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Respiratory changes in the E/A wave pattern can be an early sign of diastolic dysfunction: An echocardiographic long-term follow-up study

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
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Summary

Background: The left ventricular filling pattern may show changes during respiration, which are generally used in the diagnosis of diastolic dysfunction. The clinical importance of the respiratory E/A wave pattern change has been investigated in a limited number of studies. The aim of the present study was to assess the diastolic function of hypertensive patients with respiratory changes in mitral flow over a long-term follow-up period.

Material/Methods: Our study included 107 newly diagnosed and untreated hypertensive patients (49 males; mean age, 46±10 years) with respiratory changes during transthoracic echocardiography (TTE). In addition, the patient group was classified into 2 groups according to the change in E/A pattern by the Valsalva maneuver. After a mean follow-up period of 44±7 month, 90% of the hypertensive patients and the entire control group were re-examined.

Results: Relaxation abnormalities developed in 84% of the patients (58/80) in the Valsalva-positive group after the follow-up period. The frequency of relaxation abnormalities was 60% in the Valsalva-negative group and 3.1% in the control group ($p<0.001$). Based on multivariate regression analysis, the echocardiographic predictors of the development of relaxation impairment were mitral E velocity, A velocity, deceleration time, isovolumetric contraction time, E/E' ratio, and the presence of respiratory change. The most important parameter for the development of an abnormal relaxation pattern was the presence of respiratory change after adjustment according to the changes with the Valsalva maneuver.

Conclusions: Respiratory change in mitral flow can be evaluated as an early sign of diastolic dysfunction in patients with hypertension.

key words: **respiratory changes • hypertension • diastolic dysfunction • Doppler echocardiography**

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Background

One of the earliest manifestations of hypertensive heart disease is left ventricular diastolic dysfunction, followed by left ventricular hypertrophy. Doppler echocardiography has become the primary non-invasive tool for the identification of left ventricular diastolic dysfunction [1,2]. The early diagnosis of diastolic dysfunction in asymptomatic patients may provide an opportunity to manage the underlying disease and to prevent progression to heart failure. However, in some hypertensive patients, routine echocardiographic examination may not reveal any abnormalities (either diastolic dysfunction or significant left ventricular wall thickening) in spite of a documented blood pressure elevation for several months or years.

Pulsed Doppler echocardiographic examination of mitral inflow has been widely used to evaluate left ventricular diastolic function. However, it is well-known that diastolic filling indices are highly preload-dependent [3,4]. Preload alterations or other maneuvers (eg, Valsalva maneuver) may significantly change the mitral inflow pattern [5,6]. In some patients, a reversal in the mitral flow E/A ratio is observed during spontaneous respiration [7,8]. The E and A waves show an abnormal relaxation pattern during inspiration and a normal filling pattern during expiration. This phenomenon is considered as an early sign of diastolic dysfunction; however, its clinical importance has only been investigated in a limited number of studies. The aim of the present study was to assess the diastolic function of hypertensive patients with respiratory changes in mitral flow during a long-term follow-up period.

Material and Methods

Patients

The study included 137 hypertensive patients admitted to our university clinic with the diagnosis of new onset and untreated essential hypertension with respiratory reversal in E/A flow. The control group consisted of 32 normotensive subjects with normal cardiovascular histories, physical examinations, and normal diastolic function without respiratory changes in mitral flow. The study protocol was approved by the local Ethics Committee and all subjects gave written informed consent to participate in the study.

All patients underwent a thorough clinical, physical, and electrocardiographic examination. Patients with clinical findings suggesting heart failure (n=5), arrhythmic events (n=6), significant valvular disease (n=12), and coronary artery disease (n=7) were excluded from the study. As a result, 107 patients (49 males and 58 females) were evaluated.

