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ORIGINAL ARTICLE

# Early carotid atherosclerosis and cardiac diastolic abnormalities in hypertensive subjects

G Parrinello*, D Colomba, P Bologna, A Licata, A Pinto, S Paterna, R Scaglione and G Licata
*Department of Internal Medicine, University of Palermo, Palermo, Italy*

**Despite the fact that it is known that hypertension may be associated to early atherosclerosis manifestations, few data are to date available on the relationship between early carotid abnormalities and left ventricular diastolic dysfunction. To address this issue, 142 hypertensive patients (64 females and 78 males) younger than 55 years, at the first diagnosis of mild-to-moderate essential hypertension (WHO/ISH criteria), were selected from a database consisting of 3541 subjects referred to ultrasound cardiovascular laboratory in the last 5 years. Carotid intima-media thickness (IMT) was detected by high-resolution vascular ultrasound and left ventricular structure and function by the use of Doppler echocardiography. According to carotid IMT values, all patients were subgrouped into two groups consisting of 89 (62.6%) pts with IMT $\geqslant$1 mm (A) and 53 (37.4%) pts with IMT $<$1 mm (B). Our results show that isovolumic relaxation time (IVRT), deceleration time of E velocity (EDT) and left ventricular relative wall thickness (LV-RWT) were significantly ($P<0.05$) higher in group A (IVRT 112 $\pm$ 8.9 ms; EDT 288 $\pm$ 21.8 ms; LV-RWT 0.40 $\pm$ 0.08) than in group B (IVRT 92.3 $\pm$ 4.6 ms; EDT 203.3 $\pm$ 27.01 ms; LV- RWT 0.37 $\pm$ 0.06). Moreover, the prevalence of left ventricular hypertrophy (LVH) was significantly ($P<0.01$) higher in group A (30/89; 33.7%) than in group B (8/53; 15%). A positive correlation ($P<0.001$) between IMT, EDT and IVRT was found only in hypertensives without LVH. These results are consistent with the indication that IMT evaluation has to be recommended both in hypertensive patients with LVH and in those without LVH, but with left ventricular diastolic dysfunction. This approach might improve the prognostic stratification of hypertensive subjects and it might be suitable to recognize the subset of patients at a higher risk of cardiovascular disease or events early.**
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## Introduction

Hypertension and atherosclerosis are two distinguished entities, but increase in blood pressure has been hypothesized to be associated to a progression of preclinical atherosclerosis.[1]

An increase in arterial stiffness is generally related to a permanent increase in blood pressure values. The structural alteration of arterial wall as hypertrophy (intima-media thickness increase) and modification of extracellular matrix with the increase of collagen compound are the main causes of arterial stiffness and often related to elevated blood pressure.[2]

Correspondence: Professor G Parrinello, Chair of Medical Physiopathology, Department of Internal Medicine, Istituto di Clinica Medica, Piazza delle Cliniche 2, University of Palermo, 90127 Palermo, Italy.
E-mail: parrigasp@inwind.it
*Private address: Via Giovanni Dotto n. 12, 90129 Palermo, Italy
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Arterial wall hypertrophy represents a compensatory mechanism to balance an increase in vessel diameter.[3] In fact it has been demonstrated that wall shear stress, the frictional force produced by the circulating blood column on the intimal surface of the vessel, plays an important role in the progression of atherosclerosis.[4,5] Carotid IMT, assessed by ultrasonography, has been regarded as a valid indicator of generalized atherosclerosis, because it has been related to atherosclerotic risk factors, coronary and peripheral atherosclerosis, and the risk of coronary and cerebrovascular events. In addition, some authors reported that blood pressure levels are a main determinant of IMT while the interaction of BP with other risk factors such as age is more relevant for advanced intima-media thickening.[6–9] Impaired diastolic function and increased left ventricular (LV) mass are common findings in hypertensive patients and may occur early in the natural history of essential hypertension.[10–13] Left ventricular hypertrophy has been extensively studied in hypertensive patients with regard to its

