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The use of tissue Doppler imaging in the assessment of diastolic dysfunction in children with chronic lung diseases

Iman H. Draz[1*], Fatma El Zahraa Mostafa[2], Antoin F. AbdelMassih[1], Dalia El-Sayed[1] and Rania El-Kaffas[1]

Abstract

Background: Chronic lung diseases (CLD) in children such as bronchiectasis and interstitial lung disease represent a major public health problem with limited therapeutic options. These patients develop pulmonary hypertension (and core-pulmonale in severe cases) because of the recurrent hypoxia and chronic inflammation; which results in right heart enlargement and ventricular hypertrophy. The early identification and convenient treatment of diastolic dysfunction can prevent further complications of the disease including diastolic heart failure and death. We aim to demonstrate the usefulness of tissue Doppler imaging echocardiography (TDI) in the detection of subtle myocardial affection in interstitial lung disease and bronchiectasis as subgroups of (CLD) in children. We studied echocardiographic parameters of 40 pediatric patients with chronic lung disease using conventional M mode and tissue Doppler imaging and compared them with 40 healthy controls of matching age and sex distribution.

Results: Myocardial performance index (MPI) showed that 28 subjects had abnormal right ventricular (RV) MPI (10 with severe affection ≥ 0.6) and 21 subjects had abnormal LV MPI (11 severe affections ≥ 0.6). Thirty percent (30%) of the cases had affected lateral E/E' and 47.5% had affected septal E/E' when compared to controls. Grades of diastolic dysfunction were: 0, 1, 2, 3 in 18, 15, 6, and 1 patients, respectively. MPI LV and MPI RV showed statistically higher values in patients compared to controls ($P < 0.001$).

Conclusion: This study proved that TDI can accurately detect subtle myocardial dysfunction in pediatric CLD patients.

Keywords: Echocardiography, Bronchiectasis, Interstitial lung, Diastolic dysfunction

Background

Chronic lung diseases (CLD) in children such as bronchiectasis and interstitial lung disease represent a major public health problem with limited therapeutic options [1]. Patients with chronic lung diseases develop pulmonary hypertension (and core-pulmonale in severe cases) because of the recurrent hypoxia and chronic inflammation; this results in right heart enlargement and ventricular hypertrophy [2]. The early identification and convenient treatment of diastolic dysfunction can prevent further complications of the disease including diastolic heart failure and death [3].

Tissue Doppler measurements are considered as a practical echocardiographic tool in pediatrics as they are non-invasive, hardly time-consuming, relatively available, and software-independent compared to other measurements [4]. Diastolic indices measurements are of particular interest since the diastolic dysfunction is regarded as the main abnormality in heart failure with preserved ejection fraction. Moreover, the diastolic dysfunction is predictive of progression to heart failure in adults [5]. The European Society of Cardiology and the American Society of Echocardiography recommend the

* Correspondence: imane.draz@cu.edu.eg; imane.draz@yahoo.com
[1]Pediatric Pulmonology, Faculty of Medicine, Cairo University, Kasr Alainy, Street, Cairo 11562, Egypt
Full list of author information is available at the end of the article

use of tissue Doppler imaging for the evaluation of both diastolic and systolic functions [6, 7].

The current study aimed at demonstrating the usefulness of tissue Doppler imaging echocardiography (TDI) in the detection of subtle myocardial affection in interstitial lung disease and bronchiectasis as subgroups of chronic lung diseases in children.

Methods

In the period from September 2018 to March 2019, a total number of 121 patients with varying severity of chronic lung diseases were assessed during their clinical follow-up visits at the Pediatric Pulmonology Unit, in a referral Children Hospital.

Chronic respiratory diseases were defined as the presence of respiratory symptoms for 3 or more months in each of 2 consecutive years in a patient in whom other causes of such respiratory symptoms have been excluded [8]. From the 121 patients assessed, 40 patients (mean age of 6.99 ± 3.40 years, range 2–13; 24 males) were included in the study after obtaining informed consents their legal guardians. In addition, the study protocol was approved by the institutional Ethics Committee.

Patients were divided into two groups according to high-resolution computed tomography (HRCT) diagnosis: interstitial lung disease group and non-cystic fibrosis (CF) bronchiectasis group. The two groups were then compared to 40 healthy controls with matching age and sex distribution. The enrolled patients underwent a detailed history taking, physical examination, pulmonary function test (PFT) by spirometry (when applicable), and chest HRCT.

