1-13)	0.019*
Weight Centile (%)		32.61±32	28 (2-97)	34.74±36.20	18 (2-97)	0.762
Height Centile (%)		14.39±23.35	3 (2-95)	14.26±19.56	4 (2-97)	0.783
BMI Centile (%)		51.97±37.09	48 (3-97)	61.32±33.13	75 (3-97)	0.542
SBP Centile (%)		68±34.32	81 (0-100)	81.42±27.68	94 (16-100)	0.331
DBP Centile (%)		78.03±25.01	85 (1-100)	80±23.08	87 (24-100)	0.479

BMI: Body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure
*P-value is significant

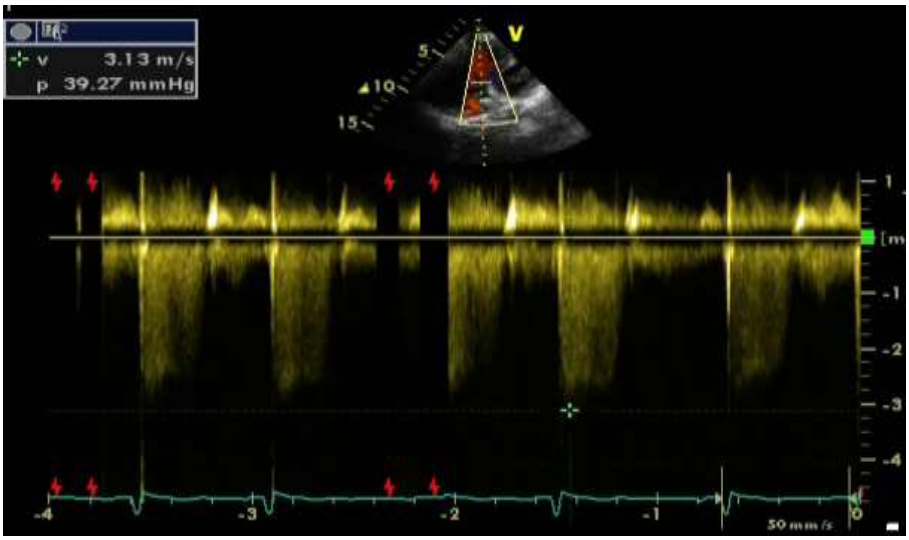

Figure 1: TR with PASP = 49.27 mmHg in a female aged 16 years old with APS of Group 1 during echocardiography.

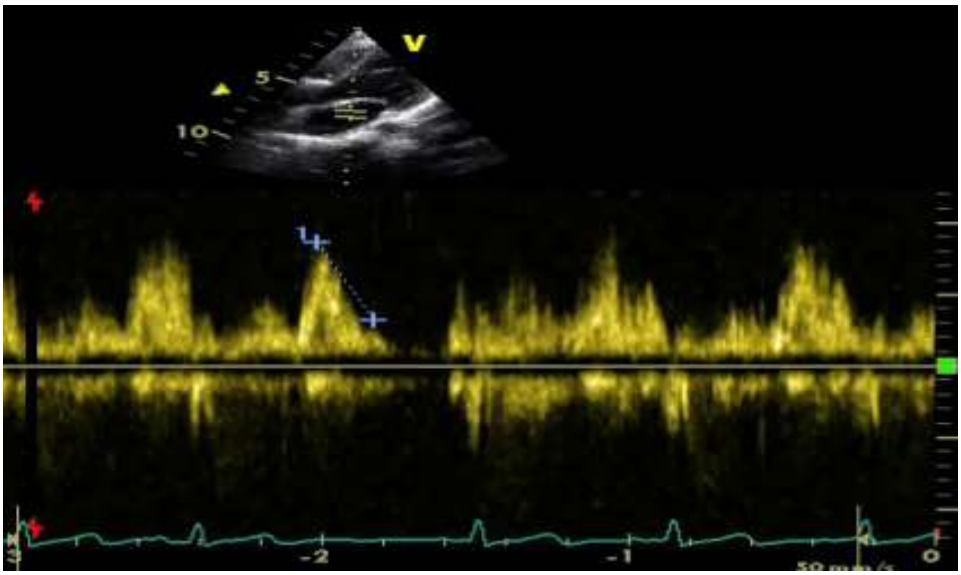

Figure 2: normal E value, and decrease A value and elevated E/A ratio of male JIA patient aged 6 years old in Group 1 during diastolic function assessment.

