

# Diastolic Dysfunction Precedes Myocardial Hypertrophy in the Development of Hypertension

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**Background:** Left ventricular (LV) hypertrophy and impaired diastolic function may occur early in systemic hypertension, but longitudinal studies are missing.

**Methods:** We performed an echocardiographic follow-up study in young initially normotensive male offspring of hypertensive (OHyp) ( $n = 25$ ) and normotensive (ONorm) ( $n = 17$ ) parents. Blood pressure (BP), LV mass, and mitral inflow were determined at baseline and after 5 years. Pulmonary vein flow pattern assessment and septal myocardial Doppler imaging were additionally performed at follow-up.

**Results:** At follow-up, BP was not significantly different between the two groups ( $128 \pm 11 / 84 \pm 10$  v  $123 \pm 11 / 81 \pm 5$  mm Hg, OHyp v ONorm) but five OHyp had developed mild hypertension. LV mass index remained unchanged and was not different between the two groups at follow-up ( $92 \pm 17$  v  $92 \pm 14$  g/m<sup>2</sup>). Diastolic echocardiographic properties were similar at baseline, but, at follow-up, the following differences were found: mitral E deceleration time ( $209 \pm 32$  v  $185 \pm 36$  msec,  $P < .05$ ) and pulmonary vein reverse A wave duration ( $121 \pm 15$  v  $107 \pm 12$  msec,  $P < .05$ ) were prolonged in the OHyp as compared to the ONorm. Compared to the normotensive

subjects, the five OHyp who developed hypertension had more pronounced alterations of LV diastolic function, that is, significantly higher mitral A ( $54 \pm 7$  v  $44 \pm 9$  cm/sec, hypertensives v normotensives,  $P < .05$ ), lower E/A ratio ( $1.31 \pm 0.14$  v  $1.82 \pm 0.48$ ,  $P < .05$ ), increased systolic-to-diastolic pulmonary vein flow ratio ( $1.11 \pm 0.3$  v  $0.81 \pm 0.16$ ,  $P < .005$ ), longer myocardial isovolumic relaxation time ( $57 \pm 7$  v  $46 \pm 12$  msec,  $P < .05$ ) as well as smaller myocardial E ( $10 \pm 1$  v  $13 \pm 2$  cm/sec,  $P < .05$ ) and E/A ratio ( $1.29 \pm 0.25$  v  $1.78 \pm 0.43$ ,  $P < .05$ ), despite similar LV mass ( $91 \pm 16$  v  $93 \pm 18$  g/m<sup>2</sup>).

**Conclusions:** Over a 5-year follow-up, initially lean, normotensive, young men with a moderate genetic risk for hypertension, developed Doppler echocardiographic alterations of LV diastolic function compared to matched offspring of normotensive parents. These alterations were more pronounced in the OHyp who developed mild hypertension and occurred without a distinct rise in LV mass. Am J Hypertens 2001;14:106–113 © 2001 American Journal of Hypertension, Ltd.

**Key Words:** Essential hypertension, genetics, echocardiography, diastole, left ventricular hypertrophy.

Offspring of hypertensive parents are at increased genetic risk for developing systemic hypertension.<sup>1,2</sup> Impaired diastolic function and increased left ventricular (LV) mass are common findings in hypertensive patients and may occur very early in the development of essential hypertension.<sup>3–6</sup> It is unknown when these abnormalities become evident and whether LV function and structure behave differently over time in subjects at risk for hypertension compared to subjects without that risk. We hypothesized that, compared to offspring of normotensive parents (ONorm), offspring of hypertensive parents (OHyp) would develop diastolic dysfunction ear-

lier and in parallel to increases in blood pressure (BP) and LV mass. Therefore, the study was aimed to investigate the degree and the respective timing of changes in BP, LV mass, and LV diastolic function in subjects at genetic risk to develop hypertension compared to individuals without this risk in a prospective longitudinal 5-year follow-up study. In addition, we evaluated whether a comprehensive noninvasive evaluation of the LV diastolic function by implementation of the pulmonary vein flow pattern<sup>7</sup> and technical innovations such as myocardial Doppler imaging<sup>8–10</sup> would improve our ability of recognizing early impaired diastolic function in the OHyp.

