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ORIGINAL ARTICLE

Aggravation of left ventricular diastolic dysfunction in hypertensives with coronary artery disease

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We investigated the combined effects of hypertension and coronary artery disease (CAD) on left ventricular (LV) diastolic function. We examined 118 consecutive hypertensives who underwent diagnostic coronary angiography. All patients underwent a complete echocardiographic study within 24 h of catheterization by operators blind to their condition. The study participants were divided into two groups according to the presence of CAD: group A, with the disease ($n = 72$); and group B, without ($n = 46$). Patients with CAD exhibited lower LV fractional shortening and ejection fraction ($P = 0.002$ and $P = 0.001$). Hypertensives with CAD had significantly prolonged isovolumic relaxation time (IVRT) compared to those without CAD ($P < 0.001$). Most interestingly, CAD patients had significantly worse Ema/Ama, Vp (flow propagation velocity), E/Vp and Vp/IVRT (all $P < 0.05$). In addition, after adjusting for confounders, univariate and multivariate logistic regression analyses revealed that IVRT increases were associated with greater odds of CAD, whereas decreases in Vp or Vp/IVRT were associated with lower odds of CAD (all $P \leqslant 0.001$). In hypertensives, the early recognition of LV diastolic performance alteration may be associated with the presence of significant CAD, indicating the need for more aggressive approaches both in terms of pharmacological treatment and interventional evaluation.

INTRODUCTION

Left ventricular (LV) diastolic dysfunction represents a common pathophysiologic consequence of arterial hypertension that can be detected in the early stages of the disease, even before the development of LV hypertrophy.[1] In addition to hypertension, myocardial ischemia is commonly observed with LV diastolic dysfunction, primarily the delayed relaxation pattern.[2]

Derangement of LV diastolic properties in hypertensive subjects has been linked to adverse cardiovascular outcomes including the augmented risk of heart failure with preserved ejection fraction[3,4] and atrial fibrillation.[5] Moreover, some authors have called for more aggressive treatment of hypertensives with impaired LV diastolic function in terms of improved prognosis.[6]

The estimation of LV diastolic properties in daily clinical practice is performed with the use of established echocardiographic indices that are primarily derived from mitral inflow Doppler studies. However, because these are dependent on LV loading conditions, other techniques such as tissue Doppler imaging have gained interest due to their more sensitive detection of LV diastolic dysfunction in hypertensive patients.[7,8]

The non-invasive detection of coronary artery disease (CAD) remains an important goal in the management of hypertensive subjects. The aim of the present study was to investigate the plausible additional role of echocardiographic LV diastolic dysfunction indices in the determination of hypertensives with CAD.

METHODS

Study population

We examined 136 consecutive hypertensive patients from the outpatient hypertensive clinic of our institution who underwent coronary artery angiography to evaluate chest pain.

Patients with a known history of myocardial infarction as well as those with congenital heart disease, clinically significant valvular disease, cardiomyopathy, chronic obstructive pulmonary disease, renal insufficiency (serum creatinine $> 1.5 \, \text{mg dl}^{-1}$), AV conduction disturbances, atrial fibrillation and diabetes mellitus were excluded from the present study.

Thus, the final study cohort comprised 118 hypertensive subjects (mean age 63 ± 8 years, 77 male) who, according to the study protocol, underwent a complete echocardiographic examination with special focus on the estimation

of LV diastolic function, with the examiners blinded to the catheterization results. The study protocol was approved by the ethics committee of our institution and complied with the Declaration of Helsinki. All participants provided written informed consent.

Office BP measurement
Sitting BP was measured three times in the right arm of the individual with a mercury sphygmomanometer after a 5-min rest and with at least a 1-min interval between readings. The mean value of the last two measurements was accepted, discarding the first. Hypertension was defined as systolic BP $\geqslant 140$ mm Hg, diastolic BP $\geqslant 90$ mm Hg or the use of antihypertensive medication. Patients with secondary hypertension were excluded from the study.

Anthropometric and biochemical parameters
Body weight and height were measured according to established methods, and body mass index and body surface area were calculated according to standard formulae. In addition, all participants underwent venous blood sampling for the determination of the typical biochemical parameters, including the lipidemic profile, serum glucose and creatinine, after an overnight fast.

Echocardiographic study
Echocardiograms were performed by two cardiac ultrasonographers, who had >5 years of experience with the Vivid 7 equipment (GE, Vigmed Ultrasound, Horten, Norway), using an adult matrix probe under continuous electro-cardiographic guidance. Data analysis was performed offline by two independent expert level III blinded observers.

A two-dimensionally guided M-mode LV study was performed along the left parasternal long axis and LV end-systolic and end-diastolic diameter. LV posterior wall and intrarventricular septal thickness measurements were performed according to the guidelines of the American Society of Echocardiography[9] in five consecutive cardiac cycles, obtaining the mean value of each parameter.