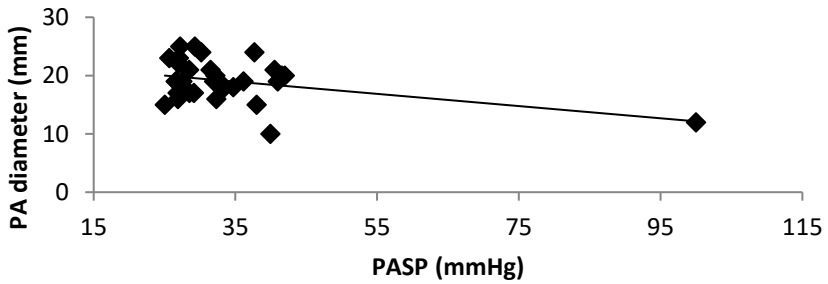

Figure (3): Correlation between PASP (mmHg) and PA diameter (mm) among cases with pulmonary hypertension

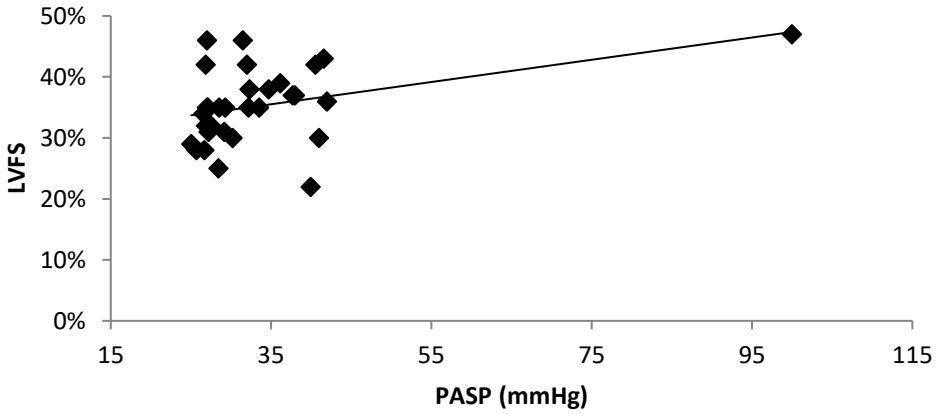

Figure (4): Correlation between PASP (mmHg) and LVFS (%) among cases with pulmonary hypertension

Table 2: Clinical manifestations and comparative analysis between Groups

Variable		Total Patients(n=50)				P- value
		Group 1(n =31)		Group 2 (n =19)		
		No.	%	No.	%	
1st Presenting symptoms	Fatigue	8	25.8	6	31.6	0.750
	Fever	20	64.5	15	78.9	0.351
	Butterfly rash	10	32.3	5	26.3	0.757
	Skin rash	3	41.9	7	36.8	0.774
	Arthralgia	25	80.6	12	63.2	0.199
	Morning stiffness	4	12.9	3	15.8	1.000
	Renal symptoms	3	9.7	1	5.3	1.000
Recent symptoms (the complain of the patient)	Fever	6	19.4	6	31.6	0.496
	Butterfly rash	7	22.6	1	5.3	0.134
	Skin rash	6	19.4	1	5.3	0.229
	Arthralgia	20	64.5	11	57.9	0.766
	Morning stiffness	10	32.3	8	42.1	0.552
	Abdominal pain	16	53.3	8	42.1	0.561
	Reynaud's phenomenon	7	22.6	3	15.8	1.000
Renal symptoms	Hypertension	11	35.5	8	42.1	0.766
	Edema	12	38.7	7	36.8	1.000
	Proteinuria	13	41.9	6	31.6	0.556
	Gross hematuria	1	3.2	5	26.3	0.024*
	Anuria	1	3.2	0	0	1.000
	Uremia	2	6.5	0	0	0.519
Chest Manifestations	Recurrent chest infections	22	71	15	78.9	0.742
Cardiac Manifestations	Dyspnea	9	61.3	12	63.2	1.000
	Excises induced dyspnea	14	45.2	10	52.6	0.772
	Chest pain	13	41.9	6	31.6	0.556
	Syncope on exercise	1	3.2	0	0	1.000
	Syncope at rest	1	3.2	0	0	1.000
	Loud S2	15	48.4	3	15.8	0.033
	RVF manifestations	6	19.4	1	5.3	0.229
	Cardiomegaly (x-ray)	6	19.4	1	5.3	0.229
	Pericardial effusion (echo)	1	3.2	0	0	1.000
Abdominal Manifestations	Abd. Tenderness	22	71	14	73.7	1.000
	Hepatomegaly	6	19.4	3	15.8	1.000
	Splenomegaly	4	12.9	3	15.8	1.000
Hematological manifestations	Pallor	16	51.6	11	57.9	0.773
	Vasculitis	5	16.1	2	10.5	1.000
	Thrompocytopenia	1	3.2	0	0	1.000
Neuro-psychiatric manifestations	Seizures	4	12.9	1	5.3	0.229
	Psychosis	4	12.9	1	5.3	0.229
	Mental-motor delay	4	12.9	0	0	0.284
	Hemiplegia	1	3.2	0	0	1.000
	Hemi-chorea	1	3.2	0	0	1.000
Degrees of anemia	No anemia	14	45.2	12	63.2	0.031*
	Mild	8	25.8	0	0	
	Moderate	7	22.6	7	36.8	
	Severe	2	6.5	0	0	

RVF: right ventricular failure
***P-value is significant**

Table 3: Comparative analysis of the laboratory findings of both groups of the studied population.