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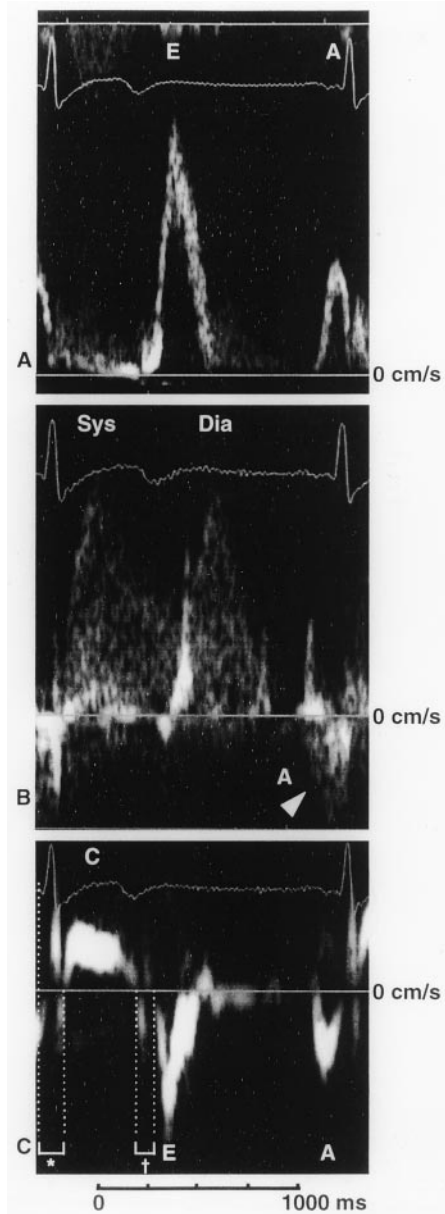
## Methods

### Study Population

A total of 42 normotensive, young, lean, and healthy men consented to participate in a 5-year follow-up evaluation. By including 17 ONorm and 25 OHyp, a nearly two-third matching was achieved. The OHyp group had at least one parent with confirmed essential hypertension. Medical history of the study subjects and their parents, and clinical examination were performed at baseline and at follow-up. Blood pressure was determined in triplicate, as reported before.<sup>11</sup> The study was approved by the local Ethics Committee.

### Echocardiography

Echocardiography and analysis of echodata were performed by investigators unaware of the family history of the subjects. To standardize the volume-loading conditions, the examinations were performed in the morning after a 12-h overnight fast, at baseline as well as at follow-up. Structural cardiac data and Doppler mitral inflow pattern were obtained as previously described<sup>12</sup> using a commercially available ultrasound system (Acuson 128/XP10c, Acuson, Mountain View, CA) with a 3.5-MHz transducer frequency for M-mode and 2.5-MHz for Doppler recordings. M-mode tracings were quantitated according to the recommendations of the American Society of Echocardiography.<sup>13</sup> LV mass was calculated using the cube formula and overestimation was corrected for by the equation proposed by Devereux et al.<sup>14</sup> Ejection fraction was calculated using the Teichholz method.<sup>15</sup> Cardiac output was determined by Doppler with a pulsed wave sample volume in the LV outflow tract. The diastolic mitral flow determinants 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.<sup>16</sup> A pulsed wave Doppler sample volume was placed 0.5 to 1.0 cm into the right upper pulmonary vein to record the pulmonary vein flow pattern.<sup>17</sup> The following pulmonary vein flow characteristics were measured (Fig. 1): systolic and diastolic velocity time integral, systolic and diastolic peak velocity, their ratios, peak velocity and duration of the reverse, and atrial-contraction-induced diastolic flow. Myocardial Doppler velocities were measured using integrated tissue Doppler software. In an apical four-chamber view the Doppler beam was aligned parallel to the interventricular septum and the pulsed Doppler sample volume was placed 1 cm apically from the mitral annulus in the interventricular septal myocardium and the following variables of longitudinal myocardial motion were recorded (Fig. 1): myocardial isovolumic contraction time, myocar-



**FIG. 1.** Explanatory example of the measured Doppler characteristics of one cardiac cycle, including the corresponding electrocardiographic tracing. To the right of the panels 0 cm/s denotes the 0 velocity level; velocities toward the transducer are displayed above the 0 level and velocities away from the transducer are displayed below the 0 line. **(A)** Mitral inflow pattern: E = early mitral inflow velocity; A = atrial contraction induced mitral inflow velocity. **(B)** Pulmonary vein flow pattern: Sys = pulmonary vein systolic flow; Dia = pulmonary vein diastolic flow; A (arrowhead) = pulmonary vein reverse flow during atrial contraction. **(C)** Myocardial longitudinal movements. \*Isovolumic contraction time of the interventricular septal myocardium (IVCT); C = contraction velocity of the interventricular septal myocardium; †isovolumic relaxation time of the interventricular septal myocardium (IVRT); E = peak early relaxation velocity of the interventricular septal myocardium; A = late relaxation velocity of the interventricular septal myocardium.