effects on systolic[14,15] and diastolic left ventricular function.[16–18] It is well established that LV relaxation is often abnormal in hypertensives with[19] or without[20] LV hypertrophy, suggesting that abnormal relaxation may be an early response to cardiac overload caused by hypertension.[20,21] In addition, LV hypertrophy (LVH) detected at echocardiography is a powerful independent risk factor for atherosclerotic cardiovascular and cerebrovascular events in hypertensive patients.[22] It has also been claimed that natural history of hypertensive LV hypertrophy may be characterized by abnormalities in LV diastolic function in the presence of maintained LV function.[23] On the contrary, the relationship between carotid atherosclerosis and diastolic dysfunction remains controversial to date. Accordingly, the present study was designed to evaluate the relationship between hypertension, carotid morphology and LV diastolic function. The main goal of the study was to evaluate whether an association between higher carotid IMT values and left ventricular diastolic dysfunction may be detectable in hypertensive patients early. In view of this, to minimize the influence of age and duration of hypertension on IMT values and LV diastolic function, we selected hypertensive subjects at first diagnosis of hypertension and who never had been treated.

## Methods

### Study population

The present study included 142 (64 females and 78 males) hypertensive subjects selected from a database consisting in 3541 patients who were referred to the ultrasonography cardiovascular laboratory of the Department of Internal Medicine of University of Palermo in the last 5 years.

The sample population was closely selected at first diagnosis of mild-to-moderate hypertension according to the WHO/ISH criteria, younger than 55 years.

The subjects with concomitant presence of the major cardiovascular risk factors such as diabetes mellitus, hyperdyslipidaemia, smoking habit, familial history of early cardiovascular events (age $\leqslant 55$ years), with cardiovascular disease and other diseases that may interfere with the analysis, were excluded.

The major inclusion criteria consisting of an accurate evaluation of carotid morphology and left ventricular geometry and function.

### Echocardiography

The M-mode, two-dimensional and Doppler echocardiography examinations of the left ventricle was performed with subjects in the left decubitus position using an ultrasound system (ESAOTE SPR 8000) with a 3.5 MHz transducer frequency for M-Mode and 2.5 MHz for Doppler recordings.

M-Mode tracings were quantified according to the recommendation of the American Society of Echocardiography.[24] Only frames with optimal visualization of interfaces and simultaneously showing septum, LV internal diameter and posterior wall were used or read.

The left ventricular mass was calculated using the cube formula and overestimation was corrected for the equation: 0.832[(LVIDd+IVSTd+PWTd)3 −LVIDd 3]+0.6 proposed by Devereux *et al*,[25] where LVIDd = left ventricular end-diastolic diameter; IVSTd = interventricular septum thickness in diastole; PWTd = posterior wall thickness in diastole.

Left ventricular mass (LVM) was normalized for height$^{2.7}$ to correct the effect of overweight.

Accordingly, the value of 51 g/m$^{2.7}$ has been demonstrated to be the most powerful predictor of cardiovascular complications both in males and in females.[26]

Left ventricular relative wall thickness (LV-RWT) was calculated as $2\times$ posterior wall thickness/LV internal diameter. Patterns of left ventricular (LV) geometry were defined according to Ganau *et al*:[27]

(1) LV concentric remodeling when a normal LVM was combined with LV-RWT $>0.45$;
(2) concentric LVH when LVH occurred with LV-RWT $>0.45$;
(3) eccentric LVH when increased LVM was associated with an RWT $<0.45$.