Variable		Total Patients (n = 50)						P- value
		Group 1 (n = 31)			Group 2 (n = 19)			
		No.	Mean ± SD	Median (range)	No.	Mean± SD	Median (range)	
C3 (mg/dl)		12	84.39±64.83	72.75 (12-257)	7	94.91 ±58.728	113 (20-180)	0.422
C4 (mg/dl)		12	32.77±30.61	19.95 (4.9-98.9)	7	34 ± 38.2	21.3 (0.8-117.8)	0.612
APL U/ml	ACL IgG	4	14.1±11.44	13.15 (1.1-29)	1	44	44	0.157
	Anti B2 IgG	2	7.95±5.87	7.95 (3.8-12.1)	1	46.5	46.5	0.221
	LAC	2	39.85±11.10	39.85 (32-47.7)	1	32.2	32.2	1.000
CK-MB (ng/ml)		3	984.53±1675.34	29 (6-2919)	2	45 ±5.66	45 (41-49)	0.564
LDH(U/L)		3	755± 203.47	824 (526-915)	2	241.5±44.55	241.5 (210-273)	0.083
GGT(U/L)		1	67	67	0	0	0	0
ESR (mm/hr)		29	70.69±36.79	65 (3-145)	18	69.17 ±38.53	55 (8-150)	0.638
Hb (gm/dl)		31	11.61±2.13	11.7 (7-16.4)	19	11.65 ±1.81	12 (8-13.9)	0.764
Hct. (%)		28	35.96 ±6.23	37.75 (19.2-47.5)	18	38.47 ±12.22	37.50 (26.7-83)	0.778
WBCs (x 10^3/µL)		30	7.63 ±3.50	6.55 (4.32-17.3)	19	8.11±3.21	7.07 (3.58-16.3)	0.406
Lymph (%)		28	6.28 ±8.95	2.74 (0.3-34)	16	11.58±14.34	3.82 (0.6-40.2)	0.464
PLT (mm^3)		30	364.17±158.29	318.5 (83-732)	19	391.95±114.45	392 (225-687)	0.166
Urea (mg/dl)		27	23.89±10.13	21 (10-49)	18	25.44±8.99	22 (15-48)	0.429
Creat (mg/dl)		27	0.60±0.20	0.6 (0.3-1.1)	18	0.53±0.1	0.5 (0.3-0.9)	0.328
ALT (U/L)		28	32.11±19.6	29 (7-89)	8	27.94±12.38	28.5 (9-47)	0.822
AST (U/L)		27	29.55 ±22.46	23 (10-120)	18	28±11.02	25.5 (13-57)	0.347

C3: complement 3; C4: complement 4; APL; Antiphospholipid antibodies ACL IGg: anti cardiolipin immunoglobulin G; Anti B2IGg: anti B2 glycoprotein immunoglobulin G; LAC: lupus anticoagulant; CK-MB:creatine kinase MB; LDH: Lactate dehydrogenase; GGT: Gamma-glutamyl transferase; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; Hct: haematocrit; WBCs: white blood cells; Lymph: lymphocytes; PLT: platelets count; Creat: creatinine; ALT: alanine aminotransferase; AST: aspartate aminotransferase. mg/dl: milligrams per deciliter; gm/dl: gram per deciliter; mm^3: millimeter cube; %: percent; mm/hr: millimeter per hour; U/L: units per liter.

