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ORIGINAL ARTICLE

Effect of the Valsalva manoeuver on diastolic filling indices in patients with essential hypertension

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In some hypertensive patients, echocardiographic examination does not reveal any pathologic finding in spite of a documented blood pressure elevation. In our study, we investigated the effect of preload reduction with Valsalva manoeuver on transmitral flow velocities in hypertensive patients with normal mitral flow pattern and compared the results with a healthy control group. Sixty-eight patients without evidence of coronary artery disease or heart failure (28 female, 40 male, age 50 ± 7) were divided in two groups according to their E/A ratio as those with diastolic dysfunction (n = 36) and without diastolic dysfunction (DD$^-$: n = 32). DD$^-$ patients and the control group (n = 20) performed Valsalva manoeuver and their pulsed-Doppler mitral flow measurements were repeated at the strain phase. During Valsalva manoeuver, E wave velocity decreased in all subjects. In the controls, peak A velocity showed a similar decline and E/A ratio remained over 1.0. However, in 72% of DD$^-$ patients A velocity did not change or increased and their E/A ratio fell below 1.0. In 47% of the patients with an E/A ratio reversal after Valsalva manoeuver, myocardial perfusion scintigraphy revealed reversible defects whereas none of the patients whose E/A ratio remained over 1.0 had perfusion defects. It is concluded that: (1) in hypertensive patients with normal E/A ratio Valsalva manoeuver should be performed in order to unmask a probable false normal finding, (2) an important percent of hypertensive individuals have left ventricular relaxation abnormalities, and (3) diastolic dysfunction develops together with a decrease in coronary reserve.
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Introduction

Assessment of end organ damage plays an important role in the diagnosis and treatment of essential hypertension.[1,2] Previous clinical studies suggested that the earliest manifestation of hypertensive heart disease is diastolic dysfunction, which is followed by left ventricular hypertrophy.[3–5] In some of the hypertensive patients, routine echocardiographic examination may not reveal any abnormality—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.[6,7] In the last decade this feature of diastolic flow has been used in the differentiation of normal and pseudonormal flow patterns.[8–10] The Valsalva manoeuver is a simple noninvasive method recommended to reduce left atrial pressure. Inversion of E to A ratio, which seems normal before the manoeuver, has been accepted as diastolic dysfunction.

The aim of our study is to investigate the effect of Valsalva manoeuver on transmittal inflow indices in hypertensive patients with normal E to A ratio in routine echocardiographic examination and to compare the findings with a healthy control group and with hypertensive patients presenting with relaxation abnormalities.

Patients and methods

Patients

Consecutive patients (103 male, 160 female, mean age 58 ± 10 years) admitted to our university clinic with the diagnosis of untreated essential hypertension were included in the study. All patients underwent a thorough clinical, physical and electrocardiographic examination. Patients with symptoms

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suggesting heart failure, arrhythmic events or with findings for significant valvular disease were excluded at the beginning of the study. Patients with a symptom of typical or atypical angina ($n = 145$) were investigated with exercise thallium myocardial perfusion scintigraphy and patients with reversible perfusion defects underwent coronary angiography in order to eliminate accompanying coronary artery disease. Sixty-eight patients not complaining of angina pectoris, or with normal myocardial perfusion scintigraphy or with normal coronary arteries in coronary angiograms (28 female, 40 male, mean age 50 ± 7 years) were included to the study. Age and sex-matched healthy subjects (8 female, 12 male, mean age 47 ± 8 years) without clinical or electrocardiographic signs of hypertension or coronary artery disease were selected to serve as the control group.

Methods

Echocardiographic examination of the patients and the controls was performed with a Toshiba SSH 140 A ultrasound machine using a 2.5 MHz transducer. Evaluation of the patient group was done at entry of the study in order to detect the presence of end organ disease and to prevent the effect of antihypertensive treatment. Left ventricular end-diastolic dimension (LVDD) and wall thickness (interventricular septum, IVS and posterior wall, PW) were measured from parasternal long axis view according to the guidelines of American Society of Echocardiography.[11] Left ventricular mass (LVM) was calculated by Devereux formula.[12] Left ventricular mass index was determined by dividing LVM to body surface area. Left ventricular hypertrophy was defined as a left ventricular mass index greater than 134 g/m^2 in male and greater than 110 g/m^2 in females.[13]

