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Heart Failure in Pressure Overload Hypertrophy

The Relative Roles of Ventricular Remodeling and Myocardial Dysfunction

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OBJECTIVES We sought to explore the relative contributions of ventricular remodeling and myocardial dysfunction to heart failure in pressure overload hypertrophy (POH).

BACKGROUND The mechanism that underlies heart failure in POH is adverse left ventricular (LV) chamber remodeling or decreased myocardial function, or a combination of these.

METHODS Twenty weeks after suprarenal aortic banding in rats, animals with POH were classified as those with heart failure (POH-HF) or those with no heart failure (POH-NHF). The LV chamber and myocardial systolic and diastolic functions were determined from in vivo and ex vivo experiments.

RESULTS The LV mass was similar in both POH groups. Chamber remodeling in the POH-HF group was characterized by marked LV enlargement with a normal relative wall thickness (eccentric remodeling), whereas remodeling in the POH-NHF group was characterized by a normal chamber size and increased relative wall thickness (concentric remodeling). The LV systolic function, as determined in vivo from the end-systolic pressure–diameter relationship and ex vivo from the pressure–volume relationship, was lower in the POH-HF group than in the POH-NHF and sham-operated control groups. In contrast, myocardial function was similar in both POH groups, as determined in vivo from the stress–midwall fractional shortening relationship and myocardial systolic stiffness, and ex vivo from the slope of the LV systolic stress–strain relationship. The diastolic chamber stiffness constant was lower in the POH-HF group than in the POH-NHF group, but the myocardial stiffness constant was similar in the two POH groups.

CONCLUSIONS The two POH groups differed primarily in their remodeling process, which led to a chronically compensated state in one group and to heart failure in the other. Hence, heart failure in POH is more closely related to deleterious LV remodeling than to depressed myocardial function. (J Am Coll Cardiol 2002;39:664–71) © 2002 by the American College of Cardiology

Left ventricular (LV) failure in pressure overload hypertrophy (POH) is heralded by a decrement in LV systolic and diastolic function (1,2). The mechanism that is likely to underlie such decompensation is adverse LV chamber remodeling (3–5) or decreased myocardial contractile function (6–10), or a combination of these (4,7). Cohn (5,11) has suggested that chronic structural remodeling of the LV may be the major impetus to heart failure and that such remodeling, not primary myocardial contractile dysfunction, is the principal contributor to the failure of the heart as a pump.

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This notion is supported by the observation that postinfarction remodeling with global LV dysfunction has been shown to occur with little or no myocyte contractile abnormalities (12). However, the relative contributions of detrimental remodeling and depressed myocardial contractile function to pump failure in POH are unknown. If LV remodeling is the dominant factor, prevention or reversal of such a detrimental process becomes an important therapeutic goal (4,5). Therefore, we studied the functional properties of the LV chamber and the mechanical properties of the myocardium in compensated and failing rats with POH, and we tested the hypothesis that LV failure in POH is predominantly related to deleterious LV remodeling rather than depressed myocardial function.

METHODS

Experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health, publication no. 86-23, 1996). The protocol was approved by the Animal Research Committee of the University of Massachusetts Medical School. Male Sprague-Dawley rats (weight 200 g) were subjected to either suprarenal aortic banding or a sham operation, as previously described (13). Of the 200 banded rats, 88 animals survived for 20 weeks. Eight rats were excluded, because their LV weights were similar to those of the control group (n = 30).

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Abbreviations and Acronyms

BP	= blood pressure
FS_{mw}	= midwall fractional shortening
LV	= left ventricular
POH	= pressure overload hypertrophy
POH-HF	= pressure overload hypertrophy with heart failure
POH-NHF	= pressure overload hypertrophy with no heart failure

Of the remaining 80 animals, 39 rats had a lung weight/body weight ratio >2 SD above the mean for the control group and were classified as POH with heart failure (POH-HF). The rest of the rats were classified as POH with no failure (POH-NHF). Twenty weeks after the operation, the control, POH-HF and POH-NHF rats were randomly used for either groups' in vivo or ex vivo experiments.