Table 4: Comparative analysis of laboratory findings of the study groups

Variable		Total patients (n =50)				P- value
		Group 1 (n= 31)		Group 2 (n= 19)		
		Numb.	%	Numb.	%	
Renal Biopsy (Total = 29)	Free	9	47.4	4	40	0.251
	Type 2 GN	2	10.5	4	40	
	Type 3 GN	6	31.6	1	10	
	Type 4 GN	2	10.5	1	10	
ANA pattern (total=50)	Not done	7	22.5	5	26.3	0.383
	Free	12	38.7	9	47.4	
	Coarse speckled	0	0	1	5.3	
	Homogenous speckled	12	38.7	4	21.1	
ANA Titer (total=50)	Not done	21	67.7	15	78.9	0.534
	Free	4	12.9	3	15.8	
	1/160	2	6.5	0	0	
	1/40	4	12.9	1	5.3	
Anti-ds DNA (Total =24)	Positive	5	38.5	4	36.4	
	Negative	8	61.5	7	63.6	1.000
RF (Total = 8)	Negative	4	100	4	100	0
ANCA (Total =2)	Positive	1	50	0	0	0
	Negative	1	50	0	0	0
ASMA (total=50)	Not done	29	93.5	18	94.7	0.414
	1 /20	1	3.2	1	5.3	
	Free	1	3.2	0	0	
ALKM (total=50)	Not done	29	93.5	19	19	0.528
	< 1/20	1	3.2	0	0	
	855	1	3.2	0	0	
Albuminuria (total=50)	Not done	2	6.5	2	10.5	0.833
	Free	13	41.9	8	42.1	
	1+	5	16.1	2	10.5	
	2+	6	19.4	2	10.5	
	3+	3	9.7	2	10.5	
	Trace	2	6.5	3	15.8	
Hematuria (total=50)	Not done	2	6.5	2	10.5	0.120
	Free	27	87.1	12	63.2	
	1+	0	0	2	10.5	
	2+	1	3.2	3	15.8	
	3+	1	3.2	0	0	

GN: glomerulo nephritis; ANA: antinuclear antibodies; Anti-ds DNA: anti double stranded (ds) DNA; RF: rheumatoid factor; ANCA: Anti-neutrophil cytoplasmic antibody; ASMA: anti-smooth muscle antibodies; ALKM: anti-liver/kidney microsomal antibodies; Negative ANA test: no detectable ANA in the blood. Low titers ANA are in the range of 1:40 to 1:60. A positive ANA is much more significant if you also have antibodies against the double-stranded form of DNA.

Table (5): Comparative analysis of the Echocardiographic findings of both Groups

Variables	Total	Group 1 (n= 31)				Group 2 (n = 19)				P-value
		Min.	Max	Mean ±SD	Median	Min.	Max	Mean±SD	Median	
PASP(mmHg)	50	25.04	100	33.95±13.378	30.19	17.22	24.79	22.58 ±1.917	23	0.000*
TRV(m/s)	50	1.31	4.8	2.46 ±0.584	2.36	0.89	2.45	1.58 ±0.462	1.50	0.000*
MaxTRG(mmHg)	50	15.04	90	25.24±13.665	22	7.22	15	12.58±1.897	13	0.000*
E (m/s)	50	0.5	1.7	0.845 ±0.296	0.760	0.5	1.1	0.763±0.1497	0.770	0.653
A (m/s)	50	0.3	2	0.601 ±0.318	0.520	0.4	1.7	0.648 ±0.298	0.550	0.317
E/A	50	0.56	4.67	1.6047±0.762	1.492	0.31	2.37	1.352 ±0.505	1.333	0.197
Aortic Flow (m/s)	49	0.7	1.7	1.191±0.1923 (n =30)	1.155	1	1.5	1.209±0.1772	1.250	0.727
PA flow (m/s)	50	0.9	2.9	1.248±0.3595	1.190	1	2	1.295±0.286	1.250	0.298
RV diam (mm)	50	7	30	18.52±6.088	19	2	34	16.99±7.934	16	0.362
PA diam (mm)	50	10	25	19.06±3.540	19	2	27	17.93±5.849	17	0.026*
PAT (mm/s)	50	67	177	111.26±24.522	111	85	170	114.21±26.676	104	0.912
RVET (mm/s)	50	229	355	297.32±36.907	303	214	348	280.11±35.300	274	0.071
PAT/RVET	50	0.24	0.56	0.374±0.0645	0.3706	0.29	0.67	0.414±0.113	0.385	0.374
LA (mm)	50	19	41	27.06±5.422	26	18	31	26.05 ±3.613	27	0.595
AO (mm)	50	17	33	23.39±3.765	23	19	28	22.21±2.898	22	0.248
LA/AO	50	0.58	1.60	1.1699±0.2080	1.1500	0.78	1.58	1.191±0.224	1.174	0.780
LV mass (gm)	50	45	207	116.94±46.798	113.13	56	214	110.50±42.43	107.23	0.704
LV mass index	50	40.66	164.96	93.78±32.16	88.29	58.50	134.41	95.07±21.68	91.91	0.787
IVS (mm)	50	5	11	8.16±1.89	8	6	13	8.16±1.95	8	0.863
LVESD (mm)	50	17	38	27.10±5.19	27	10	39	26.32±5.65	26	0.616
LVEDD (mm)	50	7	52	39.68±8.55	41	29	54	41.26±5.63	40	0.896
LVPW (mm)	50	5	25	9±3.49	8	5	13	8.55±2.45	8	0.709
LV FS (%)	50	22	47	35.32±6.17	35	29	45	34.71±4.14	34	0.043*
SV (ml)	46	24	82	49.80±14.81 (n= 30)	52	22	79	48.69±15.52 (n=16)	46.50	0.695