Colour guided pulsed Doppler echocardiographic examination was made from apical four-chamber view placing sample volume between the tips of the mitral leaflets. Parameters used to evaluate diastolic filling were peak early flow (E) velocity, peak atrial contraction (A) velocity, E to A ratio and deceleration time (DT). Patients with an E to A ratio greater than 1.0 were accepted as those without diastolic dysfunction (DD$^-$) and those with an E to A ratio equal or less than 1.0 were accepted as those with diastolic dysfunction (DD$^+$). DD$^-$ patients and the controls were taught how to perform the Valsalva manoeuver and were asked to keep straining for at least 10 seconds. Measurements were repeated at the straining phase of the manoeuver. An adequate Valsalva manoeuver was defined as more than 10% reduction in maximal E wave velocity from baseline.[8] Patients with inadequate response repeated the manoeuver for two to three times until best recording could be obtained. Subjects whose E to A ratio decreased below 1.0 after the manoeuver were defined as Valsalva(+) and patients whose E to A ratio remained over 1.0 were defined as Valsalva(−).

Statistical analysis

All analysis was performed using SPSS for Windows (version 6.1). Data are expressed as mean value and one standard deviation. Clinical and echocardiographic findings of the patients and the control group were compared with unpaired two-sample *t*-test or Mann–Whitney U test. Nonparametric variables were compared with χ^2 test. In subjects who performed Valsalva manoeuver, data before and after the manoeuver were compared with paired samples *t*-test for variables with a Gaussian distribution or Wilcoxon signed rank test for variables with a nonGaussian distribution. A P value less than 0.05 was accepted as statistical significance.

Results

In pulsed-Doppler examination 36 hypertensive patients (53%) had an E to A ratio equal or below 1.0 (DD$^+$) and 32 (47%) had an E to A ratio higher than 1.0 (DD$^-$). None of the controls had an E to A ratio below 1.0. Clinical characteristics of the patients and the controls were given at Table 1. Age, gender and body mass index were similar in the three groups. Duration of hypertension was significantly longer in DD$^+$s compared with the DD$^-$s. Systolic blood pressure in DD$^+$s was slightly but not statistically higher than DD$^-$s.

In echocardiographic examination, left ventricular wall thickness in DD$^-$s were higher than the controls (IVS: $P < 0.001$ and PW: $P < 0.001$). In DD$^+$ patients both of these parameters were significantly higher than the other two groups (Table 2). LVDD and ejection fraction determined by the Teichholz method were similar in DD$^-$ patients and the control group. In DD$^+$ patients, LVDD was significantly smaller and ejection fraction was in normal limits but significantly lower than DD$^-$s ($P = 0.03$ and $P = 0.02$ respectively).

In pulsed-Doppler examination peak E velocity showed a progressive decline from controls to DD$^-$s

Table 1 Clinical characteristics of the patients and the controls

	Controls (n = 20)	*EH/DD$^-$ (n = 32)*	*EH/DD$^+$ (n = 36)*
Age (y)	47 ± 9	50 ± 6	50 ± 8
Gender (F/M)	8 F/12 M	12 F/20 M	16 F/20 M
BMI (kg/m^2)	27 ± 6	28 ± 5	29 ± 5
Duration of ht (y)	–	5 ± 5	8 ± 7
Systolic BP (mm Hg)	115 ± 22	170 ± 23	175 ± 27
Diastolic BP (mm Hg)	76 ± 10	100 ± 11	101 ± 14

EH, essential hypertension; DD$^-$, subjects with an E to A ratio over 1.0 in mitral flow; DD$^+$, subjects with E to A ratio below 1.0 in mitral flow; y, years; F, female; M, male; BMI, body mass index; ht, hypertension.

Table 2 Echocardiographic findings of the patients and the controls

	Controls	*EH/DD⁻*	*EH/DD⁺*	*P*[1]	*P*[2]
IVS (mm)	9 ± 2	12 ± 2	14 ± 2	<0.001	<0.001
PW (mm)	9 ± 2	11 ± 2	12 ± 2	<0.001	0.04
LVDD (mm)	47 ± 5	49 ± 5	44 ± 6	NS	0.03
LVH (%)	1 (%5)	10 (%31)	18 (%50)	0.04	NS
EF (%)	65 ± 7	67 ± 6	64 ± 10	NS	0.02
E (cm/s)	98 ± 15	78 ± 18	58 ± 11	0.001	<0.001
A (cm/s)	69 ± 11	62 ± 15	75 ± 17	NS	0.002
E/A	1.4 ± 0.2	1.3 ± 0.2	0.8 ± 0.1	NS	<0.001
DT (ms)	179 ± 29	182 ± 45	244 ± 80	NS	0.03

P[1], Difference between the controls and DD⁻ groups; *P*[2], difference between DD⁻ and DD⁺ groups; IVS, thickness of interventricular septum; PW, thickness of posterior wall; LVDD, left ventricular diastolic diameter; LVH, left ventricular hypertrophy; EF, ejection fraction; E peak E. velocity in mitral flow; A peak A velocity in mitral flow; DT deceleration time; NS, not significant.

