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EXPERIMENTAL STUDIES

Alterations in Diastolic Function in Response to Progressive Left Ventricular Hypertrophy

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To examine the time course of the functional consequences of progressive left ventricular hypertrophy, diastolic left ventricular inflow and wall thinning variables were analyzed in 13 dogs before and 2, 4, 8 and 12 weeks after creation of perinephritic hypertension. Left ventricular echocardiograms were digitized for dimensions, mass and peak rates of wall thinning (−dh/dt/h) and cavity enlargement (dD/dt/D). Doppler recordings of left ventricular inflow were analyzed for peak early (E) and late (A) diastolic inflow velocities, their ratio and atrial filling fraction.

At 2 weeks, systolic blood pressure increased from 151 to 233 mm Hg, wall stress from 52 to 80 kdynes/cm^2 and posterior wall thickness from 0.68 to 0.84 cm (all $p < 0.05$). Left ventricular mass increased from 90 to 115 g over 12 weeks ($p < 0.05$). Heart rate, cavity size and systolic shortening were unchanged at all data points. Diastolic abnormalities accompanied the developing hypertrophy and included impairment of early function, as demonstrated by a peak rate of wall thinning, from −13.4 to −8.9 l/s at 2 weeks ($p < 0.05$), increased dependence on atrial systolic filling, a decrease in E/A from 1.68 to 1.29 at 4 weeks ($p < 0.05$) and an increase in atrial filling fraction from 30% to 43% at 8 weeks (p = NS).

Thus, diastolic dysfunction is an early consequence of experimental left ventricular hypertrophy. Different aspects of diastolic impairment are sensitively reflected by echocardiographic Doppler recordings, suggesting that these methods should be useful for the detection of diastolic dysfunction in human patients.

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Hypertension is commonly associated with increased left ventricular mass and abnormal diastolic function expressed echocardiographically by reduced peak rates of wall thinning, cavity enlargement and an altered left ventricular inflow pattern (1–7). Increasingly, such abnormalities are recognized as clinically important components of heart disease, with or without concomitant systolic dysfunction. The finding of diastolic dysfunction in patients with mild hypertension and in children suggests that it may develop early in the course of the disease (2,4,5).

Although left ventricular hypertrophy occurs rapidly after the imposition of a pressure load in animal models (8–13), little is known about the time course of any associated functional abnormalities or the relative sensitivity of methods used for their detection. Accordingly, the present study used echocardiographic and Doppler techniques to assess serial changes in left ventricular mass and diastolic function and their interrelations after creation of a canine model of hypertensive heart disease.

Methods

Experimental protocol. Thirteen conditioned mongrel dogs, aged 1 to 2 years and weighing 17 to 22 kg, constituted the study group. Baseline studies performed under light sedation (morphine, 2 mg/kg body weight, intramuscularly) included direct femoral puncture for systolic and diastolic arterial pressures, two-dimensionally guided M-mode echocardiograms of the left ventricle and Doppler recordings of left ventricular inflow velocities. Perinephritic hypertension was then created by silk wrap of one kidney, with contralateral nephrectomy performed 1 week later (14,15). For each procedure, the dogs were premedicated with morphine (2 mg/kg, intramuscularly), and anesthesia was induced with pentobarbital sodium (Nembutal) (10 to 15 mg/kg, intravenously) and morphine (3 mg/kg). The dogs were mechanically ventilated and positioned on their side. For the silk

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wrap, the left kidney was approached sterilely through a flank incision, carefully dissected free of its capsule, and placed in a loosely fitting pouch of unbleached undyed silk. The pouch was secured around the renal vessels, and the kidney returned to its normal position. For the nephrectomy, the right kidney was approached sterilely through a flank incision and removed with careful oversewing of the vascular pedicle. After either procedure, the incision was closed, wound drainage maintained and the dog given trimethoprim sulfa (one tablet twice a day for 5 days). Serial measures of direct femoral artery pressures, M-mode echocardiography and Doppler velocimetry were performed 2, 4, 8 and 12 weeks after nephrectomy. After termination of the study, the dogs were killed with intravenous potassium chloride, and the heart was examined grossly and microscopically.