PASP: Pulmonary Artery Systolic Pressure; **TRV**: Tricuspid regurgitant jet velocity; **Max TRG**: maximum tricuspid regurgitation gradient; **E**: peak early tricuspid inflow velocity(peak early filling velocity) ; **A**: peak atrial velocity (peak late filling velocity); **AO**: Aortic diameter; **LA**: Left atrial diameter; **PA**: pulmonary artery diameter; RVET: Right ventricular ejection time; PAT: Pulmonary acceleration time; RV: right ventricle diameter; **LV**: left ventricle; **IVS**: Interventricular septum diameter; **LVEDD:** Left ventricular end-diastolic diameter; **LVESD**: Left ventricular end-systolic diameter; **LVPW**: Left ventricular posterior wall diameter; **LV FS**: Left ventricular Fractional shortening; **SV**: stroke volume.
SD: standard deviation; m/s: meter per second; mm: millimeter; mm/s: millimeter per second; %: percentage; ml: milliliter; sec.: second; gm: gram.

Table (6): comparative analysis of the TDI findings of both study groups

Variables		Num.	Group 1 (n =31)				Group 2 (n =19)				P-value
			Min.	Max.	Mean ±SD	Median	Min.	Max.	Mean ±SD	Median	
LV IVRT (sec.)		43	41	104	62.25 ±13.72 (n= 28)	59	41	85	65.67 ±11.68 (n=15)	68	0.219
LV IVCT (sec.)		43	37	100	65.36 ±14.74 (n=28)	63	52	81	65.80 ±9.85 (n=5)	70	0.739
Lateral Mitral annulus	**E_m (m/s)**	50	0.03	0.20	0.1142 ±0.04272	0.1100	0.5	0.19	0.1026 ±0.03397	0.273	0.273
	A_m (m/s)	50	0.04	0.17	0.0729±0.02877	0.0700	0.04	0.16	0.0789±0.0365	0.731	0.731
	S_m (m/s)	50	0.05	0.20	0.0861±0.02741	0.0800	0.06	0.70	0.1137±0.1432	0.671	0.671
	E/E'	50	2.13	8.67	4.9708±1.7060	4.5000	2.57	6.24	4.8509±1.2384	0.704	0.704
Septal	**E_s (m/s)**	50	0.06	0.18	0.1194 ±0.02851	0.1200	0.05	0.17	0.1132±0.0306	0.1100	0.469
	A_s (m/s)	50	0.04	0.18	0.0784±0.0263	0.0700	0.05	0.17	0.0979±0.0384	0.0800	0.076
	S_s (m/s)	50	0.06	0.16	0.1035±0.0226	0.1000	0.07	0.17	0.1137±0.0265	0.1100	0.238
Lateral Tricuspid annulus	**E_t (m/s)**	50	0.08	0.23	0.1461±0.04022	0.1400	0.09	0.19	0.1447±0.0344	0.1500	0.904
	A_t (m/s)	50	0.05	0.21	0.1177±0.0381	0.1100	0.06	0.60	0.1579±0.1156	0.1300	0.127
	S_t (m/s)	50	0.09	0.20	0.1390±0.03124	0.1400	0.08	0.19	0.1358±0.02795	0.1400	0.841
	E/E'	50	2.00	9.71	4.5518±1.74518	4.1250	2.50	6.08	4.3141±1.15006	4.4865	0.826

LV IVRT: left ventricle Isovolumic relaxation time; **LV IVCT**: left ventricle Isovolumic contraction time; **E_m**: peak early diastolic lateral mitral annular velocity wave; S_m: Peak systolic lateral mitral annular velocity wave; A_m: peak late diastolic lateral mitral annular velocity wave. **E_s**: peak early diastolic septal annular velocity wave; S_s: Peak systolic septal annular velocity wave; A_s: peak late diastolic septal annular velocity wave. **E_t**: peak early diastolic lateral tricuspid annular velocity wave; S_t: Peak systolic lateral tricuspid annular annular velocity wave; A_t: peak late diastolic lateral tricuspid annular annular velocity wave. **E/E'**: peak early tricuspid inflow velocity /early diastolic velocity by TDI at septal and lateral annular sites; E'= E/ ((Es+E_L)/2).where E_L is eitherE_m : peak early diastolic lateral mitral annular velocity wave or E_t : peak early diastolic lateral tricuspid annular velocity wave.