Methods

Echocardiographic examination of the patients and the controls was performed with a Vivid 7 ultrasound machine (GE Medical Systems, Horten, Norway) using a broadband transducer. Evaluation of the patient group was performed at the time of entry into the study in order to detect the presence of end-organ disease and to prevent the effect of antihypertensive treatment. The left ventricular end-diastolic dimension (LVDd) and wall thickness (interventricular septum [IVS] and posterior wall [PW]) were measured from the parasternal long axis view according to the guidelines of the American Society of Echocardiography [9]. The left ventricular mass (LVM) was calculated by the Devereux formula [10]. The left ventricular mass index (LVMI) was determined by dividing the LVM by body surface area. Left ventricular hypertrophy was defined as a LVMI >134 g/m^2 in males and >110 g/m^2 in females [11].

A color-guided pulsed Doppler echocardiographic examination was performed from the apical 4-chamber view, placing a sample volume at the tips of the mitral leaflets. Echocardiographic studies were performed under spontaneous respiration in all subjects. The early diastolic peak flow velocity (E velocity), late diastolic peak flow velocity (A velocity), E velocity deceleration time (DT), isovolumetric relaxation time (IVRT), and isovolumetric contraction time (ICT) were measured and the ratio of E/A was calculated at end-inspiration and end-expiration. An E/A ratio <1.0 was accepted as diastolic dysfunction.

The diastolic inflow propagation velocity (PV) was also measured at end-inspiration and end-expiration. At Doppler color flow mapping, color gain was set at sub-saturation levels. Adjustments were made to obtain the longest column of color flow of the left ventricular inflow. Then, an M-mode cursor was positioned through the center of the inflow with the cursor line in parallel with the inflow jet. The maximum detectable mean velocity moving toward the transducer was lowered serially until the first isovelocity line of the rapid filling flow wavefront could be clearly identified. Then, the PV was measured as the slope of this isovelocity line segment.

The pulsed-wave tissue Doppler echocardiography (PW-TDE) recordings of peak early (E') and late (A') diastolic mitral annular velocities were obtained in apical 4- and 2-chamber views by placing the PW-TDE sample volume at the septal, lateral, anterior, and inferior sides of the mitral annulus while aligning the long-axis motion of the mitral annulus along the direction of the ultrasound beam. To obtain optimal recordings, all filter settings and gains were adjusted to minimize noise and to eliminate signals produced by the transmitral flow.

The patients and controls were taught how to perform the Valsalva maneuver and were asked to strain for at least 10 seconds. Measurements were repeated at the straining phase of the maneuver. An adequate Valsalva maneuver was defined as a >10% reduction in maximal E wave velocity from baseline [12]. Patients with an inadequate response repeated the maneuver 2 to 3 times until the best recording could be obtained. Subjects in whom the E to A ratio decreased to <1.0 after the maneuver were defined as Valsalva-positive and patients in whom the E to A ratio remained >1.0 were defined as Valsalva-negative.

After the follow-up period hypertensive patients and the controls were re-examined with echocardiography. The frequency of diastolic dysfunction was compared between the patient and control groups.

Statistical analysis

All analyses were performed using SPSS for Windows (version 11; SPSS Inc., Chicago, IL, USA). Data are expressed as the mean value and 1 standard deviation. Clinical and

Table 1. Baseline characteristics of the patients and the controls.

	Hypertensive patients	Controls	*p*
Age (years)	46±10	39±7	<0.001
Gender (F/M)	58/49	21/11	NS
Body mass index (kg/m^2)	28±5	27±5	NS
Smoking	28 (26)	10 (31)	NS
Diabetes mellitus	12 (11)	3 (9)	NS
Systolic blood pressure (mmHg)	183±20	120±8	<0.001
Diastolic blood pressure (mmHg)	103±10	78±5	<0.001
IVS (mm)	9.2±1.0	8.6±0.9	<0.001
PW (mm)	9.0±0.9	8.4±0.8	<0.001
LVDd (mm)	48.9±3.4	46.8±3.2	0.003
LA (mm)	36±3	35±3	0.02
LVMI (g/m^2)	98±19	86±16	<0.001
EF (%)	71±4	71±5	NS
FS (%)	40±4	40±4	NS

The results are expressed as mean ±SD or n (%). F – female; M – male; NS – not significant; IVS – interventricular septum; PW – posterior wall; LVDd – left ventricular end-diastolic dimension; LA – left atrium; LVMI – left ventricular mass index; EF – ejection fraction; FS – fractional shortening.

echocardiographic findings of the patient and control groups were compared with an unpaired 2-sample t test or a Mann-Whitney U test. Non-parametric variables were compared with a chi-square test. In subjects who performed the Valsalva maneuver, data before and after the maneuver were compared with a paired samples *t* test for variables with a Gaussian distribution or the Wilcoxon signed rank test for variables with a non-Gaussian distribution. A *p* value <0.05 was accepted as statistical significance.

