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Echocardiographic abnormalities and their correlation with bronchiectasis score in primary antibody deficiencies

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Background **Primary antibody deficiencies are characterized by defective antibody production and recurrent infections. Patients usually present with recurrent respiratory tract infections with consequent chronic pulmonary damage and bronchiectasis, which could potentially influence cardiac function. Our aim was to assess noninvasively the cardiac complications due to pulmonary disease in patients with primary antibody deficiency.**

Methods **A cross-sectional series of patients with primary antibody deficiency syndromes from our referral immunology center were recruited. Individuals undergoing high-resolution computed tomography (HRCT) and transthoracic echocardiography were reviewed.**

Results **Thirty primary immunodeficient patients aged 5–55 years of age (21 males and 9 females) were enrolled in this study. Half of the patients (50%) were found to have bronchiectasis in HRCT imaging. In echocardiographic examination, 20 patients (67%) had at least one abnormality; among which pulmonary hypertension was the most common (33%). Patients with bronchiectasis had higher pulmonary artery pressures and HRCT bronchiectasis score was strongly correlated with pulmonary artery pressure (regression $R = 0.59$, P value $= 0.001$).**

Conclusion **Echocardiographic evaluation of right ventricular function and noninvasive estimation of pulmonary artery pressure could have an important diagnostic role in the follow-up and therapeutic management of patients with primary immune deficiency.** ***J Cardiovasc Med*** **11:244–249 © 2010 Italian Federation of Cardiology.**

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Introduction

Primary antibody deficiencies (PAD) are the most common primary immunodeficiency diseases, characterized by defective antibody responses to pathogens [1–3]. The main manifestation of patients with PAD is recurrent bacterial infections that predominantly occur in the respiratory tract by pyogenic bacteria such as *Haemophilus influenzae*, *Moraxella catharrhalis* and *Streptococcus pneumoniae* [3–6]. The best-characterized PADs are X-linked agammaglobulinaemia (XLA), common variable immunodeficiency (CVID), and IgA deficiency (IgAD) [2].

Delay in diagnosis and inadequate management is associated with considerable morbidity. Recurrent pneumonias result in structural lung damage and even death from overwhelming infections [7–10]. Bronchiectasis and bronchial wall thickening are well recognized complications of PADs, ranging in prevalence between 17 and 76% [11–15]. Bronchiectasis may lead to cor pulmonale and pulmonary hypertension [16–18] that contribute to significant morbidity, exercise limitation and poor prognosis [19,20]. Early diagnosis and treatment of pulmonary hypertension associated with structural lung damage is essential in these patients. A noninvasive diagnostic technique utilizing echocardiography allows for detection of right ventricular dysfunction at an earlier stage and, in most cases, precludes the need for right heart catheterization [19–21].

Chest high-resolution computed tomography (HRCT) scan and echocardiography might be considered in all PAD patients with chronic chest symptoms to monitor parameters of lung and cardiac complications. The purpose of this study was to assess cardiac and pulmonary complications secondary to underlying chronic lung diseases in PAD patients, using echocardiography.

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Patients and methods

Patients

We enrolled 30 patients with PAD, including 22 CVID, six XLA, one IgAD, and one specific antibody deficiency (SAD). The diagnosis of CVID and XLA was made according to the diagnostic criteria of ESID (the European Society for Immunodeficiencies) and PAGID (the Pan-American Group for Immunodeficiency) [22]. The research protocol was approved by the Institutional Ethics Review Committee of our center. Informed consent was obtained from all the patients before any intervention. Clinical and laboratory data of each patient were obtained using a designed questionnaire.

High-resolution computed tomography scan

Bronchiectasis was recognized as bronchial dilatation, often with thickening of the wall. Bronchial dilatation was considered present when the internal diameter of a bronchus was greater than that of the adjacent pulmonary artery. The degree of bronchiectasis was assessed by HRCT scan and the bronchiectasis score of each patient was calculated according to the severity and/or the extent of nine morphological changes of the Bhalla system score [23]. The highest possible score was 25.

