Right ventricular diastolic function in chronic obstructive lung disease

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ABSTRACT: Early detection of diastolic dysfunction in chronic obstructive lung disease (COLD) patients could have great prognostic value. Echocardiography has been shown to be a useful technique in studying left ventricular diastolic function. A noninvasive method of studying right ventricular diastolic function has not yet been reported.

Pulsed Doppler echocardiography was used to assess right ventricular diastolic function in three groups of subjects: Group I: 35 COLD patients with pulmonary hypertension; Group II: 32 COLD patients without pulmonary hypertension; and Group III: 18 control subjects. Ratios between peak atrial filling velocity (A) and peak early filling velocity (E) (A/E), deceleration half times of the right ventricular rapid filling wave (DHT), and the interval between pulmonary valve closure and tricuspid valve opening (isovolumic relaxation times) (Pc-To) were significantly different in Group I in comparison to Groups II and III. Sensitivity of A/E ratio and Pc-To were 82 and 77%, respectively, and specificity 90 and 72%, respectively; positive predictive values were 90 and 75%, respectively, and negative predictive value 82 and 74% respectively. The multiple correlation coefficient between A/E, acceleration time (ACT), DHT, Pc-To and mean pulmonary artery pressure was 0.75 for Groups I and II together.

In conclusion 2D echo-Doppler proved to be useful in evaluating right ventricular diastolic function in all hypertensive COLD patients, revealing a high correlation between diastolic parameters and mean pulmonary artery pressure in both normotensive and hypertensive COLD patients.
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Recent studies have demonstrated that diastolic abnormalities are one of the earliest manifestations of cardiac dysfunction and are frequently detected more easily than the abnormalities in systolic ventricular performance in cardiopulmonary diseases [1, 2]. The study of left ventricular diastolic function using a variety of techniques has revealed an impairment of the compliance and of the ventricular relaxation in coronary artery disease, hypertrophic cardiomyopathy, hypertensive heart disease, aortic valve disease, congestive cardiomyopathy, and pulmonary hypertension primary and secondary to chronic obstructive lung disease (COLD) [3, 4]. Despite growing interest in such techniques, none has been shown to be completely accurate and the precise assessment of intrinsic right ventricular (RV) diastolic function remains elusive [5–7]. The reason for this is that diastole is a complex sequence of interrelated events which are not completely understood.

Among the methods still available, echo-Doppler has been used with relative success by several investigators in the study of left ventricular diastolic dysfunction in cardiological diseases [8–12]. However, fewer studies have been conducted on right ventricular diastolic dysfunction which is especially associated with cardiopulmonary diseases [13].

The present study was undertaken to investigate the usefulness of Doppler echocardiography in determining right ventricular diastolic function in three groups of subjects: one group with COLD and pulmonary hypertension, one group with COLD without pulmonary hypertension, and a control group.

Patients and methods

Patients

The study sample considered 67 COLD patients who needed a right heart catheterization. An echo-Doppler was systematically performed. A mean pulmonary artery pressure of ≤20 mmHg was considered normal.

The patients were divided in two groups:
Group I: 35 patients, 33 males, 2 females, mean age 62±9 yrs (30–79 yrs), with COLD and pulmonary hypertension, mean pulmonary artery pressure (mPAP) 27.5±6.1 mmHg, (20–45 mmHg).

Group II: 32 patients, 29 males, 3 females, mean age 58±12 yrs (21–76 yrs), with COLD and without pulmonary hypertension, mPAP 14.3±4.6 mmHg (4–19 mmHg).

Nine patients from Group I and four patients from Group II were excluded because their recordings were not satisfactory. In these patients it was difficult to obtain the tricuspid flow velocities with a good spectral envelope. The rate of success of Doppler examination in Group I was 78% and in Group II was 88%. Group III: a control group of 18 normal subjects, all males, mean age 53±13 yrs (32–78 yrs), who were asymptomatic and showed no evidence of cardiovascular or pulmonary disease as confirmed by physical examinations.

At the time of the study, Group I and II patients were being treated with inhaled $beta_2$-agonist bronchodilators and theophylline. Some patients were also being treated with diuretics. No patient was undergoing domiciliary oxygen therapy. All patients (in Groups I and II) were in a stable clinical condition and sinus rhythm. The patients with clinical evidence of hypertensive, ischaemic, valvular (in particular severe tricuspid or pulmonary regurgitation) heart disease and neuromuscular disease were excluded from the study.

Informed consent was obtained from each subject studied.