Group 2: Out of 19 patients, 10 (52.6%) had SLE (4/19 (21.1%) had no organ affection, 4/19 (21.1%) had nephritis, 1/19 (5.3%) had both cerebritis and nephritis, and 1/19 (5.3%) had JDM as well). Seven (36.9%) patients had JIA which classified to Pauciarticular JIA 2/19(10.5%) and systemic-onset JIA 4/19 (21.1%), JIA associated with ankylosing spondylitis in 1/19 (5.3%) 2/19 (10.5%) patients diagnosed JDM.

Frequency of clinical manifestations of both groups is demonstrated in table 2. Loud S2 on pulmonary area was significant in group 1 (P=0.033). No statistically significant differences were found between both groups regarding CTD investigations (Tables 3 and 4).

Table 5 shows comparative analysis of echocardiographic findings between groups. Max. Tricuspid gradient, TRV and PASP were highly significant in CTD patients (P=0.000). PA diameter and LV fraction shortening were also significant (P=0.026 and =0.043, respectively).

Table 6 shows comparative analysis of TDI findings of both groups, there were no significant differences between regarding Lateral Mitral annulus (E_m, A_m, S_m, E/E_m), Septal (E_s, A_s, S_s) and Lateral Tricuspid annulus (E_t, A_t, S_t, E/E_t) (P>0.05).

Some echocardiographic findings found in our patients are demonstrated in figures 1, and 2.

PASP had a strong significant positive correlationwith severe TR (r=+0.902, P=0.000), andmild significant negative correlation with Trivial TR (r=-0.452, P=0.007). PASP had no significant correlation with MR (Trivial and Moderate) and TR (Mild and Moderate).

Degrees of anemia had mild significant positive correlation with both PASP (r=+0.370, P=0.031) and severe TR (r=+0.349, P=0.014). Degrees of anemia had insignificant correlation with RV diameter, MR (Trivial and Moderate) and TR (Trivial, Mild and Moderate). PASP had significant positive correlation with LV fraction shortening (r=+0.349, P=0.043). PASP had mild significant negative correlation with PA diameter (r=-0.380, P=0.026). PASP had no significant correlation with systolic BP centile, diastolic BP centile, E, A, PA flow, RV diameter, PAT/RVET, LA/AO, LV mass, LV mass index, IVS, LVESD, LVEDD, LVPW and SV.

Correlations between PASP (mmHg) and PA diameter (mm) and between PASP (mmHg) and LVFS (%) among cases with pulmonary hypertension are shown in figures 3, and 4 respectively.

DISCUSSION

CTD is a group of autoimmune disorders with common clinical and serological characteristics; CTD has various clinical manifestations; PAH is a major focus of attention (Confalonieri et al., 2013). PAH is a hemodynamic condition that characterized by progressive vascular remodeling of the pulmonary arteries, leading to increased pulmonary vascular resistance and increased pressure in the pulmonary circulation, and right ventricular overload and ultimately failure (Galiè et al., 2009). Doppler echocardiography allows non-invasive estimation of PASP, as well as Mean and End diastolic pulmonary arterial pressure. PASP was equivalent to RVSP assuming there was no gradient in systole between the right ventricle and pulmonary artery (e.g., infundibular or valvular pulmonary stenosis) (Ginghină et al., 2009 and Seyfeli et al., 2006).

In Our study, out of fifty patients, 68% were females and 32% were males (F:M=2.125/1). That was related to the more possibility of autoimmune diseases among females *(*Kelly, 2012*).*The mean age was 12.36±2.926 years (range 6-16 years), and mean age of onset was 7.45±3.420 years (range 1-14 years). Comparable with ages and age of CTD onset was described by other studies (Moradinejad, 2006, Salah et al., 2009, Martin et al., 2012, and Chipeta et al., 2013). Our study revealed a progressive course of the disease in 52% of patients. Young age at onset may be associated with a more severe disease that could be attributed to age-related variation in the maturing immune system or differences in exposure to environmental pathogens between children in preschool and those who had started school (Wedderburn and Rider, 2009). However, large retrospective multicentric studies did not find that early onset of JDM symptoms to be a predictive of poor outcome (Ravelli et al., 2010, and Guseinova et al., 2011).

The incidence of SLE in our patients was 56%; and lupus nephritis was the most common manifestation. Lupus nephritis is a prevalent manifestation among juvenile SLE patients (Moradinejad, 2006 and Salah et al., 2009). Systemic-onset JIA was the most prevalent form of JIA in our patients, followed by pauciarticular JIA, polyarticular JIA, and enthesitis-related arthritis, Bahabri et al., 1997 reported systemic onset JIA in 44% of patients . However, Chipeta et al., 2013 reported polyarticular JIA as the most common JIA type.