LV mass was estimated according to the formula of Deveraux and Reichek[10] and was divided by body surface area for the calculation of the LV mass index. Moreover, we measured the mitral inflow maximal velocities of the E and A waves, as well as the isovolumic relaxation time (IVRT) and E wave deceleration time (DT), based on established methodology.[9] Each of the aforementioned parameters was estimated in five consecutive cardiac cycles, and the mean value was obtained for the purposes of our study.

Color M-mode was used for the estimation of transmitral flow propagation velocity, which is an index of relaxation independent of the LV loading conditions.

Tissue Doppler imaging was performed by placing the sample volume in the endocardial surface of the basal lateral LV segment in the apical four-chamber echocardiographic view. Maximal Em and Am velocities were measured in five consecutive cardiac cycles, and the mean value was obtained for the purpose of the present study.

Coronary artery angiography
Coronary artery angiography was performed by the femoral route, using the standard JL4 and JR4 diagnostic catheters in nearly all cases. A coronary lesion was defined as hemodynamically significant if the normal coronary vessel lumen diameter was narrowed by $\geqslant 60\%$.

Statistical analysis
Categorical variables are expressed as percentages, and continuous variables are expressed as the mean ± standard deviation if they are normally distributed or as medians (range) in the case of non-normal distributions. We used the t-test for independent samples to compare the means of continuous variables or the Mann–Whitney U-test for non-normally distributed variables and the χ^2-test for qualitative variables. Continuous variables were tested for normal distribution using the Shapiro–Wilk test for normality. Logistic regression was used to evaluate the association between echocardiographic indices on the likelihood of having CAD. The results are expressed in crude odds ratios and

odds ratios adjusted for several confounders with corresponding 95% confidence intervals. Deviance residuals and the Hosmer–Lemeshow criterion were used to evaluate the goodness of fit of the logistic models.

Receiver operating characteristic curves of the IVRT, Vp, Em and Vp/IVRT and the corresponding areas under the curve were used for the discriminative ability of each echocardiographic index between CAD and non-CAD group patients. All findings were considered statistically significant at $P < 0.05$.

RESULTS
The participants in this study were divided into two groups according to the presence of CAD, based on the results of diagnostic coronary angiography: group A, with the disease ($n = 72$); and group B, without ($n = 46$).

The two groups did not differ in the usual demographic and clinical parameters except for gender (Table 1). Male gender was more frequent in group A than in group B (75% vs 50%, respectively) ($P = 0.005$). Moreover, no significant difference was recorded between the two groups in terms of the received antihypertensive regimens ($P > 0.05$).

The echocardiographic structural indices in the two groups are reported in Table 2. No differences were found in LV interventricular septal thickness, LV posterior wall thickness, LV mass index or relative wall thickness between the two groups (all $P > 0.05$). However, patients with CAD exhibited lower LV fractional shortening and ejection fraction ($P = 0.002$ and $P = 0.001$, respectively), although they remained within the range of preserved LV systolic function (Table 2). Hypertensives with CAD had significantly prolonged IVRT compared to those without CAD (129.2 ± 13.2 vs 110.5 ± 14.5 ms, $P < 0.001$).

Table 1 Patient characteristics of the two study groups

	Group A (n = 72)	Group B (n = 46)	P-value
Age (years)	63.6 ± 9.5	61.6 ± 8.2	0.224
Male sex (%)	54 (75%)	23 (50%)	0.005*
Smoking status (%)	37 (51.4%)	20 (43.5%)	0.402
Dyslipidemia (%)	33 (45.8%)	23 (50%)	0.658
BMI (kg m^{-2})	27.9 ± 4.1	28.4 ± 3.9	0.521
SBP (mm Hg)	141 ± 13	138 ± 7	0.129
DBP (mm Hg)	82 ± 8	80 ± 8	0.259
Pulse pressure (mm Hg)	59 ± 12	58 ± 8	0.479
Hypertension history (months)	48 (441)	60 (239)	0.532

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.
*$P < 0.05$.

Table 2 Echocardiographic parameters of the two study groups

	Group A (n = 72)	Group B (n = 46)	P-value
IVS (mm)	11.7 ± 1	11.4 ± 1.3	0.215
PW (mm)	11.5 ± 1	11.3 ± 1.2	0.390
LAD (mm)	39.9 ± 5.7	37.4 ± 4.2	0.010*
LVFS (%)	28.1 ± 5.8	31.5 ± 5.3	0.002*
LVEF (%)	54.1 ± 8.6	59.2 ± 7.1	0.001*
LVMI (g m^{-2})	118.4 ± 22.2	121.9 ± 28.3	0.453
RWT	0.52 ± 0.058	0.50 ± 0.088	0.151

Abbreviations: IVS, interventricular septal thickness; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVMI, left ventricular mass index; PW, posterior wall thickness; RWT, relative wall thickness.
*$P < 0.05$.