Echocardiographic recordings. Two-dimensionally guided M-mode echocardiograms of the left ventricle at the high chordal level were performed from above, with the dog lying on its left side. Recordings were made with use of a mechanical ultrasonograph with a 5.0 MHz transducer at a paper speed of 50 mm/s. Imaging location and time-gain settings were adjusted to yield optimal definition of endocardial and epicardial borders. Special efforts were made to ensure reproducible body position and transducer alignment in each dog in each serial study.

All echocardiographic analyses were performed by the same observer who did not know the timing of the study in relation to surgery. Echocardiograms of three to five cardiac cycles were manually digitized at 10 ms intervals along the left septal and posterior wall endocardium and posterior wall epicardium to determine continuous cavity and wall dimensions. End-diastolic and end-systolic cavity dimensions and wall thicknesses were taken as maximal and minimal cavity dimensions, respectively. Relative wall thickness and fractional shortening were calculated. Digitized data were then differentiated to yield normalized peak rates of cavity enlargement (dD/dt/D) and posterior wall thinning (−dh/dt/h). Validation of the computerized analysis of the echograms has been performed by comparison with angiographic data (16,17) and, in our laboratory, such data have proved to be reproducible (18).

An index of end-systolic meridional stress was assessed by combining peak femoral artery pressure obtained by direct puncture with echocardiographic measurements according to the formula (0.334P × LVID/PWT [1 + PWT/LVID]), where P = cuff systolic blood pressure, LVID = left ventricular internal dimension, and PWT = posterior wall thickness. This formula was previously validated in a group of both normal and hypertensive subjects (19).

Echograms were also digitized, excluding right and left septal and posterior wall endocardial thicknesses, for measurement of left ventricular mass by a previously validated method (20): (1.04 × [LVID + PWT + IVST]^3 − [LVID^3] − 13.6 g]), where IVST = intraventricular septal thickness.

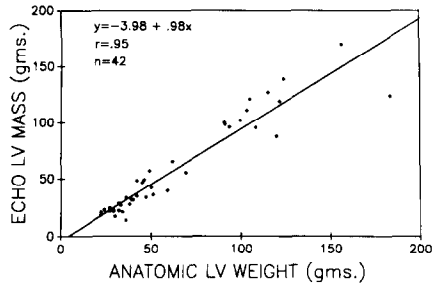


Figure 1. Relation between echocardiographically (ECHO) measured left ventricular (LV) mass in normal and hypertrophied canine ventricles as compared with postmortem left ventricular weight. Echocardiographic left ventricular mass was assessed with Penn convention methods, as described in the text.

The accuracy of the measurement of echocardiographic mass was confirmed in normal and hypertrophied canine left ventricles by anatomic validation. Postmortem left ventricular weight correlated closely with echocardiographic mass performed just before death in 42 dogs, with a correlation coefficient (r) of 0.94; the regression equation was echocardiographic mass = 1.02 (weight) − 5.49, and the standard error of the estimate was 6.3 g (Fig. 1). Similarly, a close relation between echocardiographic and anatomic left ventricular weight in the dog has been reported by others (21).

Doppler velocimetry. Two-dimensional Doppler recordings of left ventricular inflow velocity at the level of the mitral anulus were obtained with a mechanical ultrasonograph equipped with a 5.0 and 2.5 MHz combined imaging and Doppler transducer. All recordings were performed with use of pulsed Doppler ultrasound with a sample volume size of 3 to 6 mm and were obtained from the apical two or four chamber view parallel to flow, with optimal definition of the spectral envelope. A single observer unaware of the timing of Doppler study in relation to the creation of hypertrophy analyzed all data. Three to five cardiac cycles were manually digitized and averaged for the peak velocities and integrals of left ventricular inflow in early and late diastole. Calculated variables included the ratio of inflow velocities and atrial filling fraction or the late flow velocity integral divided by the total diastolic flow velocity integral. Validation of Doppler assessment of left ventricular filling has been performed by comparison to angiographic and nuclear data (22–24), and reproducibility studies in our laboratory (18) have shown excellent correlations between data obtained at repeat study (r = 0.980 to 0.997).

Postmortem examination. Necropsy specimens of the heart and the remaining kidney of each dog were fixed in formalin and submitted for qualitative gross and microscopic examination in comparison with tissues taken from normal animals of similar age and weight. Qualitative assessment of vascular hypertrophy and interstitial fibrosis was performed.