Left ventricular diastolic filling was assessed by echo-pulsed Doppler analysis. The diastolic mitral flow by early diastolic peak flow velocity (*E*), late diastolic peak flow velocity (*A*), the ratio of *E* to *A* (*E*/*A*) and the deceleration time of the early mitral velocity were recorded with the sample volume at the mitral leaflet tips. Deceleration time was measured as the time from peak *E* velocity to the time when the *E* wave descent intercepted the zero line. Isovolumic relaxation time (IVRT) was measured with a continuous wave Doppler beam intersecting LV outflow and inflow tract.[28] Pulsed Doppler recordings of trans-mitral flow velocities were obtained between the tips of the mitral leaflets for measuring peak early LV filling velocity/peck atrial filling velocity (*E*/*A*) and deceleration time (EDT). Pulsed Doppler recording from LV outflow tract were used to measure Isovolumic relaxation time (IVRT) from the closure spike of the aortic valve to the onset of mitral flow. Measurements up to three cycles were averaged.

According to European Society of echocardiography, diastolic dysfunction has been defined when the patients had an *E*/*A* ratio $<1$, an IVRT $\geqslant 105$ ms and an EDT $\geqslant 280$ ms.[29]

### Vascular ultrasound

Arterial carotid wall was evaluated with high-resolution B-mode ultrasonography. The examination of both common carotid arteries was performed with an ultrasound device (TOSHIBA SSA 270 HG) equipped with a linear (7.5 MHz) transducer. Subjects were examined in the supine position with slight hyperextension of the neck on a longitudinal two-dimensional ultrasound image of carotid, the near and far arterial wall are displayed as two bright white lines separated by a hypoechogenic space. The distance between the leading edge of the first bright line on the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the IMT of the far wall. A 1.5 cm segment of the common carotid artery (immediately caudal to the carotid bulb) and the proximal 1.5 cm segment of the internal carotid artery was considered. Within each segment, three measurements of IMT were taken and wall thickness was not measured at the site of a discrete plaque. The mean carotid IMT was defined as the average of all IMTs (as many as 12 readings: common and internal carotid arteries far wall, right and left side, three sample points per segment.[30,31]

According to IMT values, all selected subjects were subgrouped as follows:

Group A consisting of 89 hypertensives with IMT values equal to or higher than 1 mm;

Group B consisting of 53 hypertensives with IMT values less than 1 mm.

### Statistical analysis

Differences between the two groups were assessed by unpaired Student's *t*-test; comparison between groups was performed by one-way analysis of variance (ANOVA) with Neuman–Keuls *post hoc* test. Differences in the prevalence were analysed by $\chi^2$ test. Pearson's correlation coefficient was used to test association. Linear regression analysis was performed to correlate arterial wall thickness and diastolic measures. Data are expressed as mean $\pm$ s.d. or as percentages. A value of $P<0.05$ was considered to be statistically significant.

### Results

Demographic and clinical characteristics of the 142 subjects subgrouped according to carotid IMT status are reported in Table 1.

The two group of subjects with IMT $\geqslant 1$ (group A) and with IMT $<1$(group B) were comparable for age, gender, body height, BMI, total cholesterol and triglyceride serum values.

Table 2 shows blood pressure and ultrasound measurements in the study subjects. Systolic and diastolic blood pressure were significantly ($P<0.05$) higher in group A than in group B (SBP $152.2 \pm 7.7$ *vs* $146.9 \pm 5.4$ mmHg); (DBP $98.4 \pm 4.2$ *vs* $94.2 \pm 3.7$ mmHg). Carotid IMT was significantly ($P<0.05$) greater in group A than in group B ($1.07 \pm 0.01$ *vs* $0.79 \pm 0.17$ mm).

IVRT, EDT and LV-RWT were significantly ($P<0.05$) higher in group A (IVRT $112 \pm 8.9$ ms; EDT $288 \pm 21.8$ ms; LV-RWT $0.40 \pm 0.08$) than in group B (IVRT $92.3 \pm 4.6$ ms; EDT $203.3 \pm 27.01$ ms; LV-RWT $0.37 \pm 0.06$) (Table 2).

