Clinical Investigations

Impaired Systolic Dysfunction of Left Ventricular Longitudinal Fibers: A Sign of Early Hypertensive Cardiomyopathy

SPYRIDON N. KOULOURIS, M.D., KOSTANTINOS G. KOSTOPOULOS, M.D., KONSTANTINOS A. TRIANTAFYLLOU, M.D., ILIAS KARABINOS, M.D., TANIA P. BOUKI, M.D., HARIS I. KARVOUNIS, M.D., HEYDER OMRAN, M.D., GERASIMOS FILIPPATOS, M.D., ATHANASIOS I. KRANIDIS, M.D.

First Department of Cardiology, "Evangelismos" Hospital, Athens, Greece

Summary

Background: Atrioventricular plane displacement (AVPD) study by M-mode echocardiography can supply useful clinical information about left ventricular (LV) long-axis function.

Hypothesis: We assessed the hypothesis that AVPD estimation could be used to detect early hypertensive cardiomyopathy.

Methods: The study population included 81 hypertensive patients with normal LV ejection fraction and fractional shortening, and 50 age- and gender-matched healthy controls. By utilizing M-mode and apical views, the following parameters were estimated: early mitral flow peak velocity (E) and deceleration time (DT), peak velocity of late mitral flow (A), A/E ratio, isovolumic relaxation time (IVRT), total AVPD, AVPD motion during atrial systole (At), systolic AVPD (total AVPD-At), and At/total AVPD ratio.

Results: Of 81 hypertensive patients, 16 (19.7%) had a normal (Group 1) and 65 (80.3%) an impaired LV relaxation filling pattern (Group 2). Mean total AVPD-At was significantly lower in Group 2 than in Group 1 (7.1 ± 2 vs. 10.3 ± 3 mm, $p < 0.001$) and in Group 1 compared with healthy subjects (10.3 ± 3 vs. 13.1 ± 1 mm, $p < 0.001$). Mean At and At/total AVPD were significantly higher in Group 2 than in Group 1 (46.9 ± 8.6 vs. 37.7 ± 8.7%, $p < 0.001$), but not in Group 1 compared with healthy subjects (37.7 ± 8.7 vs. 36 ± 6%, $p > 0.05$).

Conclusions: Hypertensive patients without overt systolic dysfunction demonstrate LV long-axis systolic dysfunction, while long-axis diastolic dysfunction always coexists with abnormal diastolic filling patterns. This suggests that long-axis systolic dysfunction precedes diastolic dysfunction at the same axis in hypertensive patients.

Introduction

Left ventricular (LV) myocardial fibers are predominantly arranged longitudinally or obliquely in the subendocardium and subepicardium and circumferentially in the intermediate layer.[1] Measurement by M-mode echocardiography of the atrioventricular plane displacement (AVPD) has been proven to constitute a simple method for the assessment of systolic and diastolic function of the LV longitudinal fibers.[2–4] In various clinical settings, this index has been shown to carry important diagnostic and prognostic information by suggesting early LV dysfunction.[5, 6] Indeed, some experts have proposed its use as a screening tool complementary to conventional echocardiographic indices for the detection of patients with subtle myocardial dysfunction.[7, 8]

The aim of this study was to assess the diagnostic information offered by atrioventricular plane motion study by M-mode in addition to the usual echocardiographic indices of LV performance in hypertensive patients without overt systolic dysfunction.