Most interestingly, with respect to the most load-independent LV diastolic performance indices, including Ema/Ama, Vp, E/Vp and Vp/IVRT, CAD patients had significantly worse values, reflecting the plausible effects of myocardial ischemia on these parameters (all $P < 0.05$) (Table 3).

After adjusting for confounders, including age, gender, body mass index, arterial hypertension duration, smoking status, dyslipidemia, LV mass index and EF, univariate and multivariate logistic regression analyses demonstrated that IVRT increases were associated with greater odds of CAD, whereas decreases in Vp and Vp/IVRT were associated with lower odds of CAD. However, Ema values were associated with the presence of CAD in a univariate analysis, but the effect was attenuated in the multivariate analysis (Table 4).

In addition, we estimated the areas under the curve of each echocardiographic index as a crude estimation of the discriminative ability between CAD and non-CAD patients (Figure 1). As shown in Figure 1, IVRT, Vp, Em and Vp/IVRT strongly discriminated CAD patients from non-CAD patients, as indicated by the reported areas under the curve.

DISCUSSION

The main finding of this study was that severely depressed LV diastolic function, as suggested by various echocardiographic indices, particularly the E/Vp and Vp/IVRT ratios, is indicative of CAD coexistence in patients with uncomplicated essential hypertension.

Arterial hypertension is one of the major risk factors associated with the development of CAD, acting primarily by promoting atherosclerosis. Additionally, it is an important determinant of LV diastolic dysfunction, and it can be present even before the appearance of LV hypertrophy.[1] Notably, hypertension-induced myocardial ischemia may have a crucial role in the development of LV diastolic dysfunction even in the case of hemodynamically non-significant coronary stenosis.[11] In hypertensive subjects, several studies[11,12] have shown a significant reduction of the coronary flow reserve even in the presence of intact coronary blood flow at rest.

In addition, coronary blood flow is positively related to IVRT,[13] and intact SERCA function, which facilitates the efflux of calcium ions from the cytoplasm during diastole, is energy-dependent on ATP. Thus, myocardial ischemia may lead to LV relaxation impairment.[2] In this study, hypertensive patients with CAD exhibited prolonged IVRT as well as lower E mitral inflow and Vp values compared to patients without CAD, indicating that the intraventricular pressure gradient, which is responsible for normal LV filling, is reduced in the setting of ischemia.[14]

Despite the important contribution of invasive hemodynamic studies in the estimation of LV relaxation, echocardiographic examination prevails in daily clinical practice. Several methods are available, including conventional pulsed Doppler of mitral inflow and pulmonary venous flow, which are highly dependent on LV loading conditions. Consequently, the estimation of LV diastolic performance based solely on these is more or less inadequate and most likely inconclusive.[15,16] Novel echocardiographic techniques, such as mitral flow propagation velocity and tissue Doppler imaging, are primarily independent of LV preload changes and are considered superior to conventional pulsed Doppler mitral inflow measurements for the comprehensive evaluation of LV diastolic function.[15,17,18]

Table 3 Doppler echocardiographic left ventricular diastolic function indices of the two study groups

	Group A (n = 72)	Group B (n = 46)	P-value
Ema (cm s^{-1})	8.06 ± 1.85	7.57 ± 1.93	0.176
Ema/Ama	0.66 ± ± 0.16	0.75 ± 0.22	0.014*
Vp (cm s^{-1})	44.2 ± 15.8	59.7 ± 20.8	<0.001†
E/Vp	1.28 ± 0.49	1.10 ± 0.47	<0.001†
Vp/IVRT	0.35 ± 0.15	0.55 ± 0.22	<0.001†
E/Ema	6.73 ± 2.26	8.11 ± 2.25	0.002*
IVRT (ms)	129.2 ± 13.2	110.5 ± 14.5	<0.001†
DT (ms)	251.9 ± 59.1	225.5 ± 57.2	0.019*
E (m s^{-1})	51.9 ± 15.3	58.9 ± 14.2	0.015*
A (m s^{-1})	73 ± 20	73.2 ± 18.5	0.962
E/A	0.74 ± 0.27	0.83 ± 0.20	0.068

Abbreviations: A, diastolic mitral inflow wave corresponding to atrial systole; DT, mitral E wave deceleration time; E, early diastolic mitral inflow wave; Ema, TDI-derived lateral mitral annular E wave; IVRT, isovolumic relaxation time; Vp, flow propagation velocity.
*$P < 0.05$
$^\dagger P < 0.001$

Figure 1 Receiver operating characteristic curves of the IVRT *(ivrt)*, Vp *(vp)*, Em *(em)* and Vp/IVRT *(vp_ivrt)* for the discrimination between coronary artery disease (CAD) and non-CAD group patients. A full color version of this figure is available at the *Hypertension Research* journal online.