Echocardiography

The examination was carried out by the same operator, a pediatric cardiologist who is an expert in echocardiography and TDI. Studies were done for the cases in a supine or left lateral position using General Electric Vivid 5 series system with a probe of 3 or 6 MHz (multifrequency transducer) according to the patient's age.

Pulmonary artery systolic pressure

Pulmonary artery systolic pressure was estimated by measuring the TR jet maximum velocity by continuous wave (CW) spectral Doppler. If there is no significant stenosis at the right ventricular outflow tract, or the pulmonic valve, the RVSP is equivalent to the systolic pulmonary artery pressure [9].

Tissue velocity imaging

Tissue velocity imaging (TVI) was done in the four-chamber view with the mitral annular planes perpendicular to the ultrasound beam. A 5-mm pulsed TD sample volume was placed at the septal and lateral aspects of mitral annulus as well as at the lateral aspect of tricuspid annulus. Care was taken to eliminate Doppler inflow and noise signals. Peak systolic (S′) (systolic myocardial function), peak early diastolic (E′) (early diastolic filling velocity), and late peak diastolic myocardial (A′) (late diastolic filling velocity) velocities, IVRT, and Ea/Aa ratio at both the septal and lateral mitral annulus and free-wall tricuspid annulus were determined. The ratio of E to E′ velocity (E/E′) was computed as a surrogate of left ventricular (LV) filling pressure [10]. Diastolic dysfunction was graded as follows: grade 0 no diastolic dysfunction, grade 1 (impaired relaxation) E/E′ ≤ 8, grade 2 (pseudonormal) E/E′ 9–12, and grade 3 (restrictive grade) E/E′ ≥ 13 [11].

Global myocardial performance index

Global myocardial performance index (MPI) (Tei index), defined as the sum of the isovolumic contraction and relaxation times divided by the ejection time and was calculated by pulsed tissue velocity imaging for Tissue Doppler [12]. It is a simple Doppler-derived index combining systolic and diastolic ventricular function, and has been reported to have good correlation to invasive measurement of LV systolic and diastolic functions. It was calculated by pulsed tissue velocity imaging for tissue Doppler. All the interval measurements were performed within one cardiac cycle. Tei index was calculated as Tei index=$a'-b'/b'$ where a' is the time interval from the Aa-wave end to the Ea-wave onset and b' is the time from the S-wave onset to its end [13]. The mean normal value of the Tei index is 0.39 ± 0.05 for the LV, and 0.28 ± 0.04 for the RV [14].

Statistical analysis

Statistical analysis was done using NCSS© 12 Statistical Software 2018 (NCSS, LLC. Kaysville, Utah, USA. Continuous numerical data were presented as mean and standard deviation and intergroup differences were compared using the unpaired t test. Categorical data were presented as ratio or number and percentage and intergroup differences were compared using Fisher's exact test. Correlations were tested using the Pearson product-moment correlation or Spearman rank correlation if appropriate. The diagnostic value of echocardiographic measures was examined using receiver-operating characteristic (ROC) curve analysis.

Results

Echocardiographic results of all subjects revealed that both conventional and tissue Doppler parameters were significantly affected in patients compared to controls (Table 1).

The analysis of patients' MPI showed that 28 subjects had abnormal right ventricular (RV) MPI (10 with severe