Methods

We studied 81 hypertensive patients in sinus rhythm (48 men and 33 women, 52.7 ± 11 years old, range 30–69 years), diagnosed within the preceding 5 years and treated with various antihypertensive medications. Patients with arrhythmias,

Address for reprints:

Konstantinos A. Triantafyllou, M.D.
79-81 Platonos Street
Kallithea 176 73
Athens, Greece
e-mail : tricon@otenet.

coronary artery disease, valve disease, systemic diseases, or unsatisfactory echocardiographic recordings were excluded from the study. All patients had a normal thallium-201 stress test according to a standardized multistage exercise test protocol. At the time of investigation, all patients had been undergoing antihypertensive therapy for at least 2 months. Fifty age- and gender-matched healthy subjects with no previous history of cardiac or other diseases, and who had normal physical examination, exercise tolerance test, and echocardiogram, served as controls. Just after measurement of blood pressure in supine position had been taken, complete transthoracic echocardiograms were obtained with a Sonos 1000 ultrasonic instrument (Hewlett Packard, Andover, Mass., USA) equipped with a 2.5 MHz phased array transducer. The study protocol complies with the declaration of Helsinki and was approved by the hospital Scientific Committee.

Echocardiographic techniques and measurements of cardiac dimensions were performed according to the instructions of the American Society of Echocardiography.[9, 10] Calculation of the percent fractional shortening was done according to a previously described method.[9] All patients were examined in partial left lateral decubitus position after an overnight fasting state. Left ventricular mass was calculated according to the formula:

$$LVM = 0.8 \times 1.05 \times [(LVIDD + LVPW + IVS^3) - (LVIDD^3)] + 0.6$$

where LVM = LV mass (gr), LVIDD = LV internal diastolic diameter (cm), LVPW = LV posterior wall thickness (cm), and IVS = interventricular septum thickness (cm).[11, 12] Left ventricular mass index (LVMI) was calculated by dividing the LVM by the body surface area (g/m^2), since correction for body surface area standardizes for obesity as a factor associated with increased LVM.[13] Hypertrophy of the left ventricle

was diagnosed if LVMI was > 131 g/m^2 for men and 100 g/m^2 for women.[14]

Recordings of the motion of the left atrioventricular plane were obtained with the M-mode cursor directed from apical views. Initially, the M-mode cursor was oriented toward the right septal margin of the left atrioventricular plane and then toward its lateral margin from the apical four-chamber view. Consequently, the M-mode cursor was positioned at the anterior and posterior borders of the left atrioventricular plane in the apical two-chamber view.

Using the leading edge of echoes, total AVPD as well as its motion due to atrial systole (At) were measured in mm (Fig. 1). Total AVPD was measured as the total vertical distance between the two maximum excursions toward and away from the transducer. The At was recorded at the last part of the diastolic phase, when the atrioventricular plane moved from the cardiac apex toward the atrial roof during the inscription of the P wave of the electrocardiogram. Systolic AVPD (total AVPD −At) and the At/total AVPD ratio were calculated subsequently. The average of the measurements at the above four reported sites out of five consecutive cardiac cycles was used for the analysis.

A separate well-experienced investigator, who was blinded to the M-mode examination results, performed the cardiac Doppler study. The isovolumic relaxation time (IVRT) was defined as the interval from the end of the aortic flow to the onset of mitral flow as assessed by pulsed and continuous-wave Doppler recordings from the apical five-chamber view. The average of three cardiac cycles from both recordings was taken as the representative measurement. Pulsed Doppler transmitral flow velocities were recorded during expiration between the tips of the mitral leaflets from the apical four-chamber view. The sample volume size was adjusted to 3 mm. From these velocity tracings, early mitral flow peak velocity (E), deceleration time (DT), and peak velocity of late mitral flow (A) were also measured.
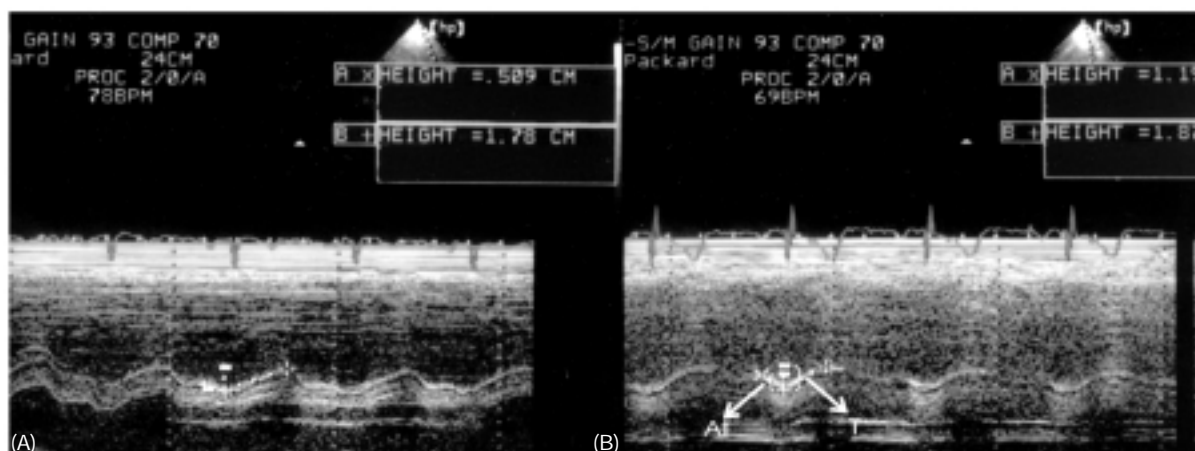