Doppler echocardiography was used as a screening tool for detection of asymptomatic PH,

our patients were divided into; group 1: CTD with PH (n=31) 62%, and group 2: CTD without PH (n=19) 38%. *In Group;* SLE had the highest prevalence rate 58% (6.5% of total SLE had APS), JIA 35.5% and JDM 6.5%. No significant difference between both groups regarding different types of CTD. Xing et al., 2008 reported the occurrence of PH in 54.8% of SLE patients, 9.7% of JDM patients and 6.5% of APS patients (22), Falcao et al., 2002 and Dorfmüller et al., 2003 reported occurrence of PH in SLE from 4%-21% and 0.9-10.5%, respectively. However; Funauchi et al., 2007 found that Scleroderma was the most commonly associated CTD with PH.

Our results revealed a significant difference between both groups regarding their ages and their age of onset of CTD with a higher mean of age and mean age of onset among group 1 patients (P=0.03, and 0.019 respectively), that was comparable to ages described by other studies (Günal et al., 2003, Xing et al., 2008, and Kamel et al., 2011). Xing et al., 2008 stated that CTD-associated PAH occurred in the 3rd week to 5th year after initial manifestations (median: 1.5 years). Takatsuki et al., 2011 observed that patients with CTDa-PAH had more progressive disease; we found a more progressive course in Group 2 that was of no significant difference; however, the evidence of increase morbidity should be considered.

In our study; no significant differences between both groups regarding weight, height, BMI centiles, and systemic BP were reported. Similar results were noted by other studies (27-29).Reynaud's phenomenon was found in 10 patients, 7/10 were in group 1. The correlation between occurrences of Reynaud's phenomenon with PAH suggests that pulmonary arterial vasospasm may be involved in the pathogenesis of PH; children with Raynaud's phenomenon are prone to have more severe PAH (Xing et al., 2008, Kamel et al., 2011, and Takatsuki et al., 2011).

In our study, no significant differences were noted regarding positive Anti-ds DNA and positive ANA between groups (26). However, RF was negative in both groups; that was inconsistent withKamel et al., 2011; that found positive RF in (50%) of SLE-PH patients with a significant difference between controls and studied groups. Lian et al., 2012 found positive RF in 46.3% of SLE-PH .

In Group 1*;* positive aCL IgG, LAC, and negative AntiB2 IgG were reported; these tests were used to diagnose APS-SLE. We thought that these auto-antibodies might facilitate the formation of micro-thrombi in pulmonary vasculature and contribute to PASP elevation (Günal et al., 2003, Takatsuki et al., 2011, and Lian et al., 2012). PH was unrelated to the severity or activity of SLE such as high anti-ds-DNA and/or grossly elevated ESR and renal affection and can occur when non-pulmonary disease activity is quiescent (Robbins et al., 2000 and Kamel et al., 2011).

Anemia was classified according to age and sex to mild, moderate and severe, with significant difference between both study groups and mild significant positive correlation with elevated PASP. No similar results were reported. Renal affection did not differ significantly between both groups, and weren't correlated with PAH (Kamel et al., 2011).

Echocardiography findings revealed a high significant difference between both groups regarding PASP, TRV and Max TRG. Group 1, severe PASP (100 mmHg) was observed in one patient. We attributed severe PASP to the presence of APS with SLE. PA diameter was elevated in both groups with a significant difference between both but with a mild significant negative correlation with PASP elevation. No similar results were found in other studies. Kamel et al., 2011 reported PASP ranged from 34–61.02 mmHg. Seyfeli et al, 2006 reported 29% JRA patients with PAH (mean 35±5 mmHg). In Takatsuki et al., 2011 study; TRV was done by TTE, ranged from 4.2 m/s to 5.5 m/s.

In our study**,** PAT decreased in group 1 and was normal in group 2. RVET was normal in both groups with decreased PAT/RVET ratio in group 1 only with no significant difference. On the contrary, Lammers et al., 2012 showed shorter PAT of PAH patients than controls with a significant difference that was a marker of less severe PAH. This can be explained as all his patients had PAH.

In our study; LVEDD was elevated in group 1 and normal in group 2. LVESD and IVS were normal in both groups while LVPW was obviously elevated in Group 1 and mildly elevated in Group 2 while LA and AO were elevated in both Groups with normal LA/AO ratio. RV diameter was normal in group 1 and decreased in group 2. Lammers et al., 2012 found both LVEDD with mean 1.6±0.5 cm and LVESD with mean 2.1±0.8 cm to differ significantly from healthy controls. RV diameter had a mean=2.73±1.29 cm (P=0.0002) was significantly different between patients and controls, but LA diameter was insignificant

(mean=7.6±3.7cm).