Intra-observer variability

All echocardiographic studies and measurements were performed by the same cardiologist (T. S.). The intra-observer variability was as follows: r=0.98 for Doppler measurements; r=0.96 for PV measurements; and r=0.98 for PW-TDE measurements.

Results

The demographic and clinical characteristics, as well as echocardiographic parameters of 107 hypertensive patients and 32 healthy volunteers, are presented in Table 1.

The age, baseline blood pressure, and IVS, PW, LVDd, left atrium (LA), and LVMI values were higher in the hypertensive group compared to the control group.

Table 2. Pulsed-wave Doppler findings at end-expiration and end-inspiration of the patients and controls.

	Hypertensive patients	Controls	p
	Mean ±SD	Mean ±SD	
End-expiration			
E (cm/s)	0.81±0.14	0.87±0.16	0.04
A (cm/s)	0.70±0.13	0.67±0.11	NS
E/A	1.16	1.3	0.001
DT (ms)	198±20	181±16	0.001
IVRT (ms)	90±7	86±7	0.005
PV (cm/s)	409±58	470±47	0.001
End-inspiration			
E (cm/s)	70±16	88±18	<0.001
A (cm/s)	80±15	66±14	<0.001
E/A	0.93±0.74	1.35±0.25	0.002
DT (ms)	234±22	197±21	<0.001
IVRT (ms)	108±7	94±7	<0.001
Valsalva maneuver			
E (cm/s)	68±19	83±18	<0.001
A (cm/s)	80±18	67±14	<0.001
E/A	0.92±0.69	1.25±0.24	0.009
DT (ms)	274±39	216±13	<0.001
IVRT (ms)	121±12	100±7	<0.001

SD – standard deviation; NS – not significant; E – early diastolic peak flow velocity; A – late diastolic peak flow velocity; DT – deceleration time; IVRT – isovolumetric relaxation time; PV – propagation velocity.

The pulsed-wave Doppler findings at end-expiration and end-inspiration of patients and controls are summarized in Table 2.

While the E and PV values at end-expiration were significantly lower in the hypertensive patients compared to the controls, the A, E/A, DT, and IVRT values were significantly higher. The E and PV values at end-inspiration were significantly lower in the hypertensive group compared to the control group; however, the A, E/A, DT, and IVRT values were significantly higher. The E and E/A values in measurements during the Valsalva maneuver were significantly lower in the hypertensive group compared to the control group, while the A, DT, and IVRT values were significantly higher. The mitral annulus TDE values are presented in Table 3.

A significant difference was found between the parameters of the hypertensive and control groups. The E'/A' values were significantly lower in the hypertensive group compared to the control group in the 4 measurement regions, and the septal and inferior mitral annulus values were <1.0.

Table 3. The pulsed-wave tissue Doppler echocardiography findings of the patients and controls.

	Hypertensive patients	Controls	p
	Mean ±SD	Mean ±SD	
Lateral mitral annulus			
E′	0.15±0.03	0.18±0.03	<0.001
A′	0.14±0.03	0.13±0.03	NS
E′/A′	1.20±0.30	1.50±0.20	<0.001
Septal mitral annulus			
E′	0.13±0.03	0.16±0.02	<0.001
A′	0.14±0.03	0.12±0.02	0.003
E′/A′	0.97±0.30	1.30±0.20	<0.001
Anterior mitral annulus			
E′	0.14±0.03	0.18±0.03	<0.001
A′	0.14±0.03	0.12±0.02	0.03
E′/A′	1.10±0.30	1.50±0.30	<0.001
Inferior mitral annulus			
E′	0.30±0.02	0.17±0.03	<0.001
A′	0.50±0.02	0.13±0.02	<0.001
E′/A′	0.90±0.20	1.30±0.20	<0.001

SD – standard deviation; NS – not significant; E′ – peak early diastolic mitral annular velocity; A′ – peak late diastolic mitral annular velocity.