In vivo studies. The rats were anesthetized, and their carotid blood pressure (BP) was measured as previously described (13). Echocardiography was performed from below using a 7.5-MHz transducer and a Hewlett-Packard Sonos 1500 sector scanner, as outlined previously (13). After baseline BP and echocardiographic recordings were obtained, the load was manipulated by slowly infusing angiotensin II (5 nmol/liter, dissolved in 1 ml of normal saline) through the carotid catheter over a 10- to 20-s period. Once the BP had stabilized, normal saline was infused (0.5 to 3 ml) to determine whether maximal peak systolic BP had been attained. Blood was then withdrawn (0.5 to 1 ml per 5 min period to a maximum of 6 ml) to decrease the load. Echocardiographic dimensions were obtained at the maximal systolic BP and when hemodynamic measurements were stable during blood withdrawal. Data were excluded if peak systolic pressure was <120 mm Hg. The LV internal dimensions and wall thickness were measured according to the American Society for Echocardiography's leading edge method (14). Measurements were made from three consecutive beats, and relative wall thickness and fractional shortening were calculated as previously described (13).

LEFT VENTRICULAR CHAMBER FUNCTION. In vivo LV systolic chamber function was evaluated by constructing the end-systolic pressure–dimension relationship from a range of pressure and diameter coordinates obtained during the loading interventions.

MYOCARDIAL FUNCTION. In vivo myocardial systolic function was assessed by constructing LV midwall stress–shortening and end-systolic stress–strain (stiffness) relationships. Midwall fractional shortening (FS_{mw}) and end-systolic stress were derived as previously described (15,16). To compare shortening at a similar stress value, FS_{mw} was calculated at a stress rate of 75 $g \cdot cm^{-2}$ from the slope and intercepts of these relationships. The end-systolic stress–strain relationship was calculated as previously described (17). Because end-systolic diameters were not available at 0 mm Hg, we adopted the approach that is commonly used in isolated papillary muscle studies, where strain is determined as a fraction of the length of the muscle strip (in our case, the end-systolic diameter as a surrogate for length), which achieves maximal tension (stress).

Ex vivo studies. The isolated, perfused heart preparation used in this study was previously described by Chung et al. (13). After the rats were anesthetized, their hearts were excised, rinsed and weighed in ice-cold physiologic saline solution. The hearts were then perfused at a flow rate adjusted to achieve an approximate flow of 12 ml/min per g heart weight, which was kept constant throughout the experiment. Coronary perfusion pressure was monitored throughout the experiment. The hearts were paced at 300 beats/min. A thin-walled latex balloon with a capacity beyond the maximal lumen capacity of the LV was then inserted into the LV cavity through the left atrium and attached to a Statham P23 Db transducer. The volume of the balloon wall was assessed using a water displacement technique. A micromanipulator was used to gradually increase the LV volumes. The LV diastolic and developed pressures were recorded with every increment in volume, so that a range of pressure–volume data were obtained.

SYSTOLIC AND DIASTOLIC LV CHAMBER FUNCTION. Ex vivo LV systolic and diastolic chamber functions were assessed by constructing the systolic (developed) and diastolic pressure–volume relationships from developed and diastolic pressure–volume data coordinates.

SYSTOLIC AND DIASTOLIC MYOCARDIAL FUNCTION. Ex vivo myocardial function was assessed by constructing the developed systolic stress–strain and diastolic stress–strain relationships. Developed systolic stress and strain were calculated by using previously described equations (18), assuming a thick-walled, spherical LV geometry. Diastolic myocardial stiffness was calculated using previously described formulae (19).

Myocardial collagen. Samples of LV tissue from all rats were weighed and stored at −80°C for hydroxyproline analysis. The myocardial hydroxyproline concentration was determined by using the method of Stegemann and Stalder (20).

Data analysis. The slopes of pressure–dimension, systolic and diastolic pressure–volume, stress–shortening and end-systolic and end-diastolic stress–strain relationships of each animal were determined by linear regression analysis. Differences in LV geometry, hemodynamic variables and biochemical variables between the groups were assessed using one-factor analysis of variance, followed by Tukey's post hoc test. A p value <0.05 was considered significant. All data are expressed as the mean value ± SEM.

Table 1. In Vivo Data in Control Rats and Rats With Pressure Overload Hypertrophy With or Without Pulmonary Congestion