Table 1 Basic clinical and ecocardiographic parameters of cases vs controls

	Group				
	Cases		Controls		
	Mean ± SD	Range	Mean ± SD	Range	*P* value
Age in years	6.99 ± 3.40	2.00–13.00	66.49 ± 2.88	2.00 – 13.00	0.067
BMI (kg/m^2)	15.58 ± 4.25	9.38–25.51	17.1 ± 2.57	12.2–26.00	0.06
Respiratory rate (breath/min)	39 ± 10	36–53	25.2 ± 5	20–35	0.04
Heart rate (beat/min)	110 ± 25	100–135	100 ± 21	95–120	0.06
ESPAP (mmHg)	45.83 ± 17.9	20.0–100	25.58 ± 4.43	18.0– 34.0	< 0.001*
FS (%)	40.68 ± 8.56	22.0–62.0	36.49 ± 3.19	30.0- 46.0	0.009*
EF (%)	71.75 ± 10.2	47.0–92.0	67.06 ± 3.90	58.0- 77.0	< 0.001*
TAPSE (mm)	17.15 ± 3.70	11.0–28.0	22.25 ± 2.47	15.0–27.0	0.006*
Tricuspid annular E′/A′/	1.46 ± 0.43	0.66–2.33	1.48 ± 0.34	0.64–2.43	0.985
Mitral annular E′/A′	1.60 ± 0.72	0.48–4.10	1.54 ± 0.22	0.92–2.10	0.534
Septal E′/A′	1.6 ± 0.41	0.7–3.2	1.7 ± 0.32	0.85–3.5	0.554
Mitral annular E′/A′	2 ± 0.2	1.1–2.2	1.9 ± 0.1	1.2–2.5	0.62
Tricuspid annular S′ (cm/s)	7 ± 2	6–12	8 ± 1.4	6–13	0.625
Tricuspid annular E′ (cm/s)	6 ± 2	4–10	8 ± 1.4	6–12	0.04*
Tricuspid annular A′ (cm/s)	4 ± 1.2	4–8	5 ± 1.1	3–8	0.631
Septal S′ (cm/s)	8 ± 1	7–10	9 ± 2	6–11	0.541
Septal E′ (cm/s)	5 ± 1	3–7	8 ± 2	6–12	0.03*
Septal A′ (cm/s)	3 ± 1	2–4	4 ± 1.4	2–6	0.233
Mitral annular S′ (cm/s)	6 ± 2	5–8	7 ± 2	5–10	0.321
Mitral annular E′(cm/s)	6 ± 1.3	5–8	8 ± 2	6–10	0.03*
Mitral annular A′(cm/s)	3.2±1.1	2–4	4.2 ± 1.8	3–8	0.7
Mitral E(cm/s)	83±12	70–120	77 ± 10	65–110	0.88
Mitral A(cm/s)	65±10	50–90	64 ± 8	55–85	0.77
Tricuspid E(cm/s)	79±9	66–92	71 ± 6	50–92	0.66
Tricuspid A(cm/s)	52±8	40–62	55 ± 5	42–75	0.642
Mitral annular E/E′	13±3	9–14	9.6 ± 2	8–10	0.04*
Septal annular E/E′	16.6±2	12–19	9.4 ± 3	7–10	0.02*
Tricuspid annular E/E′	13±2	10–18	8.8 ± 2	5–9	0.02*
MPI RV by TDI	0.46± 0.2	0.17– 1.04	0.29 ± 0.05	0.19–0.40	< 0.001*
MPI (mitral annular) by TDI	0.50± 0.2	0.16– 1.00	0.33 ± 0.04	0.25–0.44	< 0.001*
MPI (septal) by TDI	0.49±0.02	0.32–0.6	0.34 ± 0.06	0.22–0.39	< 0.001*

BMI body mass index, *TAPSE* tricuspid annular plane systolic excursion, *FS fraction shortening*, *EF* ejection fraction, *ESPAP* estimated systolic pulmonary artery pressure, *RV* right ventricle, *LV* left ventricle, *MPI* myocardial performance index, *TDI* Tissue Doppler imaging
* Significant at *P* value ‹ 0.05

affection ≥ 0.6) and 21 subjects had abnormal LV MPI (11 severe affection ≥ 0.6). Thirty percent (30%) of the cases had affected lateral E/E′ and 47.5% had affected septal E/E′ of the left ventricle when compared to controls. The grading results of diastolic dysfunction were as follows: grade 0, 1, 2, 3 in 18, 15, 6, and 1 patients, respectively.

MPI LV and MPI RV showed statistically higher values in patients compared to controls (Fig. 1). The analysis of the echocardiographic parameters of the patients revealed a statistically significant negative correlation between oxygen saturation on the one hand and pulmonary artery pressure (PAP), MPIRV, and MPILV on the other hand (*P* value < 0.001, 0.028, and 0.004, respectively) (Table 2). There was no significant correlation between neither the age of the patient nor the duration of illness and MPI (LV or RV). However, after reviewing the patients with very high MPI, whether RV or LV, we found that all of them had longer duration of illness, lower SO2 (≤ 90%), and pulmonary hypertension .