Statistical analysis. Results were analyzed with repeated measures analysis of variance; significant specific compari-

Table 1. Echocardiographic and Doppler Measurements During Progressive Left Ventricular Hypertrophy

	Time After Onset of Hypertension				
	Baseline	2 Weeks	4 Weeks	8 Weeks	12 Weeks
HR (beats/min)	104 ± 24	116 ± 37	125 ± 31	109 ± 29	109 ± 18
Systolic BP (mm Hg)	151 ± 41	233 ± 36†	247 ± 37†	229 ± 40†	243 ± 45†
PWTd (cm)	0.68 ± 0.10	0.84 ± 0.13†	0.87 ± 0.19†	0.96 ± 0.24†	0.92 ± 0.15†
LVIDd (cm)	3.89 ± 0.27	3.82 ± 0.38	3.89 ± 0.50	3.73 ± 0.30	3.76 ± 0.44
RWT	36 ± 8	45 ± 10*	46 ± 11*	52 ± 16†	50 ± 11†
LV mass (g)	90 ± 25	106 ± 23	113 ± 32	110 ± 31*	115 ± 24*
Meridional stress (kdynes/cm^2)	52 ± 15	80 ± 27*	86 ± 43*	69 ± 23	72 ± 23
Fractional shortening (%)	42 ± 7	38 ± 8	40 ± 11	31 ± 24	39 ± 7

*$p < 0.05$ versus baseline; †$p < 0.01$ versus baseline. BP = blood pressure; HR = heart rate; LV = left ventricular; LVIDd = left ventricular internal dimension at end-diastole; PWTd = posterior wall thickness at end-diastole; RWT = relative wall thickness or 2 × PWTd/LVID/d.

sons were analyzed with the Neuman-Keuls test. The relations between indexes of left ventricular hypertrophy and diastolic function were analyzed with use of linear regression.

Results

Hypertension and left ventricular mass (Table 1). Significant hypertension was produced in all dogs within 2 weeks after nephrectomy and was maintained for the 3 month period of study (Fig. 2). Accompanying the rapid increase in blood pressure was a transient increase in meridional stress, which returned toward normal at 8 and 12 weeks as left ventricular mass increased. Left ventricular hypertrophy occurred promptly in response to hypertension; significant increases in posterior wall thickness and relative wall thickness were seen 2 weeks after nephrectomy, and further mild increases thereafter (Fig. 3). Echocardiographic left ventricular mass increased substantially at 2 weeks and reached significance at 8 weeks after the initiation of hypertension. Systolic function, as measured by fractional shortening and the normalized peak rates of posterior wall thickening and cavity shortening, was unchanged throughout the course of the experiment.

Left ventricular filling pattern (Table 2). Evaluation of left ventricular filling by Doppler velocimetry showed a trend towards a decrease in the peak velocities of early inflow (E) and an increase in atrial systolic velocity (A), resulting in a significant decrease in the ratio of E/A inflow velocity at 1 month and a further decrease at 8 and 12 weeks (Fig. 4). The atrial filling fraction increased during the 1st month, but this increase did not reach statistical significance. Digitized M-mode echocardiographic variables showed no significant change in the peak rate of cavity enlargement. In contrast, the peak rate of wall thinning decreased significantly by 2 weeks after nephrectomy, decreasing further at 2 and 3 months (Fig. 5).

Relations between hypertrophy and function. When analyzed across all studies in all dogs, left ventricular mass was weakly but significantly related to systolic blood pressure ($r = 0.32$, $p < 0.02$). Comparisons of hypertrophy and diastolic functional variables showed left ventricular mass to be weakly but significantly related to late flow velocity ($r = 0.33$, $p < 0.02$) and atrial filling fraction ($r = 0.26$, $p < 0.05$) but not to other Doppler or echocardiographic variables (all $r < 0.20$). When directional changes were analyzed, the percent change in left ventricular mass was not related to changes in wall thinning or E/A ratio. In individual dogs,

Figure 2. Systolic blood pressure (BP) and meridional stress in the perinephritic model of developing hypertensive heart disease.