Echocardiography

For all selected patients with or without bronchiectasis, echocardiography (VingMed 750, operating at 3.5–5 MHz) was performed by pediatric cardiologists. In echocardiography, the following parameters were evaluated: right and left ventricular (RV and LV) dimensions both in systole and diastole, and interventricular septal and LV posterior wall dimensions. These parameters were considered abnormally high when their z values were more than 2 SDs above the normal mean values. LV and RV ejection fractions, LV fractional shortening (LVFS) and cardiac mass index were calculated from m-mode study of the long-axis view. We measured the ejection fraction of the RV in the parasternal long axis or four-chamber views like the m-mode measurement of LV ejection fraction (Teicholz).

From Doppler studies of the four heart valves, mitral E/A ratio, LV and RV deceleration times, isovolumic relaxation time (IVRT), and myocardial performance indices were obtained during three consecutive cardiac cycles. The aortic root and left atrial dimensions were measured in parasternal long-axis view. Systolic pulmonary artery pressure (SPAP) was estimated by adding right atrial pressure to the peak gradient of tricuspid regurgitation. Right atrial pressure was estimated in each patient according to the respiratory changes of caval dimension. When the caval respiratory change exceeded 50%, the assumed right atrial pressure was 5–10 mmHg; and when the dimension change was less than 50%, the assumed right atrial pressure was 10–15 mmHg. The right atrial pressure is normally between 5 and 12 mmHg [24–26]; Whenever SPAP was between 30 and less than 45 mmHg, mild pulmonary hypertension was diagnosed, and when it was between 45 and 60 mmHg, moderate hypertension was assumed. Right ventricular hypertrophy was diagnosed by echocardiography when the diastolic right ventricular wall thickness was at least 5 mm or RV end diastolic diameter at least 28 mm [27]. In younger patients, RV hypertrophy was diagnosed according to the electrocardiographic criteria and/or clinical signs (RV heave). Myocardial performance index was calculated according to the equation, previously described by Tei *et al.* [28]. The interval between atrioventricular valve closure and opening was defined as a, and the duration of ventricular ejection time as b. The Tei index was calculated by using the equation $(a - b/b)$ for both ventricles. Other abnormalities such as valvular regurgitations, pericardial effusion or possible presence of undiagnosed congenital defects were also recorded.

Statistical analysis

SPSS for Windows standard version 13 (SPSS Inc, Chicago, Illinois, USA) was used for statistical analysis. Results are expressed as mean (±standard deviation) for continuous variables. Group comparisons of echocardiographic values were made using an independent sample t-test. To compare qualitative data, the chi-square test was performed. Linear regression analysis was used to determine the correlation between echocardiographic variables and the bronchiectasis score. A value of P less than 0.05 was considered statistically significant.

Results

Thirty patients (21 males and 9 females), aged 5–55 years, with PAD were enrolled in this study (Table 1). Mean and standard deviation of the age and delay in disease diagnosis were 18.2 ± 12.1 and 5.4 ± 4.3 years, respectively. Half of the patients had bronchiectasis according

Table 1 Demographic characteristic and type of immune deficiency in the studied cohort

					Immunoglobulin (mg/dl)		
	Number	Male/female	Age (year), mean ± SD	Bronchiectasis	IgG	IgA	IgM
CVID	22	13/9	18.9 ± 13.9	11	264.95	21.00	38.77
XLA	6	6/0	17.0 ± 6.2	2	129.00	8.80	7.00
SAD	1	1/0	12	1	1250	197	82
IgAD	1	1/0	16	1	1353	0	47
Total	30	21/9	18.2 ± 12.1	15	275.86	24.24	36.64

CVID, common variable immunodeficiency; IgAD, IgA deficiency; SAD, specific antibody deficiency; XLA, X-linked agammaglobulinemia.