	Control Group (n = 18)	POH-NHF Group (n = 16)	POH-HF Group (n = 18)
Systolic BP (mm Hg)	158 ± 4	215 ± 6*	185 ± 8*†
Diastolic BP (mm Hg)	105 ± 3	125 ± 2*	112 ± 5†
Body weight (g)	433 ± 10	438 ± 12	456 ± 10
LV weight (g)	1.12 ± 0.04	1.63 ± 0.06*	1.73 ± 0.06*
LV $weight_i$	2.61 ± 0.11	3.73 ± 0.13*	3.82 ± 0.13*
RV weight (g)	0.22 ± 0.01	0.28 ± 0.02*	0.36 ± 0.02*†
Lung weight (g)	2.12 ± 0.07	2.17 ± 0.09	4.55 ± 0.33*†
LV end-systolic stress ($g \cdot cm^{-2}$)	60.4 ± 5.1	62.5 ± 8.2	83.3 ± 7.5*†
LVEDD (mm)	8.59 ± 0.17	8.80 ± 0.25	10.41 ± 0.31*†
LVESD (mm)	5.18 ± 0.16	5.28 ± 0.31	7.25 ± 0.27*†
LV relative wall thickness	0.36 ± 0.02	0.47 ± 0.03*	0.41 ± 0.02†
FS_{endo} (%)	39.7 ± 1.5	40.6 ± 2.1	28.5 ± 1.0*†
Hydroxyproline (μg/mg per dry LV weight)	3.98 ± 0.20	4.33 ± 0.31	5.47 ± 0.36*†

*$p < 0.05$ versus control group; †$p < 0.05$ versus POH-NHF group. Data are presented as the mean value ± SEM.
BP = blood pressure; FS_{endo} = fractional shortening at the endocardium; LV = left ventricular; LV $weight_i$ = LV weight/100 per body weight × 10^{-3}; LVEDD = LV end-diastolic diameter; LVESD = LV end-systolic diameter; POH-HF = pressure overload hypertrophy with heart failure; POH-NHF = pressure overload hypertrophy with no heart failure; RV = right ventricular.

RESULTS

Blood pressure and heart and lung weights. Systolic and diastolic BPs were elevated in both POH groups, with pressures being higher in the POH-NHF group than in the POH-HF group (Table 1). The LV weight increased to a similar extent in both POH groups. However, right ventricular weight was greater in the POH-HF group than in the POH-NHF and control groups. Similarly, the lungs of the POH-HF group weighed twofold more than those of the other two groups, consistent with pulmonary congestion (Tables 1 and 2). Unlike the in vivo POH-HF group, the body weight of the ex vivo POH-HF group was lower than that of the control and POH-NHF groups.

Geometric and interstitial remodeling. In response to chronic pressure overload, the POH-NHF group remodeled concentrically, whereas the POH-HF group remodeled eccentrically (Table 1). Consequently, the relative wall thickness was lower and the end-systolic wall stress was higher in the POH-HF group than in the POH-NHF group (Table 1). Myocardial total hydroxyproline concentrations were higher in the POH-HF groups of both in vivo and ex vivo experiments than in the control and POH-NHF groups (Tables 1 and 2).

Systolic and diastolic LV chamber function. The POH-HF group was characterized by a decline in fractional endocardial shortening (Table 1), as well as a rightward shift and a decrease in the slope of both the pressure–dimension and pressure–volume relationships, as compared with the control and POH-NHF groups (Figs. 1 and 2, Table 3). The changes in the pressure–volume relationship could not be attributed to differences in coronary flow (Table 2).

In response to angiotensin II infusions, fractional endocardial shortening decreased to a similar extent in the control and POH-NHF groups (34.2 ± 0.9% and 35.9 ± 2%, respectively). The LV end-systolic stress increased to levels comparable to those obtained in the POH-HF group under baseline conditions (stress measured in $g \cdot cm^{-2}$: 83 ± 3 [control group] vs. 82 ± 4 [POH-NHF group]) (Table 1). However, fractional endocardial shortening in both the control and POH-NHF groups was still significantly greater than that seen in the POH-HF group before the infusion of angiotensin II (28.5 ± 1.0%, $p < 0.01$). Thus, at common levels of systolic stress, LV chamber function was lower in the POH-HF group than in the control and POH-NHF groups.

Table 2. Ex Vivo Data in Control Rats and Rats With Pressure Overload Hypertrophy With or Without Pulmonary Congestion

	Control Group (n = 12)	POH-NHF Group (n = 25)	POH-HF Group (n = 21)
Body weight (g)	471 ± 11	449 ± 8	416 ± 10*†
LV weight (g)	1.21 ± 0.05	1.72 ± 0.04*	1.79 ± 0.04*†
LV $weight_i$	2.55 ± 0.06	3.84 ± 0.07*	4.33 ± 0.09*†
RV weight (g)	0.28 ± 0.02	0.30 ± 0.01	0.39 ± 0.03*†
Lung weight (g)	1.93 ± 0.06	1.96 ± 0.05	4.04 ± 0.32*†
Hydroxyproline (μg/mg per dry LV weight)	3.43 ± 0.14	4.17 ± 0.19	5.07 ± 0.21*†
Coronary flow (ml/min per g wet heart weight)	12.1 ± 1.9	12.9 ± 1.2	12.1 ± 1.9

*$p < 0.05$ versus control group. †$p < 0.05$ versus POH-NHF group. Data are presented as the mean value ± SEM.
Abbreviations as in Table 1.