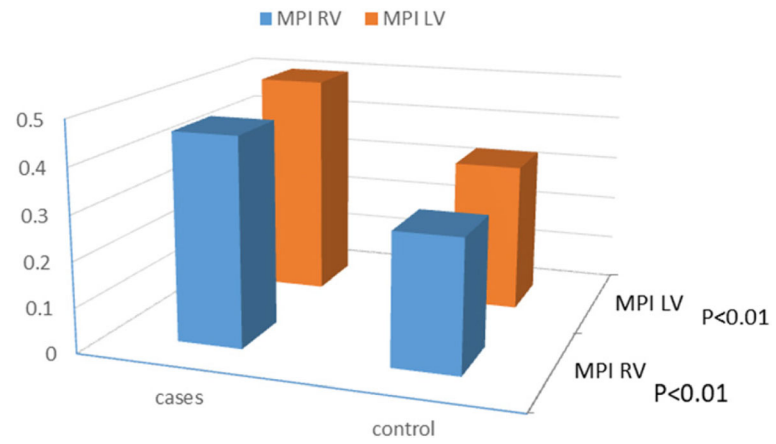

Fig. 1 Myocardial performance index in cases and control. LV: left ventricle, MPI: Myocardial performance index, RV: Right ventricle

Table 2 Correlation between oxygen saturation and echocardiographic parameters in the enrolled patients

		SO2 %
TAPSE	Correlation coefficient	0.144
	P value	0.376
	N	40
FS	Correlation coefficient	− 0.059
	P value	0.716
	N	40
EF	Correlation coefficient	− 0.051
	P value	0.755
	N	40
PAP	Correlation coefficient	− 0.555
	P value	< 0.001*
	N	40
Lateral E/E′	Correlation coefficient	− 0.246
	P value	0.126
	N	40
Septal E/E′	Correlation coefficient	− 0.108
	P value	0.507
	N	40
Average E/E′	Correlation coefficient	− 0.238
	P value	0.139
	N	40
MPI RV by TDI	Correlation coefficient	− 0.348
	P value	0.028*
	N	40
MPI LV by TDI	Correlation coefficient	− 0.446
	P value	0.004*
	N	40

TAPSE tricuspid annular plane systolic excursion, *FS* fraction shortening, *EF* ejection fraction, *RV* right ventricle, *LV* left ventricle, *PAP* pulmonary artery pressure, *MPI* myocardial performance index, *TDI* Tissue Doppler imaging
* Significant at *P* value ‹ 0.05

According to the ROC analysis results, TDI was a reliable tool in detecting global ventricular dysfunction with a sensitivity and specificity of 75%, 92.5% in RVMPI and 62.5%, 100% in LVMPI respectively (Fig. 2). Fifty-five percent (55%) (n = 22) of patients failed to perform PFT; 12 were Oxygen dependent and 10 were uncooperative. The results of the 18 subjects who successfully did PFT were: normal, restrictive, obstructive, and mixed in 2 (11.1%), 5 (27.8), 6 (33.3%), and 5 (27.8%) patients, respectively.

Discussion

Identification of patients with asymptomatic cardiac dysfunction could allow the application of pharmacological or non-pharmacological interventions that target reversing the heart's functional and structural abnormalities.

In this study, we found that the conventional echocardiographic parameters were not sensitive enough to differentiate between cases and controls regarding the detection of subclinical cardiac dysfunction. This is concordant with the findings by Akalin et al. [15] and D'Andrea et al. [16], who stated that the M-mode echocardiographic results were within normal range in their report.

In this study, FS and EF parameters were preserved as normal as controls; this could be explained by the overestimation of LV function if the calculations are based on the contractility of the basal segments of the heart only, because in this case the LV contracts sufficiently even if there is a significant systolic dysfunction [17]. We had only one patient with marked systolic dysfunction (FS = 22 and EF = 47). This patient might have developed such indices due to prolonged hypoxic myocardium. He had early disease onset and long duration of lung affection. Zhou et al.

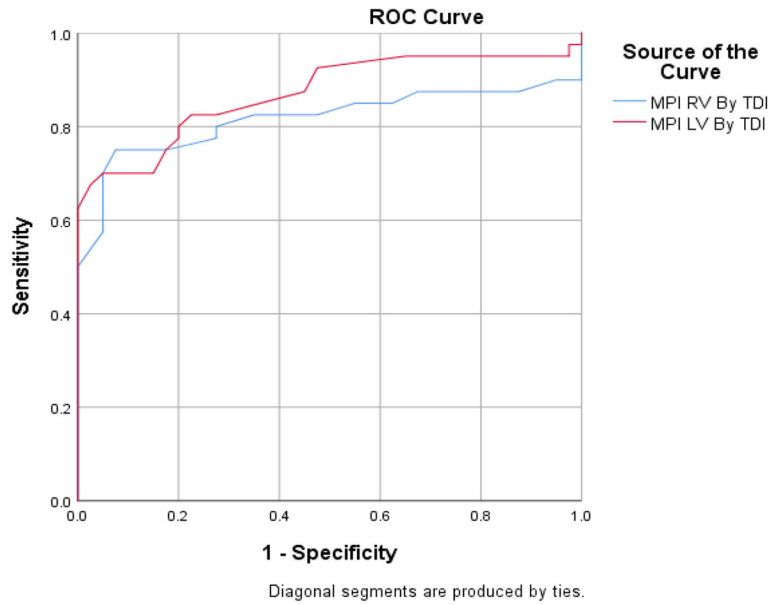

Fig. 2 ROC between cases and controls using tissue Doppler MPI. Receiver operating characteristic: ROC, MPI: Myocardial performance index, TDI: Tissue Doppler imaging