dial peak contraction velocity and myocardial contraction time, myocardial isovolumic relaxation time, myocardial early diastolic relaxation velocity E, myocardial E deceleration time, and myocardial late relaxation velocity. Be-

ginning of the IVRT was determined by simultaneously displayed phonocardiography. All recordings were performed with a sweep speed of 100 mm/sec. Three consecutive cardiac cycles were averaged on-line or on digitized S-VHS videotapes using internal calibration software of the ultrasound device. The inter- and intraobserver variability for some conventional and tissue Doppler parameters in our echolaboratory have been reported elsewhere.<sup>12,18</sup>

## Statistics

Results are reported as mean  $\pm$  SD. Unpaired and paired *t* tests and  $\chi^2$  tests were performed using Statistical Analysis System software (version 6.12, SAS Institute, Inc., Cary, NC) and StatView 4.5 (Abacus Concepts, Inc., Berkeley, CA). A *P* value  $< .05$  was considered significant.

## Results

### Subject Characteristics

Systolic and diastolic BP as well as heart rate and body mass index were not significantly different between OHyp and ONorm, both at baseline and at follow-up (Table 1). Moreover, there was no significant difference in the changes of these parameters from baseline to follow-up between the two groups (Table 1). At follow-up diastolic BP was  $>90$  mm Hg in five (20%) OHyp, and in three of these subjects systolic BP was  $>140$  mm Hg. No isolated systolic hypertension was noted. All ONorm had BP  $<140/90$  mm Hg, both at baseline and at follow-up. None of the study subjects was on medication.

### LV Structure

LV wall thickness, LV mass, and LV mass index were similar in both groups and did not change during the 5 years (Table 2). LV internal diameter increased in both groups similarly and was not different at follow-up. None of the study subjects had LV hypertrophy as defined by a LV mass index  $>134$  g/m<sup>2</sup>.<sup>19</sup> Left atrial diameter also remained unchanged at follow-up.

### LV Function

**Systolic Function** Ejection fraction of the LV was similar in OHyp and ONorm initially and at follow-up (Table 2). At follow-up, isovolumic contraction time measured by myocardial Doppler imaging in the basal interventricular septum was significantly longer in OHyp than ONorm ( $P < .05$ ) (Table 3), whereas heart rate was similar.

**Diastolic Function** Although similar at baseline ( $157 \pm 27$  v  $161 \pm 27$  msec,  $P = .61$ ), mitral E deceleration time increased more and was prolonged in OHyp as compared to ONorm at follow-up ( $P < .05$ ) (Table 4). The remaining mitral inflow variables were not different between OHyp and ONorm at both examinations, nor were their changes from

**Table 1.** Characteristics of the subjects

	OHyp (n = 25)		ONorm (n = 17)		$\Delta$ OHyp	$\Delta$ ONorm
	Baseline	Follow-up	Baseline	Follow-up		
Age (y)	25 $\pm$ 3	30 $\pm$ 3	25 $\pm$ 3	30 $\pm$ 3	1.1 $\pm$ 1.5	0.6 $\pm$ 1.0
Body mass index	22.5 $\pm$ 1.9	23.6 $\pm$ 2.3*	22.5 $\pm$ 1.5	23.2 $\pm$ 1.6†	8 $\pm$ 12	4 $\pm$ 12
Systolic blood pressure (mm Hg)	121 $\pm$ 6	128 $\pm$ 11	119 $\pm$ 11	123 $\pm$ 11	5 $\pm$ 11	3 $\pm$ 8
Diastolic blood pressure (mm Hg)	79 $\pm$ 6	84 $\pm$ 10	77 $\pm$ 5	81 $\pm$ 5	3 $\pm$ 12	2 $\pm$ 9
Heart rate (beats/min)	60 $\pm$ 6	63 $\pm$ 10	60 $\pm$ 7	62 $\pm$ 9		

OHyp = offspring of essential hypertensive parents; ONorm = offspring of normotensive parents;  $\Delta$  = difference between baseline and follow-up.

\*  $P < .001$  (OHyp, baseline v follow-up).