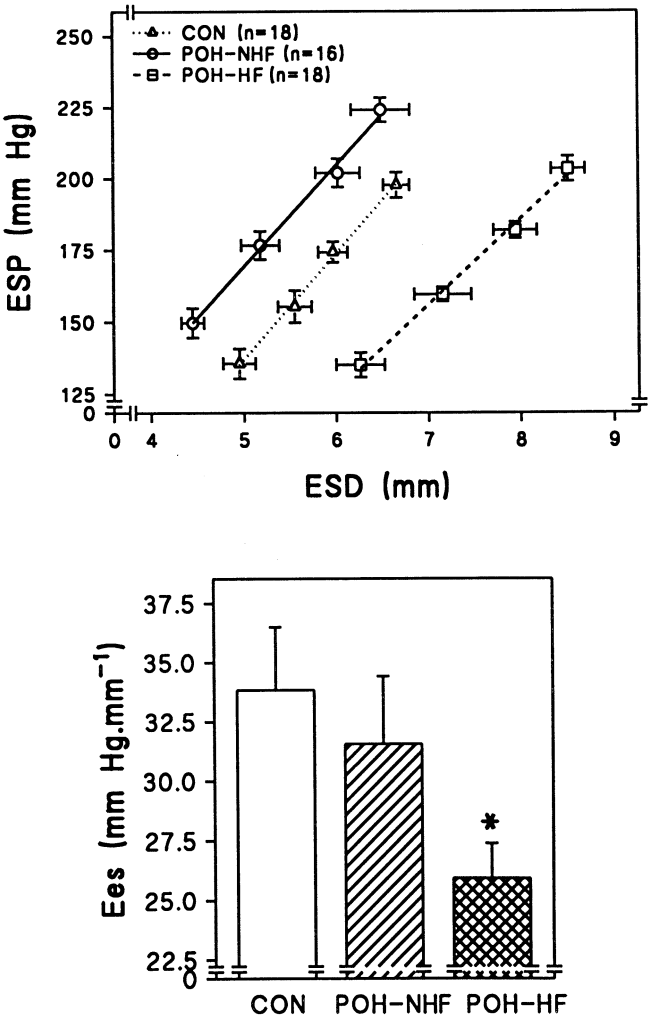

Figure 1. Left ventricular systolic function in rats with pressure overload hypertrophy (POH). The in vivo pressure–dimension relationship in the pressure overload hypertrophy with heart failure (POH-HF) and pressure overload hypertrophy with no heart failure (POH-NHF) groups exhibits a progressive rightward shift that is most pronounced in the POH-HF group **(top)**. The slope of this relationship (Ees) in the POH-HF group is significantly lower (~25%) than that in the control group **(bottom)**, although the small reduction (~10%) in the POH-NHF group is not significantly less. *$p < 0.05$ vs. control and POH-NHF groups. CON = sham-operated control group; ESP = end-systolic pressure.