Table 2 Comparison of mean (±SD) echocardiographic parameters between the bronchiectatic and nonbronchiectatic patients

	Total ($n=30$)	Bronchiectasis mean (SD) ($n=15$)	Nonbronchiectasis mean (SD) ($n=15$)	P value
Age (year)	18.23	20.00 (12.37)	16.47 (12.04)	0.43
Male/female	21/9	11/4	10/5	0.69
Delay (year)	5.4	6.86 (4.96)	3.93 (3.01)	0.04*
RVDs Index (mm/m^2)	15.85	14.02 (3.71)	17.67 (9.08)	0.16
RVDd Index (mm/m^2)	19.88	17.07 (6.57)	22.67 (10.12)	0.08
LVDs Index (mm/m^2)	23.63	22.62 (3.94)	24.64 (5.85)	0.28
LVDd Index (mm/m^2)	34.92	34.66 (5.90)	35.18 (9.15)	0.85
IVS Index (mm/m^2)	7.54	8.48 (8.68)	6.61 (3.58)	0.45
LVPW Index (mm/m^2)	5.55	5.40 (1.11)	5.71 (1.52)	0.53
LVEF (%)	67.33	64.00 (10.04)	70.66 (7.13)	0.06
LVFS (mm)	32.31	30.35 (5.31)	34.27 (5.62)	0.06
RVEF (%)	39.41	34.03 (12.06)	44.80 (16.81)	0.04*
RV E/A ratio	1.44	1.40 (0.36)	1.48 (0.33)	0.53
RV dec time (ms)	169.23	172.85 (33.6)	165.00 (34.51)	0.56
LV dec time (ms)	162.00	157.33 (29.39)	166.66 (75.48)	0.66
RV IVRT (ms)	61.52	62.30 (24.88)	60.50 (26.71)	0.86
SPAP (mmHg)	26.47	34.06 (15.34)	18.86 (10.50)	0.004*
Aortic RD index (mm/m^2)	14.8	13.57 (8.24)	16.17 (6.74)	0.36
LAD Index (mm/m^2)	18.3	17.81 (10.97)	18.87 (8.32)	0.77
LA/AO	1.24	1.30 (0.45)	1.16 (0.22)	0.34
CMI (gr/m^2)	81.43	78.32 (26.90)	84.55 (23.85)	0.53
LV MPI	0.48	0.486 (0.09)	0.482 (0.18)	0.94
RV MPI	0.37	0.43	0.31 (0.15)	0.04*

CMI, cardiac mass index; dec time, deceleration time; IVRT, isovolumic relaxation time; IVS, interventricular septum; LA/AO, left atrial/aortic root diameter; LAD, left atrial diameter; LV, left ventricular; LVDd, diastolic LV diameter; LVDs, systolic LV diameter; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVPW, LV posterior wall thickness; MPI, myocardial performance index; RD, root diameter; RV, right ventricular; RVDd, diastolic RV diameter; RVDs, systolic RV diameter; RVEF, right ventricular ejection fraction; SPAP, systolic pulmonary artery pressure. * Statistically significant.

to the findings of HRCT scan. The diagnosis delay in the patients with bronchiectasis was significantly higher than others without bronchiectasis (Table 2).

Abnormal echocardiographic findings in each patient are shown in Table 3. Comparison of echocardiographic parameters between the bronchiectatic and nonbronchiectatic patients is demonstrated in Table 2. Of the 30 enrolled patients, 20 had at least one abnormal result. Left ventricular ejection fraction (LVEF) and fractional shortening were normal in all patients, except one: Case 26 had abnormally low systolic function consistent with

Table 3 Echocardiographic findings in individual patients

Patient	Echocardiographic findings	Bronchiectasis score
1	RV systolic dysfunction	0
2	Pericardial effusion, RV systolic dysfunction, RV diastolic dysfunction	7
3	RV diastolic dysfunction	3
4	Mild PR, moderate TR, RV dilatation and failure, Increased SPAP (60 mmHg)	11
5	Normal	0
6	Normal	6
7	Moderate TR, RV hypertrophy, Increased SPAP (60 mmHg)	4
8	Normal	0
9	Normal	0
10	Mild LV hypertrophy and septal hypertrophy, Increased cardiac mass	0
11	Normal	2
12	Increased cardiac mass and RV hypertrophy, Increased SPAP (38 mmHg)	7
13	Increased cardiac mass and RV hypertrophy, Increased SPAP (39 mmHg)	0
14	RV systolic dysfunction, RV hypertrophy and dilatation	0
15	Mild TR, RV hypertrophy, Increased SPAP (45 mmHg)	6
16	Normal	6
17	Mild TR, RV hypertrophy, RV failure, Increased SPAP (40 mmHg)	0
18	Normal	0
19	RV diastolic dysfunction, increased SPAP (34 mmHg)	0
20	RV diastolic dysfunction	0
21	RV diastolic dysfunction	7
22	Normal	3
23	RV diastolic dysfunction	10
24	RV dilatation, RV diastolic dysfunction, increased SPAP (46 mmHg)	10
25	Normal	0
26	RV systolic and diastolic dysfunction, LV systolic and diastolic dysfunction	0
27	Normal	0
28	RV diastolic dysfunction	0
29	Mild TR, increased SPAP (40 mmHg)	10
30	Mild TR, RV hypertrophy, RV diastolic dysfunction, increased SPAP (50 mmHg)	17