LV hypertrophy/$h^{2.7}$, defined according to the prognostic validated cut-off value (LV mass $\geqslant$ 51 g/$m^{2.7}$) was detected in both groups. The prevalence of LVH was significantly ($P<0.01$) higher in group A (30/89; 33%) than in group B (8/53; 15%).

Normal diastolic function was found in 6.7% (6/89) patients of group A, while diastolic abnormalities occurred in 3.7% (2/53) patients of Group B.

IMT values were significantly higher ($P<0.05$) in hypertensives with LVH and diastolic dysfunction in comparison with hypertensives with LVH and normal diastolic function ($1.9 \pm 0.11$ *vs* $0.83 \pm 0.10$). A positive correlation between IMT, IVRT

**Table 1** Demographic characteristics of subjects classified by IMT status

| | *Group A IMT* $\geqslant 1$ | *Group B IMT* $<1$ | P< |
|---|---|---|---|
| Patients (*n*) | 89 | 53 | |
| Gender (M/F) | 44/41 | 34/23 | |
| Age (year) | $45.5 \pm 6.4$ | $43.9 \pm 5.2$ | NS |
| BMI (kg/$m^2$) | $26.5 \pm 3.1$ | $26.2 \pm 2.9$ | NS |
| Body height (m) | $1.65 \pm 0.08$ | $1.67 \pm 0.08$ | NS |
| Total cholesterol (mg/dl) | $198 \pm 20.4$ | $196 \pm 18.4$ | NS |
| Triglycerides (mg/dl) | $164 \pm 12.2$ | $161 \pm 132$ | NS |

IMT, intima-media thickness; BMI, body mass index.

**Table 2** Blood pressure and ultrasound characteristics of subjects classified by IMT status

| | *Group A IMT* $\geqslant 1$ | *Group B IMT* $<1$ | P< |
|---|---|---|---|
| SBP (mmHg) | $152.3 \pm 7.7$ | $146.9 \pm 5.4$ | 0.05 |
| DBP (mmHg) | $98.4 \pm 4.2$ | $94.2 \pm 3.7$ | 0.05 |
| HR (b/min) | $76.3 \pm 5.1$ | $74.8 \pm 3.9$ | NS |
| IMT (mm) | $1.07 \pm 0.01$ | $0.79 \pm 0.17$ | 0.05 |
| EDT (ms) | $288 \pm 21.8$ | $203.3 \pm 27.01$ | 0.05 |
| IVRT (ms) | $112 \pm 8.9$ | $92.3 \pm 4.6$ | 0.05 |
| LV-RWT | $0.40 \pm 0.08$ | $0.37 \pm 0.06$ | 0.05 |
| LVH/$h^{2.7}$ (g/$h^{2.7}$) | $65.5 \pm 13.46$ | $43.7 \pm 13.01$ | NS |
| LVH prevalence (%) | 33 (30/89) | 15(8/53) | 0.01* |

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; IMT, intima-media thickness; LVH/$h^{2.7}$, left ventricular hypertrophy/$H^{2.7}$; LV-RWT, left ventricular relative wall thickness; IVRT, isovolumic relaxation time; EDT, E deceleration time.
[a]Z-test.