FIG. 1 The atrioventricular plane displacement during the cardiac cycle is recorded in M-mode in a normal subject (A) and in hypertensive patient (B). The total diastolic (T) and those due to atrial systole (At) movements of the atrioventricular plane are observed. As can be seen clearly, the At/total AVPD ratio of the normal subject is much lower than that of the hypertensive patient (0.285 vs. 0.636, respectively). P = P wave of the electrocardiogram.

Impaired relaxation was defined as prolongation of IVRT (>102 ms) and DT (>261 ms) and increased A/E ratio (>1) according to the reference values of our laboratory.[15] Moreover, Doppler flow patterns were examined from the four-chamber view for the existence of more advanced diastolic dysfunction (pseudonormal and restrictive patterns). For this reason, transthoracic pulsed Doppler study of the right upper pulmonary venous flow was performed in all patients.[16]

Results are given as mean ± standard deviation (SD). Comparisons between mean values were obtained by Student's *t*-test for two variables and by one-way analysis of variance (ANOVA) for more than two variables. The degree of correlation between variables was also assessed. All p values are two tailed, and statistical significance was established as $p < 0.05$. To assess the reproducibility of AVPD and LVM measurements, 40 subjects were evaluated twice on different occasions by the same investigator, and another 40 subjects twice on different occasions by two different investigators. The intra- and interobserver variabilities of total AVPD, At, and LVM were 6.2, 5.4, and 6.6% and 6.9, 5.2, and 6.8%, respectively.

Results

Differences in clinical characteristics between hypertensive patients and healthy subjects are listed in Table I. Of 81 (67.9%) hypertensive patients, 55 had LV hypertrophy. The duration of diagnosed arterial hypertension was 4.8 ± 3.7 years. A normal LV diastolic filling pattern was found in 16 (19.7%) hypertensive patients (Group 1). An impaired LV relaxation filling pattern was identified in 65 (80.3%) hypertensive patients (Group 2). No patient demonstrated a restrictive or a pseudo-normal mitral filling pattern. This latter finding was ruled out based on the concomitant pulmonary venous flow pattern. No differences were noted regarding age (52.2 ± 9.2 vs. 52.9 ± 12.3 years, p>0.05), gender (55 vs. 52% men, p>0.05), body surface area (1.85 ± 0.5 vs. 1.83 ± 0.2 kg/m², p>0.05), heart rate (76.1 ± 9.7 vs. 71.1 ± 12.3 beats/min, p>0.05), and duration of hypertension (4.4 ± 5.7 vs. 4.9 ± 3.2 years, p>0.05) between Groups 1 and 2. Systolic blood pressure was 144 ± 13 mmHg in Group 1 and 143 ± 15 mmHg in Group 2 (p>0.05), and diastolic blood pressure was 90 ± 9 vs. 91 ± 10 mmHg (p>0.05), respectively. In addition, no significant differences were noted between patients in Groups 1 and 2 regarding the type of blood pressure lowering agents used (Group 1 vs. Group 2: beta blockers 45 vs. 50%; calcium antagonists 30 vs. 35%, angiotensin enzyme inhibitors 45 vs. 55%; diuretics 25 vs. 30%, all p>0.05).