LV, left ventricular; PR, pulmonary regurgitation; RV, right ventricular; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.

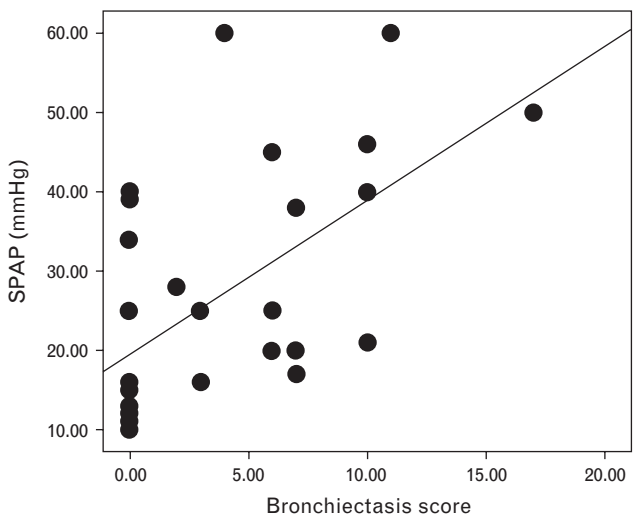
cardiomyopathy. The mean of these two systolic parameters was not statistically different between patients with and without bronchiectasis (*t*-test, $P = 0.06$). The mean of LV dimensions was also not statistically different between these two groups. RV dimensions were not different between the two groups, but RVEF was lower in the bronchiectatic group (*t*-test, $P = 0.04$). Eight patients had abnormalities consistent with RV diastolic dysfunction (according to the abnormal E/A ratio, IVRT or deceleration time in Doppler flow study of the tricuspid valve).

Ten patients had higher SPAP of more than 30 mmHg. Of those, five had mild hypertension. Moderate and severe pulmonary hypertension was found in three and two patients, respectively. Mean SPAP was higher in bronchiectatic patients than in the others (*t*-test, $P = 0.004$). In addition, there was a significant correlation between HRCT bronchiectasis score and SPAP (linear regression, $R = 0.59$, $P = 0.001$) (Fig. 1). Four patients in the bronchietatic group and three patients in the non-bronchiectatic group had right ventricular hypertrophy (Fisher exact test, P value $= 0.66$, Table 3). Left ventricular hypertrophy was identified in only one of our patients (Case 10) due to systemic hypertension. Furthermore, left ventricular systolic function was normal in all patients, except for Case 26 who had biventricular dysfunction (Table 3).

Discussion

Defective antibody production in primary antibody deficiencies causes clinical manifestations of recurrent upper and lower respiratory tract infections with consequent bronchiectasis and pulmonary hypertension. Early recognition of immunodeficiency, appropriate antibiotics and immunoglobulin replacement therapy are crucial to prevent progressive lung injuries and hence cardiac manifestation of cor pulmonale and pulmonary hypertension. Although there is not a consensus for the protective trough levels of IgG in different studies, it is suggested that if replacement therapy is instituted early, the onset of bronchiectasis, chronic sinusitis and other infections may be prevented [13,29,30].

Fig. 1



Linear correlation between systolic pulmonary artery pressure (SPAP) and high-resolution computed tomography (HRCT) bronchiectasis score (regression $R = 0.59$, P value $= 0.001$).