After a mean follow-up period of 44±7 months, 90% of the hypertensive patients (n=96) and the entire control group were re-examined with echocardiography. The results are presented in Table 4.

Relaxation abnormalities developed in 84% of the patients (58/80) in the Valsalva-positive group after the follow-up period. The frequency of relaxation abnormalities was 60% (6/10) in the Valsalva-negative group and 3.1% (1/32) in the control group (p<0.001). Based on multivariate regression analysis, the echocardiographic predictors of the development of relaxation impairment were mitral E velocity, A velocity, DT, ICT, E/E' ratio, and the presence of respiratory change. The most important parameter for the development of an abnormal relaxation pattern was the presence of respiratory change after adjustment according to the changes with the Valsalva maneuver.

Discussion

Left ventricular diastolic dysfunction (LVDD) is a preliminary finding in many cardiac disorders and diastolic dysfunction is a significant cardiac finding, even if the patient has normal left ventricular systolic function [13]. The predominant role of arterial hypertension in the development of diastolic heart failure was first noted in the Framingham study [14]. Detection of LVDD, which is an early sign in preventing heart failure in hypertensive patients, is especially important in those who are asymptomatic. Several diagnostic guidelines and echocardiographic parameters are used for the detection of left ventricular diastolic functions. The diagnosis of diastolic dysfunction can sometimes be missed due to variability in guidelines or echocardiographic parameters [15]. Owing to certain limitations and/or advantages of these parameters, it is recommended that patients be assessed by more than 1 parameter, also taking clinical features into account [16–19].

There are several physiologic variables that affect diastolic functions and may lead to diagnostic difficulties by affecting Doppler echocardiography parameters [20]. Most of the current information about the effects of various physiologic conditions, including respiration on echocardiographic parameters, comes from studies conducted in healthy volunteers or experimental animal studies [8,21–33]. The effect of respiration in patients with diastolic dysfunction has yet to be defined. In the current study we evaluated respiratory change in mitral flow as an early sign of diastolic disfunction in patients with hypertension by pulsed-wave Doppler and tissue Doppler echocardiography.

Although the exact prevalence of diastolic abnormalities in the normal population is not known, diastolic dysfunction has been reported in 3% of the population by echocardiographic evaluation [14]. Similar to this finding, relaxation abnormalities were found in 3.1% of healthy controls during the follow-up period in our study.

Tsai et al. [7] investigated the respiratory changes of Doppler transmitral flow velocity indices in 20 patients with coronary artery disease and found that left ventricular early diastolic filling can be reduced by inspiration. We also found that E values at end-inspiration were decreased in hypertensive patients. A more pronounced reduction was noted with the Valsalva maneuver. It has been reported that reduction of preload is important in determining the diastolic filling grade [34]. Performing the Valsalva maneuver as a preload reduction method during Doppler echocardiographic evaluation may facilitate the detection of LVDD through unmasking in patients who appear normal [35]. In their study involving 51 patients with hypertension, Yuan et al. [36] reported that they observed this characteristic phenomenon in 19.6% of the patients and stated that considering this phenomenon within the normal or abnormal group of pattern classification was controversial. They also suggested that because E/A <1 is usually thought to represent abnormal left ventricular filling and 1<E/A<2 with E/A<1 is thought to be pseudonormal left ventricular filling, the phenomenon of E/A<1 on inspiration E/A>1 on expiration appears to be in between the abnormal relaxation and pseudonormal patterns. In addition, this phenomenon is a strong indication that reverse E/A value on end-inspiration, rather than on end-expiration, might be a more sensitive and accurate indicator for abnormal left ventricular diastolic function, which may help early identification of diastolic dysfunction. In the present study, we found in the hypertensive group that the mean baseline E/A value was 1.16 at end-expiration and 0.93 at end-inspiration, which was compatible with the characteristic phenomenon. The mean E/A values in hypertensive patients were <1.0 at the end of the follow-up period. The LVDD can be determined at the time of initial diagnosis in hypertensive patients and the prevalence is increased during long-term follow-up.

