

Gender Differences in Post-Infarction Hypertrophy in End-Stage Failing Hearts

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OBJECTIVES	We explored whether there are gender differences in cardiac remodeling and whether etiology influences organ and cellular remodeling in advanced heart failure (HF).
BACKGROUND	Several studies have shown a survival benefit for women compared to men with symptomatic HF. This observation may be related to gender differences in cardiac remodeling.
METHODS	We studied hearts from 100 patients (72 men and 28 women) receiving cardiac transplantation at our institution. Cardiac morphology was assessed with echocardiography and direct measurement of cardiac mass. Cardiac myocyte volume, length, width, cross-sectional area, and contraction were measured using previously validated techniques.
RESULTS	Among 50 patients with idiopathic cardiomyopathy (CM), we observed no gender-based differences in cardiac or cellular remodeling. In contrast, among 50 patients with ischemic cardiomyopathy (ICM), the heart weight index was significantly greater in men, and there was a strong trend toward an increased left ventricular (LV) mass index as well. These gender differences in cardiac and LV mass were paralleled by marked gender differences in myocyte volume, such that average myocyte volume was 36% greater in men than in women, in association with a 14% increase in resting cell length.
CONCLUSIONS	Our studies demonstrate a multilevel gender difference in post-infarction remodeling, with women exhibiting reduced hypertrophy. Our studies further demonstrate that gender differences in cardiac remodeling in ICM are largely related to fundamental differences in cellular remodeling rather than simply differences in infarct size or expansion. Distinctions observed between ischemic and idiopathic CM suggest that gender may influence local myocardial responses to injury. (J Am Coll Cardiol 2003;41:300-6) © 2003 by the American College of Cardiology Foundation

The syndrome of heart failure (HF) and its sequelae are significant health problems in the U.S. and worldwide. Despite recent therapeutic advances, the mortality from symptomatic HF remains nearly 50%, and this diagnosis is responsible for significant morbidity and associated health care costs (1-4). Data obtained from the Framingham database indicate the median survival associated with symptomatic HF differs on the basis of gender, with reported values of 1.7 years for men and 3.2 years for women (1,4).

In the FIRST study, the investigators reported a similar survival advantage for women but observed this difference exclusively among patients with an idiopathic cardiomyopathy (CM) (5). This finding suggests that the etiology of HF may affect the prognostic influence of gender (5,6). Studies conflict about whether there is a gender difference in mortality among patients with an ischemic cardiomyopathy (ICM), with some studies indicating a higher mortality for

women (7-10) and others observing no gender difference (11,12).

Although few clinical studies have examined the biologic mechanisms responsible for the clinically observed gender differences in HF mortality, animal studies have shown differences in the progression toward decompensated HF. Lorell and collaborators have reported differences in global left ventricular (LV) remodeling, cardiac myocyte hypertrophy, and associated changes in gene expression in rats, with pressure overload hypertrophy induced by aortic banding (13,14). Similarly, studies in genetically hypertensive rats have shown gender differences in cardiac myocyte remodeling during the progression from the baseline state, through compensated concentric hypertrophy, to advanced HF with eccentric hypertrophy (15). To date, no studies have addressed whether gender influences cellular remodeling among humans. Therefore, in a group of patients with advanced HF requiring cardiac transplantation, we explored whether there are gender differences in cardiac and cellular remodeling and whether the etiology of HF influences myocardial remodeling. On the basis of studies showing equivalent cardiac myocyte hypertrophy in rats with decompensated HF, we hypothesized that there would be no gender difference in humans with advanced HF requiring cardiac transplantation.

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Abbreviations and Acronyms

CM	= cardiomyopathy
HF	= heart failure
HRT	= hormone replacement therapy
IDC	= idiopathic dilated cardiomyopathy
ICM	= ischemic cardiomyopathy
IVS	= interventricular septal dimension
LV	= left ventricular
LVEF	= left ventricular ejection fraction
LVEDD	= left ventricular end-diastolic dimension
MI	= myocardial infarction
PWT	= posterior wall thickness dimension

METHODS

Study design. Over a 38-month period from February 1996 through April 1999, a total of 205 orthotopic heart transplants were performed at our institution. In 152 of these patients, we were able to obtain large quantities of isolated cardiac myocytes suitable for detailed morphologic examination using recently described techniques (16). After excluding cases with prior mechanical circulatory support, there were 50 patients with idiopathic dilated cardiomyopathy (IDC) diagnosed in accordance with World Health Organization criteria and 50 patients with advanced CM due to coronary artery disease and previous myocardial infarction (MI). Clinical data, including information about the diagnosis, complications, and treatment of HF, were obtained at the time of transplantation. The duration of HF was defined as the time between the first diagnosis of HF and the time of transplantation. For patients with ICM, the time between their first MI and the time of cardiac transplantation was recorded. This protocol was reviewed by the Temple University Institutional Review Board and was determined to be exempt in accordance with paragraph 4 (protection of human subjects, title 5, Code of Federal Regulations, part 46), pertaining to research involving pathological specimens.