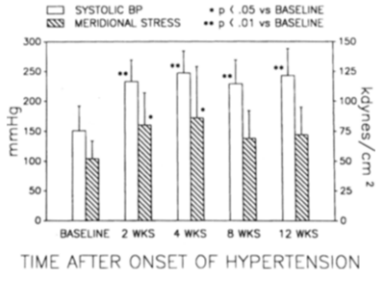


Figure 3. Left ventricular hypertrophy in the developing model of hypertensive heart disease. Posterior wall thickness (PWTd) is shown in **open bars**; left ventricular (LV) mass is shown in **hatched bars.**

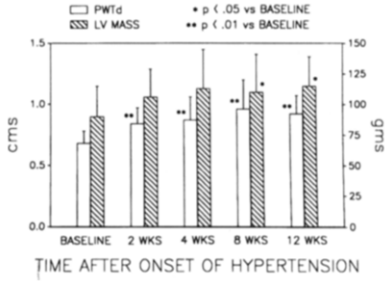


Table 2. Diastolic Function in Progressive Left Ventricular Hypertrophy

	Time After Onset of Hypertension				
	Baseline	2 Weeks	4 Weeks	8 Weeks	12 Weeks
E (cm/s)	66 ± 14	64 ± 20	56 ± 19	57 ± 9	59 ± 16
A (cm/s)	43 ± 14	43 ± 11	47 ± 15	51 ± 10	50 ± 10
E/A	1.68 ± 0.58	1.70 ± 0.98	1.29 ± 0.57*	1.16 ± 0.28†	1.22 ± 0.40*
Atrial filling fraction (%)	30 ± 7	31 ± 11	41 ± 19	43 ± 14	36 ± 7
+dD/dt/per D (1/s)	5.9 ± 1.2	5.1 ± 1.4	5.5 ± 1.9	4.6 ± 1.6	4.9 ± 1.5
−dh/dt/per h (1/s)	−13.4 ± 5.4	−8.9 ± 4.1*	−9.6 ± 3.6*	−8.2 ± 1.8†	−8.8 ± 4.0†

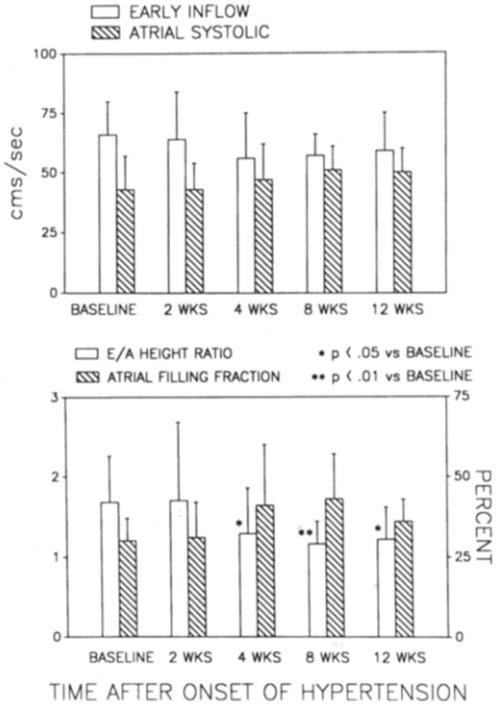
*$p < 0.05$ versus baseline; †$p < 0.01$ versus baseline. A = peak velocity of late diastolic inflow; Atrial filling fraction = integral of late inflow velocity divided by the integral of total inflow velocities; +dD/dt/D = peak rate of early diastolic cavity enlargement; −dh/dt/h = peak rate of early diastolic posterior wall thinning; E = peak velocity of early diastolic left ventricular inflow.

there were no consistent correlations between left ventricular mass and echocardiographic or Doppler variables.

To examine the possibility that relations between indexes of hypertrophy and diastolic function might differ between the steady state and the period when hypertrophy is developing, we separately examined them within 1 month after nephrectomy (2 and 4 weeks) and after 2 months (8 and 12 months). Early, only the peak rate of posterior wall thinning was related to posterior wall thickness ($r = 0.53$, $p = 0.005$) and h/R ratio ($r = 0.46$, $p = 0.02$). After 2 months, posterior wall thickness was related to atrial filling fraction ($r = 0.44$, $p = 0.02$), and relative wall thickness was related to E height ($r = -0.40$, $p < 0.04$), E/A ratio ($r = -0.50$, $p < 0.007$) and atrial filling fraction ($r = 0.55$, $p < 0.003$).