Table 4. Follow-up echocardiographic findings of the patients and controls.

	Hypertensive patients (n=96)	Controls (n=32)	p
Systolic blood pressure (mmHg)	149.3±13.7	123.3±5.9	<0.001
Diastolic blood pressure (mmHg)	86.9±5.2	81.5±3.4	<0.001
IVS (mm)	10.9±1.8	8.8±1.7	<0.001
PW (mm)	10.5±1.2	8.9±0.9	<0.001
LVDd (mm)	49.5±3.7	47.6±3.2	0.016
LA (mm)	39.5±2.6	36.5±2.3	<0.001
LVMI (g/m^2)	123±25	94±18	<0.001
EF (%)	70±5	71±4	NS
FS (%)	40±6	41±4	NS
E	72±14	86±14	<0.001
A	78±16	70±13	0.013
DT	227±26	195±11	<0.001
IVRT	107±12	91±63	<0.001
E/A	0.95±0.20	1.24±0.13	<0.001
PV	452±40	467±35	NS
Frequency of DD	64 (71)	2 (6)	<0.001

	Hypertensive patients (n=96)	Controls (n=32)	p
Lateral mitral annulus			
E'	0.11±0.03	0.17±0.03	<0.001
A'	0.13±0.02	0.12±0.02	NS
E'/A'	0.93±0.29	1.47±0.17	<0.001
Septal mitral annulus			
E'	0.09±0.03	0.15±0.02	<0.001
A'	0.12±0.02	0.11±0.01	NS
E'/A'	0.75±0.20	1.35±0.12	<0.001
Anterior mitral annulus			
E'	0.11±0.03	0.17±0.03	<0.001
A'	0.13±0.02	0.12±0.01	NS
E'/A'	0.91±0.32	1.43±0.16	<0.001
Inferior mitral annulus			
E'	0.09±0.02	0.15±0.03	<0.001
A'	0.13±0.02	0.15±0.03	0.001
E'/A'	0.72±0.19	1.28±0.21	<0.001

The results are expressed as mean ±SD or n (%). NS – not significant; IVS – interventricular septum; PW – posterior wall; LVDd – left ventricular end-diastolic dimension; LA – left atrium; LVMI – left ventricular mass index; EF – ejection fraction; FS – fractional shortening; E – early diastolic peak flow velocity; A – late diastolic peak flow velocity; DT – deceleration time; IVRT – isovolumetric relaxation time; PV – propagation velocity; DD – diastolic dysfunction; E' – peak early diastolic mitral annular velocity; A' – peak late diastolic mitral annular velocity.

DT has been used as a measure of chamber stiffness [37]. Yuan et al. [36] found that DT on expiration was significantly shortened compared to inspiration. Hsu et al. [38] showed that DT did not exhibit significant variation with respiration in hypertensive patients. We found that DT values at end-expiration were shorter in our study.

Relaxation abnormalities developed in 84% of the patients (58/80) in the Valsalva-positive group after the follow-up period. This frequency was 60% (6/10) in the Valsalva-negative group and 3.1% (1/32) in the control group (p<0.001). The most important parameter for the development of an abnormal relaxation pattern was the presence of respiratory change after adjustment according to the changes with the Valsalva maneuver.

As only newly diagnosed hypertensive patients were included in our study, the mean age of the patients was close to the middle-age range; however, the control group consisted of younger individuals. This difference between the mean age of the patients and controls may be considered a limitation of our study. Thus, larger studies, especially including elderly patients, are needed.

Conclusions

In conclusion, respiratory change in mitral flow can be evaluated as an early sign of diastolic dysfunction in patients with hypertension. A significant percentage of those patients, especially those with respiratory changes, will develop diastolic dysfunction in subsequent years. It should be kept in mind during assessment of diastolic function in patients at risk for cardiovascular disease that echocardiographic parameters may be affected by respiration. Hypertensive patients with normal transmitral Doppler pattern should also be investigated with the Valsalva maneuver.

Statement

The authors declare they have no conflict of interest regarding this article.

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