Methods

All subjects underwent spirometric (Werner Gut Diffusion-Star FG 90) and haemogasanalytic (ABL 330 Radiometer) tests. M-Mode and two-dimensional echocardiograms and pulsed Doppler were performed with a Toshiba SSH40 scanner using a 2.5 MHz transducer. All subjects were examined in a supine position from a subcostal approach with the short axis view at the aortic valve level in order to see the RV outflow tract and the pulmonary valve leaflets.

The transducer was also positioned at the cardiac apex to obtain a four chamber view, whilst maintaining the Doppler beam as parallel as possible to the long axis of the RV inflow tract. In order to measure the tricuspid inflow velocity, the Doppler sample volume was placed in the right ventricle near the tricuspid orifice. The measurements were carried out at end-expiration. The tracing was recorded on a strip-chart simultaneously with an electrocardiogram at a paper speed of 50 mm·s⁻¹. Examinations were performed by a single examiner. Measurements were taken of the RV end-diastolic diameter (RVED) and the right atrium (RA) end-systolic diameter and RA area calculated by means of a computerized trace by the echocardiogram.

The isovolumic relaxation time, the interval from the pulmonary valve closing to the tricuspid valve opening (Pc-To interval), was also calculated. This time is the difference between the interval from the Q wave on the electrocardiogram (ECG) to the onset of diastolic tricuspid flow and the interval from the Q wave on the ECG to the end of systolic pulmonary flow. The Doppler recordings of trans-tricuspid flow from the cardiac apex have a characteristic biphasic appearance. Two distinct peaks representing early diastolic, or "passive" filling, velocities (Evel) and late diastolic, or atrial velocities (Avel) were clearly identified and measured along with their ratio (A/E). Acceleration time (ACT) (the interval between the beginning and the peak of the E wave) and deceleration half time (DHT) of early diastolic rapid filling were also measured. All measurements were obtained by averaging the values of five consecutive tricuspid and pulmonary flow velocities. In all subjects, the 2D echo-Doppler was performed one or two days before right heart catheterization.

All patients remained unsedated while undergoing right heart catheterization with a floating catheter (Grandjean) to evaluate pulmonary artery, right ventricle, and right atrium pressures.

Statistical analysis

The data were expressed as means and standard deviations. A multivariate analysis of variance of the nine echocardiographic variables between the three groups was performed. Moreover, the comparisons of Group II versus Group III and between Groups II plus III versus Group I were made. The same scheme of analysis was carried out on each of the nine echocardiographic data [14].

Multiple and single regression analyses were used to evaluate the relationships between the diastolic parameters and mean pulmonary artery pressure (mPAP).

For each echo-Doppler parameter sensitivity, positivity, positive and negative predictive values in detecting patients with pulmonary hypertension were calculated [15].

Results

Group means of the functional respiratory, haemogasanalytic, and haemodynamic parameters are shown in table 1. Tables 2 and 3 show the echo-Doppler RV systolic and diastolic parameters.

The multivariate analysis of echo-Doppler variables between the three groups proved highly significant (F=8.80 with 18 and 150 degrees of freedom (d.o.f.), p<0.0001). The comparison of Group II versus Group III had low significant difference (F=2.59 with 9 and 75 d.o.f., p=0.05), whereas the comparison of these two groups versus Groups I had high significant difference (F=21.62 with 9 and 75 d.o.f., p<0.00001).

The analysis of the single echocardiographic variables showed a similar result for the global test; in the test performed between Group II and III peak early diastolic filling velocity (Evel), ratio between peak atrial filling velocity (A) and peak early filling velocity (E) (A/E), acceleration time and isovolumic relaxation time did not prove significant.

Table 1. – Clinical, respiratory and haemodynamic data

		Groups		
		I n=35	II n=32	III n=18
Age	yrs	62±9	58±12	53±13
Sex	M/F	16/19	18/14	14/4
HR	b·min⁻¹	73.1±12.3	68.1±9.9	67.8±14.1
VC	l	2.12±0.72	2.91±1.06	3.64±0.98
FEV₁	l·s⁻¹	0.93±0.52	1.37±0.83	3.03±0.84
FEV₁/VC	%	42.9±14.0	44.5±16.5	88.0±14.0
Po₂	kPa	7.2±1.4	9.6±1.7	11.5±1.1
Pco₂	kPa	6.4±1.1	5.3±8.80	4.6±0.1
PAP syst	mmHg	41.2±9.0	23.5±6.8	-
PAP diast	mmHg	17.4±7.8	9.0±4.8	-
mPAP	mmHg	27.5±6.1	14.3±4.6	-
RVP syst	mmHg	46.0±5.6	24.0±4.5	-
RVP diast	mmHg	4.7±3.0	3.9±2.0	-
RAP syst	mmHg	6.5±2.6	5.6±2.5	-
RAP diast	mmHg	2.5±1.8	1.6±1.1	-
mRAP	mmHg	4.0±2.2	3.4±2.2	-

HR: heart rate; VC: vital capacity; FEV_1: forced expiratory volume in one second; FEV_1/VC: forced expiratory volume at first second on vital capacity; PAP: pulmonary arterial pressure; diast: diastolic; syst: systolic; RVP: right ventricular pressure; RAP: right atrial pressure; Po_2: oxygen tension; Pco_2: carbon dioxide tension; m: mean. Mean±SD.