†  $P < .05$  (ONorm, baseline v follow-up).

**Table 2.** Left ventricular structure and systolic function

	OHyp (n = 25)		ONorm (n = 17)		$\Delta$ OHyp	$\Delta$ ONorm
	Baseline	Follow-up	Baseline	Follow-up		
LV mass (g)	180 $\pm$ 33	181 $\pm$ 35	180 $\pm$ 38	177 $\pm$ 31	2 $\pm$ 26	-4 $\pm$ 26
LV mass index (g/m <sup>2</sup> )	94 $\pm$ 16	92 $\pm$ 17	95 $\pm$ 19	92 $\pm$ 14	-1 $\pm$ 13	-3 $\pm$ 13
Septal end-diastolic thickness (mm)	11 $\pm$ 2	11 $\pm$ 2	11 $\pm$ 2	10 $\pm$ 1	-1 $\pm$ 1	-1 $\pm$ 1
Posterior wall diastolic thickness (mm)	10 $\pm$ 2	10 $\pm$ 1	10 $\pm$ 2	9 $\pm$ 2	-1 $\pm$ 1	-1 $\pm$ 1
LV diastolic diameter (mm)	47 $\pm$ 3	49 $\pm$ 4	48 $\pm$ 5	50 $\pm$ 4	1 $\pm$ 1	1 $\pm$ 1
Ejection fraction (%)	67 $\pm$ 9	69 $\pm$ 7	66 $\pm$ 6	68 $\pm$ 4	1 $\pm$ 9	2 $\pm$ 8
Left atrium (mm)	36 $\pm$ 4	36 $\pm$ 3	37 $\pm$ 3	37 $\pm$ 3		

LV = left ventricular; other abbreviations as in Table 1.

baseline to follow-up (Table 4). Analysis of the pulmonary vein flow pattern at follow-up showed a longer reverse A wave duration in OHyp compared to ONorm ( $P < .05$ ) (Table 5). The other pulmonary vein flow variables did not reveal further evidence for differences in LV diastolic function between OHyp and ONorm (Table 5). Pulmonary vein flow could not be compared to the initial visit as this investigation was not performed at that time. Myocardial Doppler variables of diastolic function did not significantly differ between the two groups (Table 3).

### Subjects With BP >140/90 mm Hg (hypertensives, follow-up results)

Compared to the normotensive subjects (normotensives), the five subjects with diastolic BP >90 mm Hg at follow-up had a similar LV mass index ( $91 \pm 16$  v  $93 \pm 18$  g/m<sup>2</sup>, hypertensives v normotensives) but impaired diastolic function. Mitral A was higher in the hypertensives ( $54 \pm 7$  v  $44 \pm 9$  cm/sec,  $P < .05$ ) and consequently the E/A ratio lower ( $1.31 \pm 0.14$  v  $1.82 \pm 0.48$ ,  $P < .05$ ). Similarly the pulmonary vein flow pattern showed an increased systolic-to-diastolic ratio in the hypertensive subjects ( $1.11 \pm 0.3$  v  $0.81 \pm 0.16$ ,  $P < .005$ ) as well as increased systolic/diastolic velocity time integral ratio ( $1.20 \pm 0.24$  v  $0.89 \pm 0.25$ ,  $P < .05$ ). Using myocardial Doppler imaging, the heart rate-corrected isovolumic contraction time ( $95 \pm 10$  v  $78 \pm 9$  msec,  $P = .0005$ ) and relaxation time ( $57 \pm 7$  v  $46 \pm 12$  msec,  $P < .05$ ) were significantly longer in the hypertensives as compared to the normotensives, whereas myocardial E ( $10 \pm 1$  v  $13 \pm 2$  cm/sec,  $P < .05$ ) and myocardial E/A ratio were smaller ( $1.29 \pm 0.25$  v  $1.78 \pm 0.43$ ,  $P < .05$ ). When all five hypertensive OHyp were excluded from statistical analysis no difference was found between OHyp and ONorm. Mitral E deceleration time and pulmonary reverse A wave duration were only insignificantly prolonged ( $P = .09$  and  $P = .07$ , respectively).