Table 3 Measurements before and after Valsalva manoeuver in DD⁻ hypertensive patients and the controls

	Controls			*EH/DD(⁻)*		
	B.V.	*A.V.*	*P*	*B.V.*	*A.V.*	*P*
Heart rate	73 ± 9	77 ± 8	<0.001	77 ± 9	78 ± 9	0.001
E (cm/s)	98 ± 15	80 ± 15	0.001	78 ± 18	59 ± 20	<0.001
A (cm/s)	69 ± 11	61 ± 16	0.04	62 ± 15	63 ± 21	NS
E/A	1.4 ± 0.2	1.3 ± 0.2	NS	1.3 ± 0.2	0.96 ± 0.3	<0.001
DT (ms)	179 ± 29	187 ± 31	NS	182 ± 45	201 ± 54	0.04

EH, essential hypertension; DD⁻, patients with E to A ratio over 1.0 in mitral flow; B.V., measurements before Valsalva manoeuver; A.V., measurements after Valsalva manoeuver; DT, deceleration time; NS, not significant.

and DD⁺s (Table 2). The difference between all three groups was statistically significant (controls and DD⁻: $P = 0.001$; DD⁻ and DD⁺: $P < 0.001$). Peak A velocity and E to A ratio were similar in the controls and in DD⁻s. In DD⁺s, peak A velocity was significantly higher and E to A ratio was lower compared with the other two groups.

An adequate response to Valsalva manoeuver could be obtained in all subjects. Measurements before and after the manoeuver are given in Table 3. In the control group, both peak E and A wave velocity decreased significantly with the manoeuver, E to A ratio did not change, deceleration time prolonged slightly but not statistically. In DD⁻ patients, E velocity decreased similar to controls but peak A velocity remained greatly unchanged and E to A ratio fell significantly (Figure 1). In DD⁻ patients the fall in E velocity (28%) was more prominent than in the controls (18%) ($P = 0.05$).

When DD⁻ patients were investigated according to their response to Valsalva manoeuver nine patients (28%) had a similar decrease in E and A velocity after the manoeuver (Valsalva(−)) and 23 patients (72%) had a decrease in E velocity and no change or a slight increase in A velocity (Valsalva(+)) (Figure 2).

In the comparison of Valsalva(+) and Valsalva(−) patients age, gender and duration of hypertension were not different between the two groups. In echocardiographic examination, Valsalva(+)'s had relatively higher wall thickness compared with Valsalva(−)'s (IVS: 11.7 ± 1.8 cm *vs* 11.2 ± 2.5 cm; PW: 11.1 ± 1.8 cm *vs* 10.6 ± 1.5 cm, respectively). Peak E velocity was not different (80 ± 20 cm/s *vs* 78 ± 15 cm/s), and peak A velocity was higher in Valsalva(+)'s (63 ± 18 cm/s *vs* 58 ± 15 cm/s). E to A ratio and deceleration time were similar in both groups (E to A ratio: 1.3 ± 0.2 cm/s *vs* 1.4 ± 0.3 cm/s; deceleration time: 177 ± 39 ms *vs* 187 ± 60 ms, respectively).

In Valsalva(+)'s, we have not been able to find any cutoff value in peak E velocity or E to A ratio below which E to A ratio shows a reversal. However, an important percentage ($n = 18$, 78%) of the patients had an E to A ratio below 1.39.

In Valsalva(+) group 17 patients (74%) underwent myocardial perfusion scintigraphy because of typical or atypical angina pectoris and in 11 (47%) reversible perfusion defects were observed. In Valsalva(−) group only four patients (44%) performed exercise thallium scintigraphy and none of them showed perfusion defects.

Coronary angiography was performed in all of the 11 Valsalva(+) patients with perfusion defects. Mean left ventricular end-diastolic pressure was 8 ± 5 mm Hg in these patients.