The IVRT, A/E ratio, DT, left atrial dimension, and LVMI were significantly different among Group 1, Group 2, and healthy subjects (p<0.05), whereas fractional shortening and ejection fraction of the left ventricle were not different among the three groups (p>0.05).

Total AVPD was found to be symmetric in all four LV sites (septal = 13.6 ± 2.9 mm, anterior = 14.3 ± 3.0 mm, posterior = 14.9 ± 3.3 mm, and lateral = 14.4 ± 3.5 mm, ANOVA p = 0.09). The mean systolic AVPD (total AVPD-At) correlated with LV ejection fraction (r = 0.58, p>0.001). Mean systolic AVPD was significantly lower in Group 2 than in Group 1 (7.1 ± 2 vs. 10.3 ± 3 mm, p>0.001), and in Group 1 compared with healthy subjects (10.3 ± 3 vs. 13.1 ± 1 mm, p>0.001).

A highly significant correlation was found between mean At/total AVPD and A/E in all hypertensive patients (r = 0.820, p>0.001). Compared with healthy subjects, mean At and At/total AVPD were significantly higher in hypertensive patients (6.82 ± 1.32 vs. 5.76 ± 1.35 mm, p>0.000, and 45.1 ± 9.1 vs. 36 ± 6%, p>0.001, respectively). The At/total AVPD was significantly higher in Group 2 than in Group 1 (46.9 ± 8.6

TABLE I   Comparison between characteristics of hypertensive patients and healthy subjects

	Hypertensive patients (n = 81) Mean ± SD	Controls (n = 50) Mean ± SD	p Value
Age (years)	52.7 ± 11.1	53.2 ± 10.6	>0.05
Sex (M/F)	44/37	29/21	>0.05
BSA (kg/m²)	1.84 ± 0.2	1.81 ± 0.3	>0.05
Heart rate (beats/min)	73.1 ± 11.4	72.0 ± 12.1	>0.05
LVMI (g/m²)	176 ± 31	115 ± 16.5	<0.001
FS (%)	37.5 ± 8.0	36.2 ± 7.4	>0.05
EF (%)	68.4 ± 11	65.1 ± 7.1	>0.05
SBP (mmHg)	140.1 ± 10.5	138.1 ± 5.0	>0.05
DBP (mmHg)	83.5 ± 8.5	81.4 ± 4.0	>0.05
LA (mm)	36.6 ± 5.2	34.8 ± 4.2	0.04
IVRT (ms)	120 ± 24.5	90 ± 12.5	<0.001
A/E	1.25 ± 0.42	0.9 ± 0.25	<0.001
DT (ms)	280 ± 32	198 ± 28	<0.01

Abbreviations: M = males, F = females, LVMI = left ventricular mass index, BSA = body surface area, HTN = hypertension, FS = left ventricular fractional shortening, EF = ejection fraction, SBP = systolic blood pressure, DBP = diastolic blood pressure, LA = left atrium, IVRT = isovolumetric relaxation time, A = peak velocity of late mitral flow, E= peak velocity of early mitral flow, DT = deceleration time.

vs. $37.7 \pm 8.7\%$, $p > 0.000$), but not in Group 1 compared with healthy subjects ($37.7 \pm 8.7\%$ vs. $36 \pm 6\%$, $p > 0.05$). The use of an At/total AVPD value $\geq 42\%$ as a cut-off point to diagnose impaired LV relaxation filling pattern (as defined above) in hypertensive patients demonstrated sensitivity 84.3%, specificity 90%, and positive predictive value 93.47%.