Table 2. – Right ventricular systolic parameters

Systolic parameters	Groups				
	I n=35		II n=32		III n=18
RPEP ms	129±27	*	116±21	NS	110±18
RVET ms	281±32	**	304±38	NS	306±27
RPEP/RVET	0.46±0.12	°	0.30±0.08	NS	0.38±0.08
ACT ms	93±15	°°°	140±30	NS	154±19
ACT/RVET	0.33±0.07	°°°	0.45±0.08	NS	0.50±0.05

RPEP: right pre-ejection period; RVET: right ventricular ejection time; ACT: acceleration time; NS: nonsignificant. *: $p<0.05$; **: $p<0.01$; °: $p<0.005$; °°: $p<0.001$; °°°: $p<0.0001$. Mean±SD.

Table 4 shows the sensitivity, specificity, positive and negative predictive values of the echo-Doppler indices analysed for the diagnosis of pulmonary hypertension.

The mean value of peak late diastolic or atrial filling velocity (Avel) and (A/E) ratio were significantly different in Group I patients from those of Groups II and III. The sensitivity of the A/E ratio in detecting patients with pulmonary hypertension was 82%, the specificity was 90%, the positive predictive value was 90% and negative 82%.

Mean isovolumic relaxation time (sensitivity 77%, specificity 72%, positive predictive value 75%, negative predictive value 74%) and mean deceleration half

time of the tricuspid inflow velocities were in the normal range in the control Group and in normotensive patients and changed significantly in hypertensive patients. The ACT of the tricuspid inflow velocity did not change in the analysis made between Group I and Group II but it was significantly different between Group I and Group III. The right ventricle end-diastolic diameter (sensitivity: 94%, specificity: 81%, positive predictive value: 84% and negative: 93%), right atrium diameter and right atrium area were significantly greater in Group I in comparison to subjects from Group II and Group III (table 4).

Table 3. – RV diastolic and cardiac parameters

Diastolic parameters	Groups				
	I n=35		II n=32		III n=18
RVED mm	38.0±8.7	°°	30.4±5.5	NS	27.1±4.1
Evel ms	0.75±0.20	NS	0.84±0.17	NS	0.93±0.27
Avel ms	0.92±0.23	°°	0.67±0.15	NS	0.73±0.16
A/E	1.27±0.31	°°	0.82±0.22	NS	0.90±0.18
DHT ms	104.7±21.4	°°	79.3±20.4	NS	0.83±19.2
ACT ms	97.5±14.5	NS	106.7±28.4	NS	115.8±35.6
Pc-To ms	65.0±20.8	°°	32.6±23.8	NS	34.1±25.0

RV: right ventricle; RVED: right ventricle end-diastolic diameter; Evel: peak early diastolic filling velocity; Avel: peak late diastolic or atrial filling velocity; A/E: ratio between peak atrial filling velocity (A) and peak early filling velocity (E); DHT: deceleration half time; ACT: acceleration time; Pc-To: the interval between the pulmonary valve closure (Pc) and the tricuspid valve opening (To) (isovolumic relaxation time). *: $p<0.05$; **: $p<0.01$; °: $p<0.001$; °°: $p<0.0001$. Mean±SD.

For combined Group I and II values, simple correlation coefficients between the A/E ratio and the atrium diameter and area were 0.65 ($p<0.0001$) and 0.57 ($p<0.001$), respectively. Significant simple correlations were also found between DHT and right atrium diameter r:0.57 ($p<0.001$), and between DHT and right atrium area r:0.47 ($p<0.005$). The simple correlation coefficients between mean pulmonary artery pressure and Avel, A/E ratio (fig. 1), deceleration time, and isovolumic relaxation time were 0.45 ($p<0.005$), 0.63 ($p<0.0001$), 0.51 ($p<0.0005$), and 0.62 ($p<0.0005$), respectively. The other parameters showed nonsignificant correlations with mean pulmonary artery pressure. Figure 2 shows the multiple correlation coefficient between isovolumic relaxation time, A/E ratio, acceleration and deceleration half times (mPAP predicted by these values) and mPAP (observed by right heart catheterization) was 0.75 ($p<0.0001$). The multiple regression equation was mPAP=3.22±8.49, A/E±0.10, Pc-To - 0.034, ACT + 0.080 DHT.