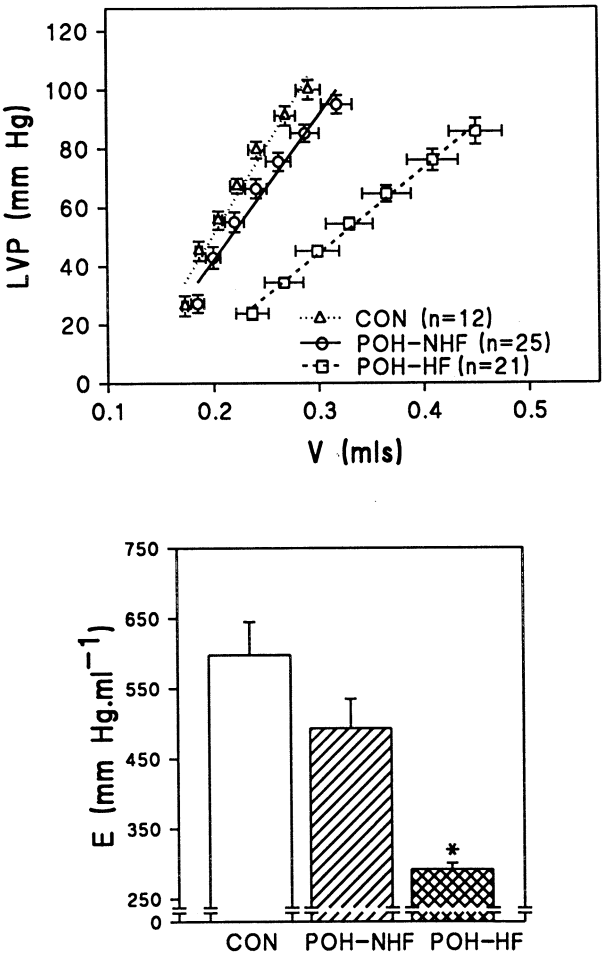

Figure 2. Left ventricular systolic function in rats with POH. The ex vivo pressure–volume relationship in the POH-HF and POH-NHF groups exhibits a progressive rightward shift that is most prominent in the group with heart failure **(top)**. The slope of this relationship (E) is significantly lower (~50%) in the POH-HF group than in the control group, although the small reduction (~15%) in the POH-NHF group is not significantly less. *$p < 0.05$ vs. control and POH-NHF groups. LVP = left ventricular pressure; V = volume; other abbreviations as in Figure 1.

The diastolic LV chamber stiffness constant (k) was lower in the POH-HF group than in the control and POH-NHF groups (Table 3, Fig. 3). The intercept of the diastolic pressure–volume relationship shifted from 0.23 ± 0.006 ml in the control group and 0.24 ± 0.007 ml in the POH-NHF group to 0.35 ± 0.009 ml in the POH-HF group ($p < 0.001$) (Fig. 3).

Systolic and diastolic myocardial function. In contrast to the differences in LV systolic chamber function noted between the POH-HF and POH-NHF groups, myocardial function was similar in the two POH groups (Figs. 4–6, Table 3). Both POH groups exhibited a nonsignificant depression of the stress–shortening relationship; approximately one-third of the stress–FS_{mw} values for both POH groups fell below the lower 95% confidence limits of the control group (data not shown). Although there was no difference in the stress–strain (stiffness) relationship, as determined from the in vivo data, both POH groups exhibited a rightward shift and a decrease in the slope of the myocardial stress–strain relationship (Figs. 5 and 6). Thus, myocardial function appears to be normal to depressed in both POH groups; all three indexes indicate that there was no difference in myocardial function between the two POH groups. Similarly, there was no difference in the diastolic myocardial stiffness constant (k) between the POH-HF and POH-NHF groups (Table 3, Fig. 3).

DISCUSSION

The major finding of the present study is that heart failure in POH is more closely related to deleterious LV remodeling than to depressed myocardial contractile function. In contrast to the concentric hypertrophic response seen in the POH-NHF group, the POH-HF group exhibited chamber

Table 3. Left Ventricular Chamber and Myocardial Systolic and Diastolic Function in the Control and Pressure Overload Hypertrophy Groups

	Control Group	POH-NHF Group	POH-HF Group
LV chamber function			
In vivo systolic elastance (E_{es}; mm Hg/mm)	34 ± 3	31.5 ± 3	26 ± 1.5*†
Ex vivo systolic elastance (E_{es}; mm Hg/ml)	598 ± 48	493 ± 41	291 ± 9*†
Ex vivo diastolic chamber stiffness constant (k; g·cm^{-2})	18.1 ± 1.3	18.2 ± 1.5	13.2 ± 1.0*†
Myocardial function			
In vivo stress–shortening relation (FS_{mw} 75%)	19.3 ± 1.1	16.6 ± 5.4	18.1 ± 1.5
In vivo systolic myocardial stiffness (g·cm^{-2})	327 ± 39	258 ± 27	327 ± 18
Ex vivo stress–strain relation (E^n)	687 ± 23	515 ± 5*	479 ± 14*
Ex vivo diastolic myocardial stiffness constant (k; g·cm^{-2})	39 ± 3.6	42 ± 2.2	44 ± 2.4

*$p < 0.05$ vs. control group. †$p < 0.05$ vs. POH-NHF group. Data are presented as the mean value ± SEM. FS_{mw} 75-fractional midwall shortening at a common stress of 75 g·cm^{-2}; other abbreviations as in Table 1.

enlargement, lower relative wall thickness, increased systolic wall stress and reduced systolic shortening. However, the two POH groups did not show significant differences in myocardial mass or myocardial contractile function. Therefore, it appears that the two POH groups differed primarily in the remodeling process, which led to a chronically compensated state in one group and to heart failure in the other (Table 4).