## Discussion

This is the first study investigating LV structure and function over time in initially normotensive offspring of hypertensive parents. During a follow-up of 5 years, compared to matched offspring of normotensive parents, young, initially lean, normotensive male offspring of hypertensive parents developed Doppler echocardiographic signs of diastolic dysfunction without a significant increase in LV mass. Mitral E wave deceleration time was the earliest conventional Doppler echocardiographic marker differing in OHyp as compared to ONorm. The E-wave deceleration time is characteristically prolonged in patients with a relaxation abnormality, because it takes longer for left atrial and ventricular pressures to be equilibrated with slower but continuous decrease in LV pressure.<sup>7</sup>

The analysis of pulmonary vein flow, which is increasingly used in the noninvasive assessment of LV diastolic



**Table 3.** Myocardial Doppler of the interventricular septal longitudinal movement at follow-up

	OHyp (n = 25)	ONorm (n = 17)
Isovolumic contraction time (ms)	85 ± 10	78 ± 12*
Peak contraction velocity (cm/sec)	7.6 ± 0.9	8.2 ± 1.0
Contraction time (msec)	314 ± 20	315 ± 24
Isovolumic relaxation time (msec)	81 ± 14	77 ± 13
Early diastolic velocity E (cm/sec)	12.6 ± 2.2	12.3 ± 1.6
Late diastolic velocity A (cm/sec)	7.4 ± 1.2	7.6 ± 1.3
E/A ratio	1.76 ± 0.45	1.67 ± 0.43
E duration (msec)	193 ± 18	192 ± 14
A duration (msec)	128 ± 13	131 ± 11
E deceleration time (msec)	111 ± 17	109 ± 15
RR interval (msec)	1081 ± 136	1040 ± 174

Abbreviations as in Tables 1 and 2, and Fig. 1.

\*  $P < .05$ .

function, revealed a significantly increased pulmonary vein reverse A wave duration in the OHyp, a further evidence of altered diastolic function in these subjects. Recently, we found a prolonged pulmonary vein reverse A duration in patients with impaired relaxation,<sup>20</sup> as well as, relative to transmitral A wave duration, an increase in pulmonary vein reverse A-wave duration during preload reduction.<sup>20,21</sup> There is no evidence for different loading conditions between OHyp and ONorm and therefore, our findings are likely to represent real alterations of LV diastolic function. Moreover, there was no significant difference at follow-up between OHyp and ONorm in gender, age, body mass index, LV mass, or heart rate, all variables known to influence mitral inflow,<sup>22,23</sup> and none of the subjects had ever been on antihypertensive treatment. However, we cannot completely exclude that the nonsignificant higher BP in OHyp might have influenced the results, as increased afterload can be accompanied by a prolongation of the E deceleration time.<sup>23,24</sup> Furthermore, signs of diastolic dysfunction were more prominent in those subjects who developed hypertension, suggesting a

possible association between higher BP per se, or perhaps a parallel effect of whatever mechanisms are causing BP to increase and diastolic (dys)function. Therefore, the lack of association, when comparing the two study groups, between BP and alterations of diastolic function could reflect an insufficient statistical power.

The inclusion of myocardial Doppler as an additional noninvasive and easy-to-perform tool in the evaluation of LV function is promising, especially because some parameters seem to be less sensitive to preload changes than Doppler mitral and pulmonary vein variables.<sup>9,10,25</sup> The prolonged septal myocardial isovolumic contraction time found in the OHyp of the present study may represent an early marker of LV systolic dysfunction. Similar findings have recently been reported in patients with LV hypertrophy due to systemic hypertension,<sup>26</sup> a structural abnormality that was not present in our OHyp. The clinical significance of an isolated myocardial isovolumic contraction time prolongation is currently largely unknown and deserves future studies that will have to investigate its possible relationship with structural and functional cardiovas-

**Table 4.** Left ventricular diastolic function: mitral valve inflow pattern

	OHyp (n = 25)		ONorm (n = 17)		$\Delta$ OHyp	$\Delta$ ONorm
	Baseline	Follow-up	Baseline	Follow-up		
Early inflow velocity E (cm/sec)	79 ± 10	74 ± 11	81 ± 15	78 ± 11	-4.5 ± 9	-3.4 ± 15.2
Late inflow velocity A (cm/sec)	43 ± 8	45 ± 8	44 ± 8	47 ± 10	2.3 ± 6.7	2.8 ± 11.8
E/A ratio	1.88 ± 0.29	1.72 ± 0.45	1.89 ± 0.37	1.75 ± 0.45	-0.17 ± 0.37	-0.15 ± 0.5
Isovolumic relaxation time (msec)	77 ± 10	67 ± 10	74 ± 20	66 ± 12	10 ± 19	7 ± 20
E deceleration time (msec)	157 ± 27	209 ± 32	161 ± 27	185 ± 36*	53 ± 40	24 ± 42†

Abbreviations as in Tables 1 and 2, and Fig. 1.