Postmortem examination. In all dogs, qualitative examination revealed mild to moderate hypertrophy of small and mid-sized arterioles in all areas of the left ventricle. In two dogs, a small area of patchy fibrosis was observed in the dorsal left ventricular free wall. There was no evidence of segmental scarring or chronic ischemia, nor did qualitative examination for collagen show an increase in connective tissue.

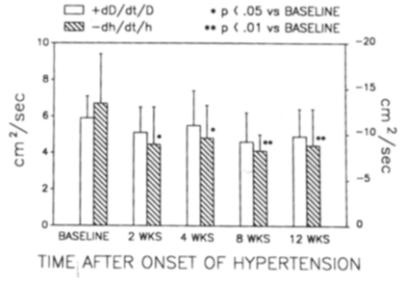
Figure 4. Left ventricular inflow velocity indexes, early (E) and late (A) in dogs with developing hypertensive heart disease.



Discussion

Effect of perinephritic hypertension on ventricular mass and diastolic filling. The present study employed a canine model of perinephritic hypertension to assess the time course of the development of diastolic abnormalities in progressive left ventricular hypertrophy and to compare the utility of Doppler velocimetry and M-mode echocardiographic methods for its detection. Significant increases in

Figure 5. M-mode echocardiographic indexes of diastolic function in dogs with developing hypertensive heart disease. The normalized peak rate of cavity enlargement (+dD/dt/D) is shown in **open bars;** normalized peak rate of posterior wall thinning (−dh/dt/h) is shown in **hatched bars.**



blood pressure and wall stress occurred within 2 weeks after the creation of the model and resulted in a substantial increase in left ventricular wall thickness over this time period. This rapid hypertrophic response is consistent with the known early (within hours) increase in nucleic acid and myosin production after imposition of a pressure load (8–11), which is closely followed by maximal increases in ventricular mass within several weeks (12). Our data clearly demonstrate that measurable diastolic dysfunction is also rapidly produced by pressure overload; from our first measurement at 2 weeks, hypertrophy was characterized by a delay in wall thinning that was soon followed by a change in the left ventricular filling pattern.

The appropriateness of some animal models of left ventricular hypertrophy, such as aortic banding, has been criticized (25) because a sudden imposition of a pressure overload may produce patchy but widespread injury leading to myocardium scarring and fibrosis. In contrast, and as might be expected from the gradual pressure increase known to characterize this model, detailed postmortem examination of the dogs in this study showed little such damage, with no evidence of segmental cardiac injury. Although quantitative assessment of collagen content was not performed, fibrosis was not qualitatively increased. The only consistent pathologic finding was mild to moderate medial hypertrophy in small and mid-sized arterioles.

In the perinephritic model employed, the earliest hemodynamic change is an increase in stroke volume and cardiac output, followed by hypertension and increased peripheral resistance (14). After approximately 4 weeks, however, cardiac output decreases, yet resistance remains elevated, becoming the dominant cause of hypertension. Thus, the hemodynamic pattern that induced hypertrophy in our dogs is similar to that postulated in some forms of human hypertension. Taken together with the marked similarity between the constellation of diastolic abnormalities developing in our animals and those known to occur in hypertensive human patients, the hemodynamic abnormalities and pathologic findings suggest that the canine preparation studied is a valuable model of human hypertensive heart disease.

Diastolic abnormalities in hypertension. Our findings corroborate clinical studies that have documented diastolic dysfunction in hypertensive humans. A wide variety of abnormalities have been reported (2,3,7,26,27) with use of the techniques we employed. These include slowed isovolumic relaxation and impaired rapid filling (delayed rates of cavity enlargement and wall thinning and reduced peak velocity and slowed deceleration of early inflow) and increased late inflow velocity and atrial contribution to stroke volume (atrial filling fraction). Furthermore, such abnormalities have been documented (2,4,5) in children and untreated mildly hypertensive adults, suggesting that a broad spectrum of diastolic functional impairment characterizes the earliest stages of hypertensive disease in humans. Thus, unlike the right ventricle, which after imposition of a pressure overload has been found to first manifest changes consistent with physiologic hypertrophy (13), the left ventricular response does not vary and displays pathologic hypertrophy from the onset. The early appearance of diastolic dysfunction provides a rationale for the treatment of even very mild hypertension, especially if such abnormalities can be lessened, and provides insight into the physiology and progression of hypertensive heart disease.