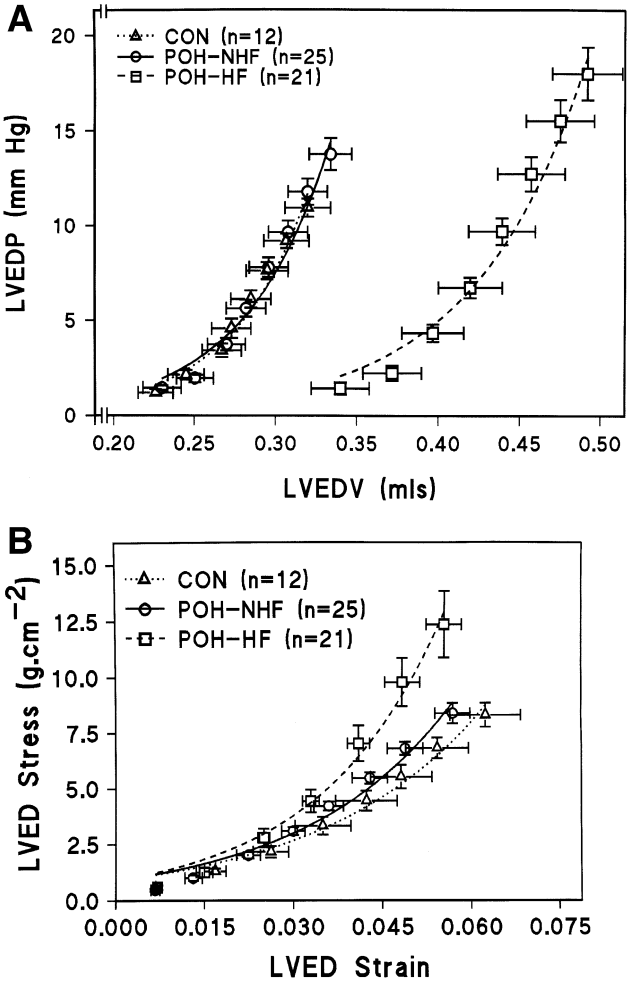

Figure 3. Left ventricular and myocardial diastolic function in rats with POH. A reduced diastolic chamber stiffness is noted for the POH-HF group **(A)**, although there is a trend ($p > 0.25$) for myocardial stiffness to increase in the same group, as compared with the control and POH-NHF groups **(B)**. LVED(P) or (V) = left ventricular end-diastolic (pressure) or (volume). Abbreviations as in Figure 1.

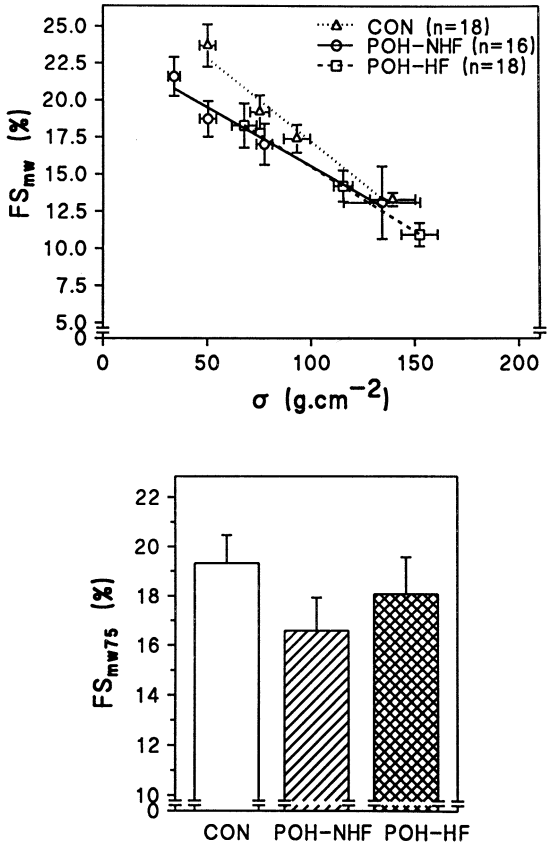

Figure 4. Myocardial systolic function in rats with POH. The in vivo stress (σ)–shortening (FS_{mw}) relationship exhibits a trend toward depression in both POH groups **(top)**. However, at a common stress of 75 g·cm^{-2}, shortening in both POH groups was similar to that of the control group **(bottom)**. Thus, myocardial function in the POH-HF and POH-NHF groups was similar. Abbreviations as in Figure 1.