Table 4. – Sensitivity, specificity, positive and negative predictive values of echo-Doppler parameters (cut-off values for tests positivity)

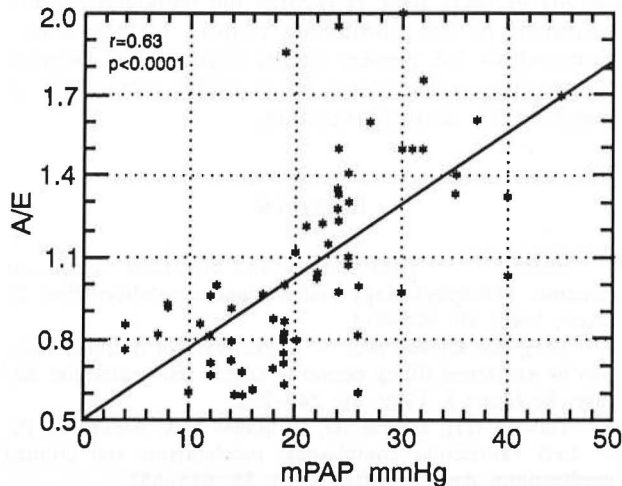|	RVED >26 mm	Evel >90 ms	Avel >70 ms	A/E >1	DHT >80 ms	ACT <110 ms	Pc-To >50 ms
Sensitivity	94	82	85	82	34	11	77
Specificity	81	43	45	90	18	40	71
Positive predictive value	84	61	62	90	31	17	75
Negative predictive value	92	70	75	82	20	29	74

For abbreviations see legend to table 3.

Fig. 1. – Correlation between A/E ratio and mean pulmonary artery pressure. Note that when A/E value >1.0 all mPAP are >19 mmHg. Some hypertensive patients present A/E valves below 1.0 A/E: ratio between peak atrial filling (A) and peak early filling (E) velocities. mPAP: mean pulmonary artery pressure.
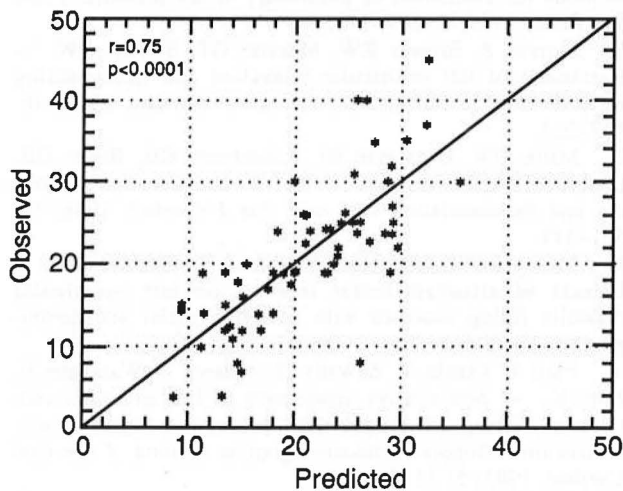
Fig. 2. – Correlation between mPAP predicted by A/E ratio, Pc-To, deceleration time, acceleration time, and mPAP observed by right heart catheterization (see text for details). Pc-To: interval between pulmonary valve closure and tricuspid valve opening (isovolumic relaxation time). For further abbreviations see legend to figure 1.

Discussion

Three factors comprise the ventricular diastolic function: the muscle stiffness that represents the resistance to myocardial stretching, the ventricular relaxation and the chamber stiffness defined as a change in pressure relative to a change in chamber volume. The opposite to this relationship is chamber compliance. The clinical phases of diastole are: a) the isovolumic relaxation time; b) the rapid filling phase; c) the slow filling phase; and d) the atrial contraction. Studies of left ventricular (LV) diastolic function and Doppler mitral inflow parameters have demonstrated that the isovolumic relaxation time depends not only on the rate of relaxation but also on the aortic pressure and left atrial pressure. The E wave velocity, point b, is affected not only by the rate of relaxation, but also by the left atrial and pre-load pressure and the presence of mitral regurgitation [6]. It was also reported that atrial contraction velocity (Avel) is affected by age [7], heart rate, rate of early filling, and atrioventricular interval [8].