Discussion

Several transmitral flow velocity patterns have been observed in the development of diastolic dysfunc-

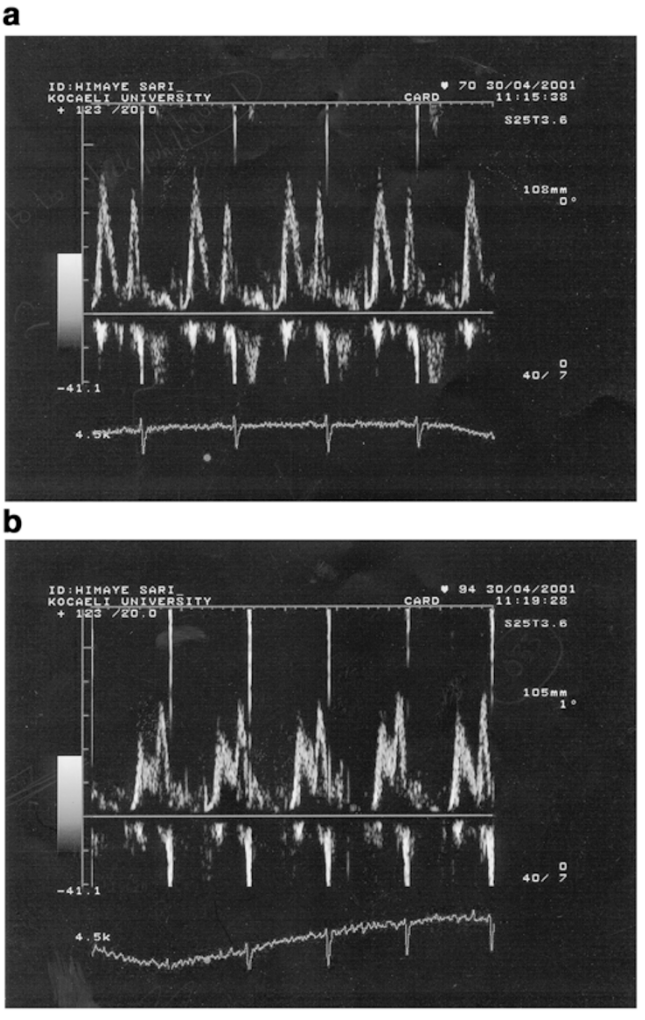

Figure 1 Effect of the Valsalva manoeuver on mitral flow pattern in a DD(−) hypertensive patient. (**a**) Before the manoeuver, (**b**) after the manoeuver.

tion in diseased hearts.[8,9] According to the results of the recent studies, the earliest change in diastolic dysfunction is a decrease in peak E wave velocity, prolongation of deceleration time and elevation of peak A wave velocity. With disease progression, peak E velocity shows an increase due to the elevation of left atrial pressure which changes E to A ratio over 1.0. This state called pseudonormalisation is followed by the restriction phase.

In our study, DD^- group consisted of relatively younger patients with normal coronary arteries, normal systolic function and without any other cardiac abnormality than essential hypertension. Their left ventricular wall thickness was greater than the controls but a high proportion of them (69%) did not meet echocardiographic criteria for the left ventricular hypertrophy. Peak E velocity was significantly lower than the controls but also significantly higher than DD^+s. No statistical difference could be demonstrated in their E to A ratio and deceleration time compared with age-matched healthy subjects, but their mean values were between the control and DD^+ groups. Therefore clinical and echocardiographic characteristics of DD^- patients suggested that hypertensive cardiac involvement had started in these patients but echocardiographic findings were not in pathological limits.

Effect of preload alteration on diastolic filling in normal subjects and in various cardiac pathologies has been investigated since the mid 1980s.[8,9,14–18] However, some contradiction exists between the results of various studies. Preload reduction leads to a decrease in E velocity in all subjects, but changes in A velocity and E to A ratio are not compatible with each other. In studies about normal subjects some authors demonstrated a decrease in A velocity similar to peak E velocity and no change in E to A ratio whereas other investigators claimed that A velocity does not change with preload reduction which causes a fall in E to A ratio and mimics relaxation abnormalities. Selection of the study groups (age, determination of normality) and methods (place of the sample volume, method to reduce preload) seem to be the main reasons for these discrepancies.

Our results were consistent with the observations of the former group. Peak A velocity decreased in our control subjects, E to A ratio did not change and none of them showed a reversal of E to A ratio after the Valsalva manoeuver.