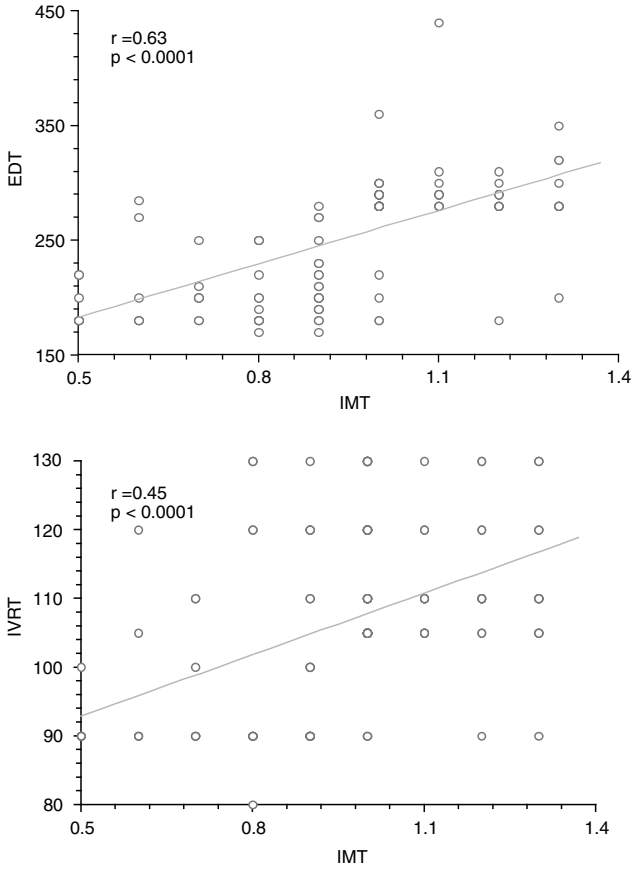


**Figure 1** Correlation between carotid intima-media thickness (IMT), Deceleration time E (EDT) and isovolumic relaxation time (IVRT) in hypertensive subjects without left ventricular hypertrophy.

and EDT was found in all the hypertensive subjects without LVH (Figure 1).

## Conclusions

The impact of hypertension on the vascular structure and the relationship between vascular wall hypertrophy and left ventricular structure and function in the early stages of essential hypertension are unclear to date.

Nevertheless, there is a correspondence between increase in arterial blood pressure and arterial wall rigidity. In fact, despite the fact that it is known that the first condition causes the second, it is also demonstrated that the second condition worsens the first.[32,33]

An increase in arterial wall rigidity leads to an increase in pressure wave propagation, reflecting the fact that pressure waves go on the centripetal direction and it reaches the aorta during ventricular systole; an increase in pressure after load is achieved and left diastolic dysfunction and/or left ventricular hypertrophy is promoted.[22,34]

Findings from the Rotterdam study[35] suggest that a mild increase in IMT, but less than 1 mm, reflects an adaptative response to altered flow shear stress and pressure. On the other hand, carotid IMT $\geqslant 1$ may be considered an early manifestation of atherosclerosis. Accordingly, the association between increased carotid wall thickness ($>1$ mm) and alteration in LV diastolic measurements by us reported indicated that early carotid atherosclerosis may be related to diastolic dysfunction in subjects with recently discovered essential hypertension.

Carotid IMT is associated with a gradual increase of the risk for future cardiovascular and cerebrovascular disease, with no clear cut-off point above which the risk increases more rapidly.[36] Our findings indicate a strong relationship between increased IMT and diastolic dysfunction independently by the presence of LVH in a cohort of uncomplicated subjects with recently discovered hypertension. The prevalence of LVH with increasing carotid IMT, observed by us, suggests that increased carotid wall thickness is only in part due to LVH. On the other hand, the association of left diastolic function measures (EDT, IVRT) with carotid IMT may contribute to explain that haemodynamic changes operating in hypertensive patients may account for vascular increasing vascular stiffness and worsening heart compliance. The main new finding of the present study is related to a recognition of an early association between carotid arterial wall thickening and left ventricular diastolic dysfunction in newly diagnosed essential hypertension. This association seems to be independent of the presence of left ventricular hypertrophy. In view of this, these results may be consistent with the indication that the evaluation of carotid wall morphology has to be performed in all hypertensive subjects and above all in those with concomitant left ventricular diastolic dysfunction.

Since, at present, hypertension check-up is based on evaluation of cardiovascular risk parameters, this approach might be suitable for an adequate follow-up of hypertensive subjects to recognize a subset of patients with higher risk of future cardiovascular disease or events.

Despite retrospective analysis of our database being the main study limitation, further prospective studies will be necessary to clarify the prognostic implication of the association between increased carotid IMT and left ventricular diastolic dysfunction.

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