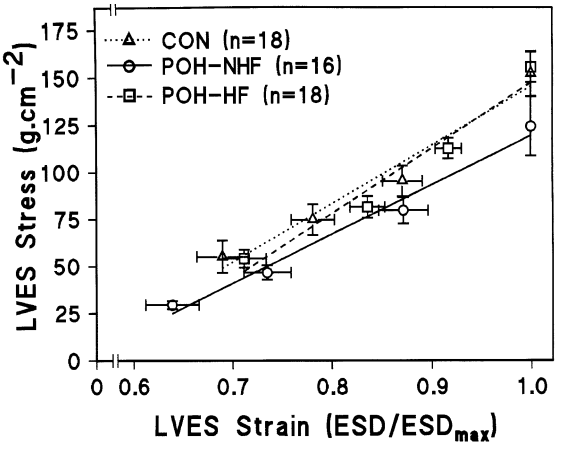

Figure 5. Myocardial systolic function in rats with pressure overload hypertrophy (POH). The in vivo left ventricular end-systolic (LVES) stress–strain (systolic stiffness) relationship was similar in both POH groups and was not different from that of the control group. ESD = end-systolic diameter; other abbreviations as in Figure 1.

Influence of geometry on the assessment of LV chamber and myocardial function. In these studies, we assessed LV function using measurements taken at the endocardial surface (e.g., dimension, volume, shortening at the endocardial surface). Such variables reflect LV (chamber) function. To overcome the limitations of using functional variables that are influenced by chamber geometry, we assessed myocardial function with normalized midwall stress–shortening and stress–strain relationships using in vivo and ex vivo techniques (Figs. 3 and 4) (15,16,21).

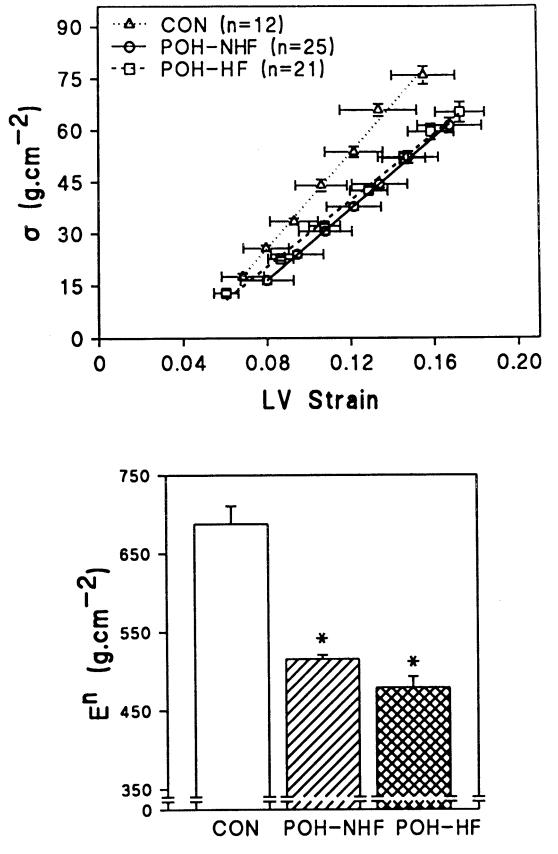

Figure 6. Myocardial systolic function in rats with POH. The ex vivo stress (σ)–strain relationship exhibits depression in both POH groups (~25% lower than that in the control group) **(top)**. The slope of this relationship (E^n) is similar in both POH groups. Myocardial function in the POH-HF and POH-NHF groups was similar. *$p < 0.05$ vs. control group. Abbreviations as in Figure 1.

Table 4. Left Ventricular and Myocardial Function in Pressure Overload Hypertrophy With or Without Heart Failure

	POH-NHF	POH-HF
LV mass	↑	↑
LV geometry		
End-diastolic diameter	N	↑
Relative wall thickness	↑	N
Fractional shortening	N	↓
Hydroxyproline concentration	N	↑
Systolic and diastolic LV chamber function		
In vivo systolic P-D relation	N	↓
Ex vivo systolic P-V relation	N	↓
Ex vivo diastolic chamber stiffness	N	↓
Systolic and diastolic myocardial function		
In vivo stress–shortening relation	N	N
In vivo systolic myocardial stiffness	N	N
Ex vivo systolic stress–strain relation	↓	↓
Ex vivo diastolic myocardial stiffness	N	N

P-D = pressure–dimension; P-V = pressure–volume; N = not different from control group; ↓ = decreased; ↑ = increased; other abbreviations as in Table 1.