In diseased hearts preload reduction may change a normal mitral filling profile to an abnormal pattern and preload elevation shows an opposite effect.[8,9,17–19] The

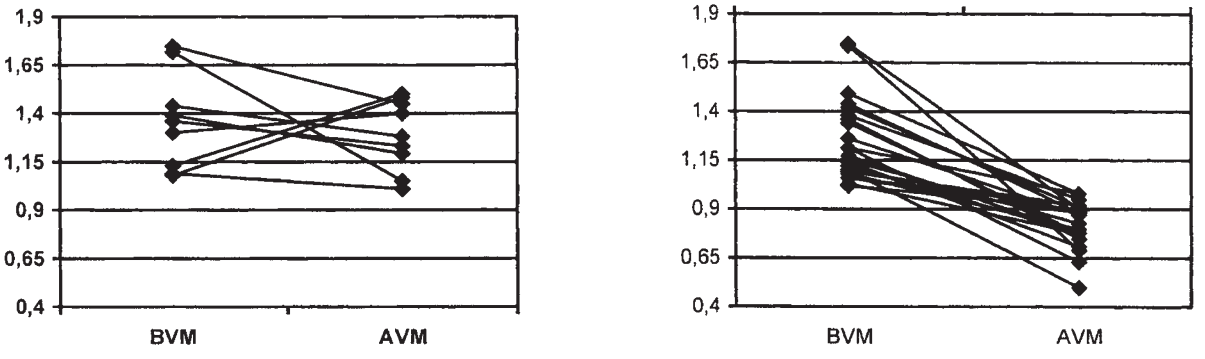

Figure 2 E to A ratio of the Valsalva(+) and the Valsalva(–) patients. (BVM, before Valsalva manoeuver; AVM, after Valsalva manoeuver.)

difference from normal individuals is the appearance of an abnormal flow pattern either at the beginning or at the end of the preload alteration. Effect of loading conditions on transmitral flow in hypertensive individuals has been investigated in a limited number of studies.[19–22] Various comments exist about their findings again. Some observed no change or even an increase in atrial filling velocity and a fall in E to A ratio; other studies showed a decrease in peak A velocity where E to A ratio did not change significantly. In these studies, selected patient groups had some differences than our DD$^-$s. They were either older or had diastolic dysfunction, coronary artery disease, heart failure or left ventricular hypertrophy. Besides, preload reduction had been achieved by different procedures other than the Valsalva manoeuver.

A high percent of DD$^-$ patients in our study showed a reversal of E to A ratio after the Valsalva manoeuver. This reversal can be attributed to an exaggerated decrease in early filling velocity when left atrium empties to a less compliant ventricle and to a compensatory augmentation of atrial filling. According to the clinical and echocardiographic characteristics of the patients, we suggest that this response should be interpreted as a latent diastolic dysfunction stage at the beginning of hypertensive heart disease rather than a misleading finding due to the altered preload.

In the DD$^-$ group, we eliminated coronary artery disease by myocardial perfusion scintigraphy or by coronary angiography. In order to preserve the consecutive nature of the study, we did no exclude patients with perfusion defects in myocardial scintigraphy and normal coronary angiograms. The high percentage of the patients with perfusion defects in Valsalva(+) group was interesting. Though to the small number of the patients ($n = 4$; 44%) who performed a perfusion scintigraphy in Valsalva(−) group, none of them had defects in their examination. This finding reminds of the results of HARVEST trial and suggests that microangiopathy, diastolic dysfunction and increase in wall thickness develop simultaneously in patients with essential hypertension and none of these abnormalities precedes the other.[23]

Limitations of the study

The findings in our study was not supported by heart catheterization therefore we could not determine left atrial pressure directly. We measured LV end-diastolic pressure in 11 patients. In the rest of the study group, only clinical and echocardiographic findings suggested that left ventricular end diastolic pressure and left atrial pressure were in normal limits.

The study had been designed as a crossover study, however clinical and echocardiographic follow-up of DD$^-$ patients will provide better knowledge about their development of diastolic dysfunction.

Conclusions

The findings in our study suggests that: (1) hypertensive patients with normal transmitral Doppler pattern should further be investigated with Valsalva manoeuver in order to unmask a probable latent diastolic abnormality, (2) if we include DD$^-$ patients with a positive response to the Valsalva manoeuver, relaxation abnormalities in essential hypertension seems to be a more frequent finding than expected, and (3) diastolic dysfunction in hypertensive heart disease occurs together with other changes such as microangiopathy and left ventricular hypertrophy.

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