Menopausal status. Clinical information regarding the gynecologic history and menopausal status of each woman was obtained retrospectively using a telephone questionnaire. The same interviewer (K. B. M.) administered all questionnaires. The participants were asked information regarding their use of hormone replacement therapy (HRT) and menopausal status at the time of transplant. The women were queried regarding the onset of irregular menstrual cycles and cessation of menses in relation to the date of transplant. Menopause was defined as cessation of menses for >12 months. On the basis of medical records and phone-based interviews, menopausal and HRT status at the time of transplant could be determined for 22 of 28 women in the study cohort. On the basis of age >55 years, menopausal status could be assumed for four of the six women unavailable for interview (17), but hormone and HRT status remained unknown for these women.

Echocardiographic assessment. Echocardiograms were obtained from patients by experienced sonographers using a Hewlett-Packard Sonos 1500 machine (Hewlett-Packard, Anasco, California) and a 2.5 MHz transducer. Left ventricular dimensions were obtained using the parasternal short-axis view at the level of the papillary muscle. M-mode measurements were obtained using the leading-edge technique in accordance with recommendations from the American Society of Echocardiography. Left ventricular mass was calculated using the following formula validated by Devereux et al. (18):

$$\text{LV mass (g)} = 0.80 \times 1.04 ([\text{IVS} + \text{LVEDD} + \text{PWT}]^3 - [\text{LVEDD}]^3) + 0.6$$

where IVS = interventricular septal dimension, LVEDD = left ventricular end-diastolic dimension, and PWT = posterior wall thickness dimension.

Left ventricular mass index was calculated by dividing LV mass by body surface area.

The left ventricular ejection fraction (LVEF) was calculated using the following equation (19):

$$\text{LVEF} = (\text{LVEDD}^2 - \text{LVESD}^2) / \text{LVEDD}^2$$

where LVESD = left ventricular end-systolic dimension.

Relative wall thickness was calculated using the following ratio:

$$\text{Relative wall thickness} = 2 \times \text{PWT} / \text{LVEDD}$$

Hemodynamics. Right heart catheterization was performed on each patient immediately before cardiac transplantation, and intracardiac filling pressures were measured. Right atrial, pulmonary artery, and pulmonary capillary pressure were measured directly using a balloon-tipped pulmonary artery catheter (American Edwards Laboratories, AHS del Caribe, Inc.). Cardiac output was measured using the thermodilution technique. Cardiac index was calculated by dividing cardiac output by body surface area. Arterial pressure was measured invasively.

Myocyte isolation technique. Cardiac myocytes were isolated from all patients using the following procedure. Briefly, at the time of transplant, the aorta was cross-clamped and the aortic root was immediately perfused with a cold-blood-buffered cardioplegic solution. After 10 to 30 min of cross-clamping, the heart was explanted and taken to the experimental laboratory. All hearts were weighed before initiation of the cell isolation protocol. Upon arrival, an epicardial vessel was cannulated and perfused with Krebs-Henseleit buffer. The perfused region of the heart was excised and rinsed with a calcium-free solution containing Krebs-Henseleit buffer with taurine (10 mM). The myocardial region selected for isolation was perfused for 30 min with a recirculation solution containing type II collagenase (180 U/ml), 2,3-butanedione monoxamine (20 mM), taurine (20 mM), and calcium chloride (0.05 mM). The tissue underwent a second exposure to a nonrecirculating rinse for 10 min with Krebs-Henseleit buffer solution containing