During parasternal long-axis and parasternal short-axis views at mid-ventricular level, we assessed left ventricular systolic function by LV-FS which was decreased in both groups but had mild significant positive correlation with elevated PASP and LV-FS. That may be an early sign of systolic impairment of left ventricular contractile function and may be explained by the presence of anemia. Kamel et al., 2011 and Lammers et al., 2012; assessed left ventricular systolic function by LV EF; which was elevated in PAH patients (means 66.3±22.7% and 61.75%±3.49%, respectively) with no significant difference . Günal et al., 2003 reported normal EF and FS values of SLE patients (EF 63% and FS 32%) with statistically significant differences (27). However, FS had many limitations regarding difficulty in accurate measurement and being affected by preload, afterload, heart rate, desynchrony, as well as myocardial contractility (Sanderson, 2007).

In our study; no diastolic dysfunction of left ventricle was found, where E and A elevated in both groups with normal E/A ratio, However, presence of normal E/A ratio did not exclude presence of diastolic dysfunction as pseudonormal E/A ratio may be the cause (Kapusta et al., 2000). Günal et al., 2003 reported that Left ventricular diastolic function impaired with decrease (peak E velocity and E/A ratio) with significant difference for both while A wave velocity was normal; authors attributed this impairment to the immunopathologic changes in myocardium or lupus myocarditis.

We performed TDI velocity analysis measurements at the tricuspid valve level of the RV free wall (the lateral tricuspid annulus), the mitral level of the LV free wall (the lateral mitral annulus), and the level of the interventricular septal crest to allow separate analysis of systolic and diastolic function in right ventricle and left ventricle through measurement of myocardial velocities (Nikitin and Witte, 2004). TDI measures TDI velocities correlate well with gold standard conductance catheter measures of ventricular function and are non-invasive and practical for use in the clinical setting (Oki et al., 1997).

In our study;LV IVRT and LV IVCT were normal in both groups with no significant difference between them. That was similar to Günal et al., 2003 who observed normal IVRT between control and studied group.

In our study, both groups had reduced E_m velocity across the mitral valve which was suggestive of LV filling impairment. In which LV filling is compromised by the septal deviation of a hypertrophied and pressure overloaded right ventricle and is aggravated by reduced pulmonary blood flow. While elevated S_s velocity and A_t velocity in both groups suggestive of normal ventricular relaxation. Group 2 patients had increased S_m velocity and A_s velocity with no significant difference between the two groups. All the TDI measurements had no significant difference between the two groups of our studied population. Lammers et al., 2012 reported a significance difference between the two groups regarding PAH occurrence and lower systolic (S) and early diastolic (E) velocities at the tricuspid and septal levels and found significantly reduced tissue Doppler LV velocities (S, E, and A) at the lateral mitral valve annular level in children with PH.

We noted,during TTE, different degrees of mitral valve regurge; (Trivial MR 16% and Moderate MR 4%) and tricuspid valve regurge (Trivial TR 14%, Mild TR 38%, Moderate TR 6% and Severe TR 2%). And it appeared that PASP had a strong significant positive correlation with Severe TR, and a mild significant negative correlation with Trivial TR. PASP had insignificant correlation with MR (Trivial and Moderate) and TR (Mild and Moderate). Similarly; Kamel et al., 2011 who classified tricuspid regurge to (mild 12.5%, moderate 62.5%, and severe 25%) only mild tricuspid regurge was statistically significant (P=0.001) between both groups but no significance with other degrees recorded . Günal et al., 2003 noted that one patient had moderate tricuspid valve insufficiency (7.14%) and one had moderate mitral valve insufficiency (7.14%) detected by Doppler echocardiography while mild tricuspid regurgitation, found in three patients (21.4%) and it was considered as a physiological finding unrelated to the disease, as can be seen in the normal population.

We compared the significant degree of anemia with some TTE findings and with different degrees of MR and TR; it was noticed that anemia had mild significant positive correlationwith both PASP and Severe TR, on the other hand, no significant correlation found between anemia and RV diameter, MR (Trivial and Moderate) and TR (Trivial, Mild and Moderate). We did not find similar comparisons in other studies.

CONCLUSION

Doppler echocardiography allows non-invasive detection of elevated SPAP that should then benefit from gold-standard techniques

including right-heart catheterization to confirm the diagnosis, as well as the cause and severity of PAH. Evaluation for CTD in the newly diagnosed PAH patient is important because early diagnosis is crucial in the successful management of these patients.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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All authors have revised and approved this manuscript.

AUTHOR CONTRIBUTIONS

AE, designed study, performed the echocardiography, and reviewed the manuscript. MF, designed study, collecting data, and wrote the manuscript. SA: collecting and analyzing data. HS, designed study, supervised the work and reviewed the manuscript. All authors read and approved the final version.

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