Table 4 Results of univariate and multivariate logistic regression^a analysis showing the association between diastolic function indices and the presence or not of coronary artery disease
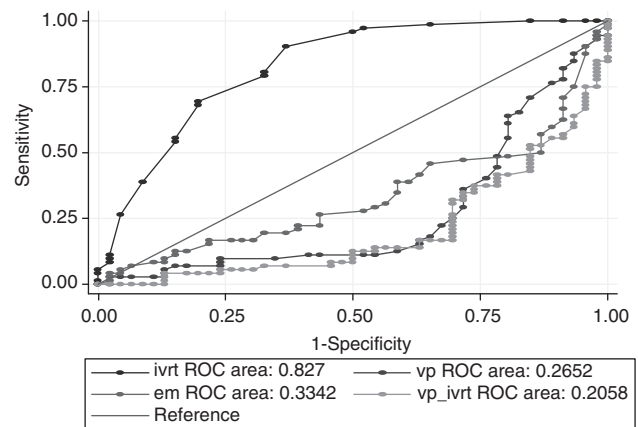
Parameter	Crude OR	95% CI	P-value	Adjusted^{a}OR	95% CI	P-value
IVRT (ms)	1.102	1.062–1.143	<0.001†	1.117	1.068–1.168	<0.001†
Vp (cm s^{-1})	0.954	0.931–0.977	<0.001†	0.956	0.931–0.982	0.001*
Vp/IVRT	0.002	0.0001–0.0299	<0.001†	0.002	0.0001–0.0372	<0.001†
Ema (cm s^{-1})	0.969	0.945–0.994	0.018*	0.973	0.946–1.002	0.073

Abbreviations: CI, confidence interval; Ema, TDI-derived lateral mitral annular E wave; IVRT, isovolumic relaxation time; OR, odds ratio; Vp, flow propagation.
*$P < 0.05$.
$^\dagger P < 0.001$.
^{a}Adjusted for age, gender, body mass index, arterial hypertension duration, smoking status, dyslipidemia, LVMI and EF.

In a study that examined the alteration of LV diastolic function during angioplasty-induced ischemia, an analysis of the flow propagation velocity showed that early filling is highly dependent on the LV relaxation rate, particularly through the phenomenon of asynchrony.[19] Moreover, in uremic patients, it has been found that a post-dialytic E/FPV ratio $\geqslant 1.5$ predicts a greater risk of adverse cardiovascular events.[20] However, there is a relative lack of such studies in the setting of essential hypertension.

As hypertension represents a major risk factor for CAD, it is crucial to thoroughly investigate hypertensive patients for the possible presence of myocardial ischemia, as ischemic symptoms in hypertensives may be atypical in nature. Moreover, the standard treadmill exercise test may be inconclusive, particularly in hypertensives with LV hypertrophy, and for this reason, alternative methods such as the echocardiographic stress test are proposed for the detection of ischemia.[6] This study indicates that impaired LV diastolic function approximated by combined echocardiographic indices, such as the E/Vp and Vp/IVRT ratios, may reveal the presence of hemodynamically significant coronary stenosis in essential hypertension. A potential clinical implication of this finding is that the abovementioned parameters can be routinely estimated in the echocardiographic examination of high-risk hypertensive patients, strengthening the role of echocardiography beyond the early recognition of LV hypertrophy only.

Our findings may not be globally applicable due to the potential limitations of the present study. The study population was small and selected using the strict inclusion criteria applied by us. Moreover, because there were no data regarding the antihypertensive therapy between the two groups, one could not exclude the possible effects of this treatment on LV diastolic function parameters. Additionally, we have no data regarding the association of echocardiographic indices of diastolic function or the severity of CAD. Further studies are required to determine whether the severity of CAD itself could have an impact on diastolic dysfunction.

In our study, we did not expect to find a lower E/E' ratio in the CAD group compared to the non-CAD group. However, there is conflicting evidence regarding the clinical value of this ratio as a marker of diastolic dysfunction. In a recent study, researchers concluded that the suboptimal sensitivity and specificity of the mitral E/E' for predicting increased LV diastolic pressure suggested that the mitral E/E' ratio is of limited clinical value in patients without heart failure.[21]

In conclusion, in the setting of uncomplicated essential hypertension, the early recognition of LV diastolic performance alteration may signal the presence of CAD, indicating the need for a more aggressive approach in terms of pharmacological treatment and invasive evaluation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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