[18] reported recently the effects of intermittent and chronic hypoxia on the myocardium. This could be the explanation to such deterioration in this patient.

Tissue Doppler imaging is a technique which has been recently used in the assessment of myocardial dysfunctions without depending on the operator's expertise, and results can be retrieved immediately during examination. Moreover, TDI can assess both systolic and diastolic myocardial motions which render it a sensitive indicator of any myocardial motion dysfunction [19].

Our results showed that patients with CLD exhibit diastolic and systolic dysfunction as demonstrated by the effect of MPI over RV and LV. However, these dysfunctions did not appear when the patients were examined by 2D M-mode Echocardiography. This could have two possible explanations; the first is that the interventricular septum distorts towards the LV as the RV adapts to pressure or volume overload and increases in size and mass, and the second is that both ventricles operate as a syncytium, a phenomenon which is known as ventricular interdependence where the function of one ventricle can affect that of the other.

After the analysis of patients with very high MPI (≥ 0.6), whether RV or LV, we found that they had longer duration of illness, low SO2 (≤ 90% which indicates hypoxemia), diastolic dysfunction (6 of them had grade 2 diastolic dysfunction), and pulmonary hypertension.

Moreover, this study revealed a significant negative correlation between myocardial performance index and SO_2. This may suggest that chronic hypoxia could result in increased pulmonary vascular resistance and a secondary decreased LV filling. It may also have a direct effect on cellular metabolism that leads to impairment in the cardiac muscle relaxation and function which directly affects both RV and LV MPI [20]. This signifies that the negative inotropic effects of hypoxia might result in decreasing the systolic functions of both RV and LV [20]. A follow-up study of these patients after supplemental O2 therapy would be interesting to evaluate the reversibility of PH and diastolic dysfunction. Thirty percent (30%) of our cases had abnormal lateral E/E′ and septal E/E′ indicating various degrees of diastolic dysfunction.

MPI has proved to be better than conventional RV and LV systolic function parameters in the prediction of the prognosis and survival rate [16]. According to our ROC analysis results, TDI was a reliable tool in detecting global ventricular dysfunction with a sensitivity and specificity of 75%, 92.5% in RVMPI and 62.5%, 100% in LVMPI, respectively. This agrees with the data published by Elguindy and Abdelkader [21]. Therefore, increased RVMPI and LVMPI in CLD patients strongly indicate the presence of RV and LV dysfunctions even if the patients have normal RV and LV conventional systolic functions [22].

Conclusion

This study proved that the TDI can accurately detect subtle myocardial dysfunction in pediatric CLD patients, a data that can be missed when evaluating these children with conventional echocardiography.

Abbreviations
CLD: Chronic lung diseases; EF: Ejection fraction; FS: Fraction shortening; HRCT: High-resolution computed tomography; LV: Left ventricle; MPI: Myocardial performance index; PAP: Pulmonary artery pressure; PFT: Pulmonary function test; ROC: Receiver-operating characteristic; RV: Right ventricle; TAPSE: Tricuspid annular plane systolic excursion; TDI: Tissue Doppler imaging; TVI: Tissue velocity imaging

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Authors' contributions
ID: conception and design of study, collection of data, writing of manuscript, and final approval of the version to be published. FM shared in putting study design, echocardiographic assessment of the studied population, and final approval of the version to be published. AF shared in echocardiographic assessment of the studied population and final approval of the version to be published. DS collection of data, writing of manuscript, and final approval of the version to be published. RK shared in echocardiographic assessment of the studied population, writing of manuscript, and final approval of the version to be published. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate
The study was approved by Cairo University Ethical Committee ref. number I-031016. Participation was subject to verbal informed consent of caregivers.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Pediatric Pulmonology, Faculty of Medicine, Cairo University, Kasr Alainy, Street, Cairo 11562, Egypt. [2]Pediatric Cardiology, Faculty of Medicine, Cairo University, Kasr Alainy, Street, Cairo 11562, Egypt.

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