These abnormalities in diastolic function have been shown in noninvasive studies of patients with coronary artery disease [9], hypertrophic cardiomyopathy [10], and systemic hypertension [11]. Left and right ventricular dysfunction has been reported in dilated cardiomyopathy [12]. It thus appears that the determining rule for calculating the isovolumic relaxation time, early and late diastolic peak flow velocities and early diastolic deceleration half-time is important to understand the interrelation between diastolic and systolic function, especially in cardiopulmonary patients [13].

In COLD patients with cor pulmonale several echocardiographic approaches are used to evaluate PAP. The M-Mode and two-dimensional echocardiography are useful to evaluate the RV wall hypertrophy and RV dilatation associated with pulmonary hypertension [16, 17]. In the past the pulmonary valve morphology was also correlated with PAP [18]. Unfortunately, these methods had low correlation with PAP.

Some authors have used pulsed Doppler ultrasound to measure the isovolumic relaxation time [19] and right ventricular systolic time intervals [20] and flow velocity in the pulmonary artery or in the RV outflow tract. In these studies, the alteration in acceleration time (AT), in the AT/RV ejection time ratio showed the best correlation with PAP [21, 22]. Continuous Doppler ultrasound techniques are used to measure the tricuspid flow velocity when tricuspid valve insufficiency is present [23]. In this case, the systolic pressure gradient between the RV and right atrium is measured by calculating the maximum leak velocity by means of the Bernouilli equation. The RV systolic pressure or systolic pulmonary artery pressure is measured by adding to this gradient the right atrial pressure obtained clinically.

In COLD patients with pulmonary hypertension, abnormalities of the inferior vena caval flow suggesting RV compliance impairment have been reported [24]. RV radionuclide angiography in COLD patients with pulmonary hypertension has been reported to show a decrease in the right atrial early diastolic emptying rate suggesting an alteration in RV compliance [25]. In the present echocardiographic study COLD patients with medium or severe tricuspid regurgitation are excluded and RV filling parameters are used to assess diastolic function. The patients with pulmonary hypertension revealed lower E velocities and higher A velocities. This suggests that an A/E ratio >1, as this has high sensitivity, specificity, positive and negative predictive values, is the best index to discriminate hypertensive from normotensive COLD patients as well as from control subject.

All of the patients with COLD and low pulmonary artery pressure had a normal right atrial pressure. The normality of the right atrial pressure excluded the presence of the diastolic dysfunction with a normal A/E ratio, according to the concept of normalized or hypernormal ratio with a increased atrial pressure demonstrated by several authors in the left ventricle. Hypertensive patients showed a lengthening of the isovolumic relaxation time interval, due to an overload of RV pressure and a low pressure gradient between RA and RV. This index also shows good sensitivity, specificity, positive and negative predictive values. The deceleration time was increased in hypertensive COLD patients which indicated prolonged myocardial relaxation [25]. The increase in the peak velocity of atrial filling indicated increased atrial contribution to ventricular filling. These parameters show that RV diastolic function was altered and was compensated by an increase in atrial filling.

Hypertensive patients also demonstrated larger right ventricle and right atrium diameters and areas in comparison with normotensive patients and the control subjects. The right ventricle shows high sensitivity, specificity, positive and negative predictive values. In Groups I and II there was a significant correlation between these right cardiac parameters and the A/E ratio and DHT. The patient parameters which showed a high correlation directly with mPAP included A/E ratio, deceleration half time, acceleration time and isovolumic relaxation time, with the multiple correlation coefficient between these indices and mPAP being 0.75. The mechanisms of the impairment of RV diastolic function in COLD patients needed further clarification. It is probable that RV wall hypertrophy plays an important role in the pathogenesis of RV impairment, but measurement of RV wall thickness is difficult since it is frequently indistinct on the echocardiogram. Also, the hypoxaemia increasing the pulmonary arterial resistance could be important but in our patients a large oxygen tension (Po_2) scattering was present and this excludes the possibility of evaluating the correlation between Po_2 and A/E.

The COLD patients with pulmonary hypertension also showed modifications of some systolic echocardiographic parameters (table 2). Therefore, in COLD patients with cor pulmonale (Group I), a diastolic dysfunction was found to be associated with systolic abnormalities.

This confirms the previously reported finding that diastole represents a complex interplay of multiple factors including RV and RA systolic and diastolic properties, sympathetic tone, and loading conditions and that the pattern of filling may not reflect all of the diastolic properties of the right ventricle. The implications of these data as regards the pathogenesis and treatment of cor pulmonale require further study. Nonetheless, the present results suggest that Doppler echocardiography could be a useful technique in assessing RV diastolic function.

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