The assessment and comparison of ventricular and myocardial function is complicated by the distinctly different remodeling patterns in the two POH groups. Eccentric geometry in the POH-HF group was accompanied by major abnormalities in ventricular function, in combination with what appears to be normal to depressed myocardial function. It is therefore possible that an earlier stage of remodeling could be accompanied by depressed chamber function and preserved myocardial function. In contrast, concentric remodeling with greater relative wall thickness is accompanied by normal ventricular chamber function and myocardial function, similar to that seen in the POH-HF group (22). These observations dictate the utilization of indexes that reflect LV chamber function, in combination with those that reflect the functional properties of the myocardium.

Left ventricular remodeling versus myocardial dysfunction. The findings in this study did not suggest that myocardial contractile function was normal in the POH groups. The in vivo stress–shortening data suggest a small functional decrement in the two POH groups (p = NS). The ex vivo stress–strain data indicate significant myocardial depression in both POH groups, as compared with the control group. These findings are concordant with a large body of data on myocardial contractile function in the hypertrophic myocardium (6–10). Thus, myocardial function, though probably depressed, was remarkably similar in the two POH groups, despite major differences in ventricular geometry and chamber function.

In agreement with the aforementioned conclusions was

the finding that the diastolic chamber stiffness constant (k) in the POH-HF group was lower than that seen in the POH-NHF group. These non-normalized chamber stiffness results are consistent with chamber dilation, and they do not necessarily represent differences in diastolic myocardial stiffness. Although the diastolic myocardial stiffness constants tended to be higher in the POH-HF group than in the POH-NHF group, and hence, may have contributed to pulmonary congestion, the differences were small and not statistically significant. These findings parallel those for systolic chamber and myocardial function. Thus, the systolic and diastolic properties of the LV chamber differ substantially between the POH-HF and POH-NHF groups, although those of the myocardium do not.

The myocardial collagen content (hydroxyproline) was significantly higher in the POH-HF group than in the POH-NHF group. Because increased collagen content occurs in response to mechanical overload and participates in the adaptation process of remodeling (23), an increased hydroxyproline concentration is probably a marker of an active remodeling process. These findings support the notion that the hearts of the POH-HF group showed evidence of more aggressive and detrimental remodeling, as compared with the hearts of the POH-NHF group.

The findings in this study appear to be at odds with the findings in some other studies of POH (6–9). First, in contrast to our observations that myocardial contractile function was similar in the POH groups with and without heart failure, Conrad et al. (9) demonstrated that active tension development and shortening velocity of isolated LV papillary muscles from spontaneously hypertensive rats with heart failure are depressed, as compared with those variables from animals without heart failure. Similar conclusions were reached on the basis of papillary muscle experiments in Dahl salt-sensitive rats with heart failure (6). Differences in the animal models used to evaluate the transition to heart failure in POH may, at least in part, explain these discrepant findings. For example, myocardial dysfunction in the aging, spontaneously hypertensive rat is likely to be due to the combined effects of aging and hypertension, rather than pressure overload alone. In the model of POH used in our study, younger animals were used, and these rats had a high mortality early after the operation (~50% died within the first 4 weeks of aortic banding). Hence, the model in this study represents a more aggressive pressure overloaded state in younger rats, which resulted in advanced hypertrophy in both POH groups. Second, although we showed that heart failure in POH is closely related to the degree of deleterious remodeling, Morii et al. (7) suggested that the transition from compensated hypertrophy to heart failure in Dahl salt-sensitive rats is due to decreased myocardial contractility and abnormal ventricular remodeling. These conclusions were based on the demonstration of a shift in the intercept and a decrease in the slope of the end-systolic pressure–volume relationship in failing hearts. However, the pressure–volume relationship of the LV is inherently an expression of the mechanical behavior of the chamber, rather than measure of its muscle properties (21).

Conclusions. The remodeling process, which involves complex molecular and cellular mechanisms, appears to be a major contributor to the process of decompensation in POH. The progressive changes in LV volume and shape associated with eccentric remodeling present a considerable mechanical disadvantage to the heart and promote worsening of LV pump function. The increased chamber volume contributes to increases in systolic wall stress, leading to afterload mismatch and sustained overload. The resultant hemodynamic abnormalities activate compensatory neurohormonal mechanisms that, over time, further contribute to disease progression. Our data and those of Anand et al. (12) identify reversal of deleterious remodeling as a potential therapeutic goal in hearts with early evidence of LV chamber enlargement in POH and after myocardial infarction.

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