Discussion

The results of our study show that hypertensive patients with normal LV ejection fraction and fractional shortening demonstrate impaired longitudinal LV systolic function as assessed by M-mode echocardiography independent of the presence of normal or abnormal LV filling. Left ventricular systolic function is commonly considered normal in the presence of normal ejection fraction and fractional shortening despite the fact that neither index reflects all aspects of LV contractile function. Recently, using tissue Doppler imaging, Poulsen *et al.*[17] found that patients with hypertension and isolated diastolic dysfunction also had reduced LV systolic longitudinal function. However, we showed that even hypertensive patients with normal LV diastolic function have impaired longitudinal LV systolic function. This is not an unexpected finding given the fact that Mottram *et al.*[18] showed that hypertensive response to exercise is associated with subtle systolic dysfunction, even in the absence of resting hypertension. These changes in longitudinal LV systolic function possibly occur before the development of LV hypertrophy or detectable diastolic dysfunction and most likely represent early hypertensive heart disease. The longitudinally arranged myocardial fibers possibly precede the circumferentially arranged ones in impairment of their systolic function in hypertensive patients. Indeed, in a recent study hypertensive patients with concentric remodeling were found to have fractional shortening and systolic mitral annular velocities decreased in the long axis, but not in the short axis, compared with controls.[19] Systolic function of the circumferential myocardial fibers seems to be impaired in the presence of normal ejection fraction only in those hypertensive patients who have developed LV hypertrophy.[20]

The ratio of AVPD caused by left atrial systole to total diastolic AVPD as assessed by M-mode echocardiography has been proposed as an index of LV diastolic function at the long axis, reflecting the contribution of atrial systole to LV filling.[4] In our study, an increased mean ratio of left atrial to total diastolic AVPD was found in hypertensive patients compared with normal subjects, most likely due to domination of impaired LV relaxation in the former. This was evident from the presence of the characteristic Doppler findings,[15] which were observed in a great percentage of our hypertensive patients. The impaired ventricular relaxation produces a reduction in early ventricular filling, resulting in a greater residual volume in the left atrium by the last part of the diastolic phase, and thus a higher atrial preload. This produces more forceful left atrial contraction and active left atrial emptying, which is reflected by an increase in the contribution of the left atrial AVPD. In contrast to longitudinal LV systolic function, longitudinal LV diastolic function

is impaired only in hypertensive patients with normal ejection fraction and fractional shortening who at least show abnormal LV filling behavior. The diastolic extension of the longitudinal fibers seems to make a major contribution to the diastolic behavior of the left ventricle. On the other hand, systolic shortening of the left ventricle across the longitudinal axis does not seem to play an important role in the whole systolic behavior of the left ventricle. This is further confirmed by our finding of a weaker correlation of the systolic AVPD with LV ejection fraction compared with the correlation of the At/total AVPD with the A/E ratio.

In our series of hypertensive patients with impaired ventricular relaxation, the At/total AVPD ratio was proved to be a particularly useful predictive index in detecting those patients with such abnormal LV filling. Indeed, the fact that AVPD was found to be symmetric at all four LV sites indicates that a single estimation of it at any site of the mitral valve annulus is enough and representative of impaired LV relaxation.

Conclusion

Patients with hypertension and normal LV ejection fraction and fractional shortening, who were originally considered to have normal diastolic function or even isolated diastolic dysfunction, were demonstrated to have reduced systolic function of the longitudinal fibers of left ventricle. This probably suggests that change in the longitudinal shortening of the left ventricle, which is determined by the function of subendocardial fibers, is an extremely sensitive marker of early systolic dysfunction. Diastolic function of longitudinal fibers becomes abnormal only when abnormal diastolic behavior coexists. Indeed, the assessment of diastolic function of longitudinal fibers using M-mode echocardiography can identify abnormal relaxation of left ventricle with high accuracy and reproducibility. Compared with the conventional parameters of diastolic function, mean At and At/total AVPD are more specific for the assessment of long-axis LV diastolic function.

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