RV dysfunction is common in patients with cor pulmonale, particularly in those with low arterial oxygen saturation [19]. RV dysfunction plays an important role in the exercise limitation of patients with chronic lung diseases [20]. When present, it can increase disability and contribute to a higher mortality rate. Hence, its recognition and treatment may lead to prolonged survival and improved quality of life. In chronic lung diseases, remodeling of the vascular bed raises pulmonary vascular resistance (PVR) and contributes to the development of pulmonary hypertension. It has been demonstrated that hypoxemia has the greatest role in the pathogenesis of this remodeling [31]. Hypercapnea, endothelial vasoactive factors and acidemia are other contributory factors in the development of pulmonary hypertension [32].

The gold standard for the measurement of pulmonary hypertension is right heart catheterization, but this is invasive with the inherent risk of complications. Doppler echocardiography offers a noninvasive and relatively sensitive and specific assessment of pulmonary hypertension [33]. In patients with tricuspid regurgitation, SPAP can be estimated with reasonably good accuracy based on the velocity of the regurgitant jet. Moreover, by echocardiography the RV could be assessed by morphology, chamber dimension, wall thickness and also functionally by means of various conventional and tissue Doppler indices and tricuspid annular plane systolic excursion (TAPSE) [34].

Johnston *et al.* [16] showed echocardiographic abnormalities of right ventricle and pulmonary hypertension in patients with PAD associated with diagnostic delay and pulmonary complications. Our results also confirmed the positive correlation of diagnostic delay and right heart echocardiographic abnormalities such as the myocardial performance index, as well as the severity of pulmonary hypertension in this patient population.

Our findings also emphasize the positive correlation and the ability of myocardial performance index to assess global RV function in patients with pulmonary hypertension and higher bronchiectasis scores and lung injuries. When pulmonary hypertension develops, the value of this index increases due to both an increase in isovolumic contraction time and a decrease in right ventricular

ejection time. It reflects the combined effects of ventricular systolic and diastolic function [21]. Hence noninvasive echocardiographic assessment of pulmonary artery pressure and RV myocardial performance index could predict the severity of bronchiectasis and pulmonary involvement in PAD patients.

Left ventricular systolic dysfunction is less common in this patient population except in cases with severe pulmonary hypertension and hypoxemia. Moreover, left ventricular diastolic dysfunction may occur as a result of right ventricular pressure overload that is related to the geometric distortion of the left ventricle [35,36]. Another reason for impaired relaxation of both ventricles is hypoxemia, which may have a detrimental effect on myocardial energy production at the cellular level, causing impairment of intracellular calcium transport that is partly responsible for impaired relaxation in patients with cor pulmonale [37]. The right ventricular systolic loading in chronic RV pressure overload is associated with prolongation of LV isovolumetric relaxation and redistribution of LV filling from early to late diastole, with abnormality of Doppler transmitral flow pattern [38]. Our bronchiectatic patients showed a greater contribution of atrial contraction to the filling of the right ventricle: E/A ratio of 1.4 versus 1.48 in patients with and without bronchiectasis, respectively. However, we could not show any statistical difference in the pattern of ventricular diastolic function, either in the right or the left ventricle except for the RV myocardial performance index, according to the severity of lung injuries or bronchiectasis scoring. Moreover, cardiovascular evaluation of children with PAD by echocardiography can also diagnose any other causes of pulmonary hypertension, such as congenital cardiac anomalies.

Therefore, Doppler echocardiography seems useful and practical for detecting noninvasively the early signs of right ventricular dysfunction and pulmonary hypertension in patients with PAD. To determine the role of echocardiography for the assessment of cardiac abnormalities in patients with primary immunodeficiencies, a prospective study with larger sample sizes and inclusion of a broader range of lung disease severity would be required.

In conclusion, early diagnosis of PAD and regular follow-up of these patients is crucial for optimal management of replacement therapy and antibiotic prophylaxis to prevent disease progression. Hence, close follow-up with the noninvasive tool of echocardiography for the assessment of right-sided heart failure and the severity of pulmonary hypertension is recommended. This would have a great impact on the modification of new vasodilator combination therapy and consequently improve the exercise tolerance and functional class of the patients with cor pulmonale.

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