\*  $P < .05$  OHyp v ONorm, at follow-up; †  $P < .05$   $\Delta$ OHyp v  $\Delta$ ONorm.

**Table 5.** Pulmonary vein flow pattern at follow-up

	OHyp (n = 25)	ONorm (n = 17)
Systolic velocity time integral (cm)	13 ± 3	13 ± 4
Diastolic velocity time integral (cm)	14 ± 2	14 ± 3
Ratio systolic/diastolic time integral	0.92 ± 0.24	0.92 ± 0.31
Systolic peak velocity (cm/sec)	47 ± 10	43 ± 11
Diastolic peak velocity (cm/sec)	55 ± 11	55 ± 9
Ratio systolic/diastolic peak velocity	0.87 ± 0.22	0.81 ± 0.16
Reverse A wave velocity (cm/sec)	25 ± 5	25 ± 4
Reverse A wave duration (msec)	121 ± 15	107 ± 12*
Mitral A minus pulmonary vein reverse A wave duration (msec)	-45 ± 21	-52 ± 25

Abbreviations as in Tables 1 and 2, and Fig. 1.

\*  $P < .05$ .

cular abnormalities. The lack of mirror image between E deceleration time measured at the mitral inflow and the septal myocardium may be partly explained by the relatively large inter- and intraobserver variability of the Doppler tissue imaging parameters<sup>18</sup> and the location used for performing Doppler tissue imaging.

An increased LV mass is a well-known risk factor in hypertensive patients and can sometimes occur very early in the course of hypertension.<sup>3,27</sup> Compared to ONorm, however, OHyp did not increase their LV mass at follow-up, even those OHyp who became hypertensive. In fact, there was no increase in LV mass or mass index in both study groups during the 5-year follow-up, despite a not significant tendency for an increased BP and body mass index in the OHyp at follow-up. These findings indicate that a distinct increase in LV mass does not precede a significant increase in BP; they favor the concept that LV mass increases primarily in response to a distinct and chronic elevation of systemic arterial pressure.<sup>28</sup> However, determinants of LV hypertrophy are only partially known and other factors than BP may play an important role,<sup>29</sup> and it has been reported that LV mass might predict BP response to exercise or even clear-cut hypertension.<sup>30,31</sup>

This, like previous studies,<sup>32–34</sup> shows a dissociation between LV mass and diastolic function. Furthermore, the data suggest that alterations of diastolic function may precede a significant increase in LV mass in subjects at risk of essential hypertension and corroborate the results of cross-sectional studies conducted in offspring of hypertensive parents.<sup>34,35</sup> The relatively small sample size prevents, however, from making conclusions on quantitative correlations between diastolic dysfunction and BP. Except for changes in BP and LV mass, we did not investigate mechanisms that might cause early diastolic dysfunction in offspring of hypertensive parents. But structural changes of the myocardium such as altered collagen and myocardial architecture<sup>36,37</sup> may take place well before overt development of detectable wall hypertrophy or hypertension, and metabolic and neurohumoral changes may

also be involved early.<sup>28,38</sup> Various alterations have also been described at the cellular level.<sup>39</sup>

There is substantial evidence that assessment of diastolic function is of invaluable help in the management of patients with advanced cardiac diseases,<sup>40–42</sup> and that the improvement of a diastolic dysfunction is related to the success of therapy.<sup>43,44</sup> No study has, so far, documented an impaired outcome in hypertension-prone subjects with diastolic dysfunction as the sole manifestation of the hypertensive heart disease. However, an early identification of subjects with or at risk for hypertension and diastolic dysfunction may help to stratify risk, guide therapy, and prevent target organ damage.<sup>45,46</sup> Future studies enrolling larger number of individuals and including serial assessment of BP and LV structure and function will be necessary to elucidate underlying causes and clinical importance of our findings.

In conclusion, during a 5-year follow-up period, compared to matched offspring of normotensive parents, initially normotensive lean male offspring of essential hypertensive parents developed Doppler echocardiographic alterations of LV diastolic function that were, however, not associated with a significant increase in LV mass. These alterations were more pronounced in the offspring of hypertensive parents who developed hypertension during the 5-year follow-up period. To optimize early risk stratification and primary prevention of end-organ damage, future studies will have to demonstrate the clinical relevance of these findings.

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