Although it is tempting to evaluate the relative sensitivity of M-mode echocardiographic and Doppler techniques, their detection of different aspects of diastole makes this difficult (28) but suggests that they may be complementary. The slightly earlier reduction in wall thinning (at 2 weeks) than in the E/A ratio (at 4 weeks) is unlikely to be clinically significant because a patient would have to undergo study too early in his or her disease process for it to matter. The lack of significant changes in early (E) or (late) (A) filling alone, but only in the calculated ratio, is also of concern. Other investigators (2) have suggested that Doppler methodology is superior, noting abnormalities in Doppler velocimetry without concomitant changes in wall thinning or cavity enlargement or that technically adequate echocardiographic recordings are harder to obtain and more subject to marked biologic variability (29,30) than are Doppler recordings. However, our data concur with many of the previous studies and indicate that both methods are useful in the clinical assessment of early as well as advanced hypertensive heart disease.

Development of diastolic dysfunction. The exact mechanism or mechanisms by which diastolic dysfunction develops is incompletely understood, and our study was not specifically designed to address this issue. However, other findings of a closer relation between peak rate of wall thinning and variables of relaxation, such as Tau rather than stiffness (31), and the lack of early increase in hydroxyproline synthesis in experimental hypertrophy (9) suggest that increased collagen content may not have been an early contributor to diastolic dysfunction. Other possibilities include ischemia caused by a decrease in coronary blood flow relative to increased mass (32,33), myocardial damage produced by the severe hemodynamic load (although evidence for this could not be detected at postmortem examination), increased myocyte size with possible alteration of cell shape, fiber orientation or stiffness (34,35) and altered adrenergic tone or calcium uptake. Similarly, the altered left ventricular filling pattern may be related to increased left ventricular afterload, increased myocardial or chamber stiffness, decreased left ventricular compliance and enhanced vigor of atrial systolic function. Other variables known to affect left ventricular inflow velocities, such as preload (as measured by left ventricular diastolic dimension) and systolic left ventricular function were not altered; heart rate was increased only at 2 and 4 weeks. Each of these changes, with

the exception of fibrosis, could occur early enough to explain the timing of our findings, and it is likely that several of these processes contributed. Perhaps even more important, we cannot exclude the possibility that the measured indexes reflect different phenomena at different times in the evolution of hypertrophy.

In the present study, the lack of a close correlation between functional abnormalities and left ventricular hypertrophy suggests that the extent of hypertrophy alone is not a primary determinant of early diastolic function. This possibility is supported by others (2), who have found functional impairment in the hypertensive heart even in the absence of left ventricular hypertrophy. However, these findings are in contrast to those reported by Fouad et al. (6) and Shapiro and McKenna (27), who noted modest relations between structure and function in subjects with long-established (rather than developing) hypertension and hypertrophy. One explanation for this difference, namely, that the origin of diastolic dysfunction may vary with the progression of the hypertrophic process, is our finding of the closer relations between left ventricular structure and diastolic function 2 months after nephrectomy rather than within 1 month.

Limitations of study. In addition to the difficulties inherent in any animal model of human disease, several methodologic points are worth noting as limitations of the techniques employed. Although extensive validation of echocardiographic and Doppler methods has not been performed in the dog, conventional methods for echocardiographic measurement of left ventricular mass did prove to be accurate with anatomic validation. In addition, our purpose was to demonstrate serial changes in such variables rather than to identify normal or abnormal values. The use of a single blood pressure recording requiring femoral artery puncture under sedation is not ideal; however, the difficulties inherent in obtaining noninvasive pressure measurements in the dog are well known, and the importance of our findings rests not on the extent of pressure overload, but rather on its structural and functional consequences.

Implications. Both delayed wall thinning and an altered left ventricular inflow pattern are characteristic of the earliest stages of left ventricular hypertrophy. Because digitized M-mode echocardiography and Doppler velocimetry measure two different aspects of diastole, it is not surprising that the results of the two methods are poorly correlated. Both, however, are sensitive and should be clinically useful in the evaluation of early hypertensive heart disease in humans. Because of the early appearance of diastolic dysfunction, it is to be expected that such abnormalities may be detected in patients with mild hypertension and may not correlate with the extent of hypertrophy. A better understanding of hypertensive heart disease is needed to more fully identify the cause of the functional consequences of pressure overload hypertrophy.

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