Table 1. Clinical Data Grouped by Etiology and Gender

	IDC Patients			ICM Patients		
	Male (n = 35)	Female (n = 15)	p Value	Male (n = 37)	Female (n = 13)	p Value
Age, yrs	52 ± 2	53 ± 3	0.754	59 ± 1	58 ± 2	0.399
Hx of DM, %	9	33	0.029	27	46	0.204
Hx of HTN, %	20	53	0.018	57	62	0.764
Hx of clinical VT, %	37	13	0.092	35	15	0.181
Hx of chronic Afib, %	23	0	0.043	22	0	0.067
Hx of CABG, %	N/A	N/A	N/A	54	54	0.990
CHF duration, months	70 ± 8	57 ± 11	0.380	27 ± 6	19 ± 8	0.429
Years since first MI	N/A	N/A	N/A	12.5 ± 1.4	6.6 ± 1.5	0.025
Medications at transplant						
Diuretic, %	60	60	0.999	57	92	0.020
Antiarrhythmic, %	17	7	0.328	27	0	0.036

Data for continuous variables are expressed as mean ± SEM.

Afib = atrial fibrillation; CABG = coronary artery bypass grafting; CHF = congestive heart failure; DM = diabetes mellitus; HTN = hypertension; Hx = history; ICM = ischemic cardiomyopathy; IDC = idiopathic dilated cardiomyopathy; MI = myocardial infarction; VT = ventricular tachycardia.

taurine (10 mM), 2,3-butanedione monoxamine (20 mM), and calcium chloride (0.2 mM). The tissue was then removed from the cannula and a mid-myocardial region was minced in the rinse solution. In hearts with ICM, isolated myocytes were obtained from viable myocardium as far as possible from previous MIs. The resulting cell suspension was filtered and centrifuged (25 × G). The cells were resuspended in a Krebs-Henseleit solution containing 1% weight/volume bovine albumin, taurine (10 mM), and calcium chloride (0.2 mM). All solutions bubbled with 95% O₂ and 5% CO₂ and kept at 37°C and pH 7.4. The yield of calcium-tolerant rod-shaped myocytes using this protocol ranged from 10% to 60% with this cell isolation protocol.

Cell morphology analysis. An aliquot of cells was fixed in an iso-osmotic solution containing 1.5% glutaraldehyde in 0.06 mol/l phosphate buffer. As shown by Gerdes et al. (20), this fixation method does not alter myocyte volume. Fixed cells were centrifuged through a Ficoll gradient to remove unwanted debris and cell fragments. For each heart studied, median myocyte volume was measured from a cell suspension containing at least 10,000 myocytes using Coulter Channelyzer analysis as previously described (16,20). Previous studies have demonstrated that inclusion of round cells does not significantly alter the final cell volume (20). From the same suspensions of fixed myocytes, evaluations of myocyte length and profile area were performed using a microscope, a charge-coupled device camera, and a frame grabber. After calibration using a stage micrometer, cell length and cell profile area were measured in 60 to 100 cells. Using NIH image software (version 1.59), myocyte length was measured as the longitudinal axis of the best-fitting ellipse. The average cell width was calculated using the ratio of the profile area to the length of the cell. For each heart studied, the average myocyte cross-sectional area was calculated as the ratio of median cell volume to mean cell length as previously described (20). Because normal adult myocyte size is consistent across mammalian species, morphometric data were not scaled to body size.

Cellular function studies. Cellular physiologic analysis of isolated human cells was conducted using a video edge detection system (Crescent Electronics, Sandy, Utah). All cells were perfused using Krebs-Henseleit buffered solution during the physiologic measurements. Myocyte contractions were assessed via field stimulation at 0.5 Hz and 37°C. Myocyte contraction magnitude was normalized to the diastolic cell length and expressed as a percentage of resting cell length (fractional cell shortening). The time to 50% relaxation was measured as the interval between the stimulus and the achievement of 50% relengthening.

Statistical analysis. Comparisons were made on organ and cellular morphologic parameters using a two-factor (etiology, gender) and three-factor (etiology, gender, diabetes/hypertension/pharmacologic therapy) analysis of variance with follow-up pairwise comparisons using Bonferroni adjustment. In addition, cell volume data were also examined using analysis of covariance to adjust for age or heart weight/body weight index. Intergroup differences in menopausal status were explored using chi-square analysis. To explore relationships between two continuous variables, simple linear regression analyses were performed. In all cases, statistical significance was defined as $p < 0.05$.

RESULTS

Clinical characteristics. GENERAL. Within each etiologic subgroup, clinical characteristics of patients included in this study are shown in Table 1. There were no differences between mean age of men and women. Among patients with IDC, a history of diabetes mellitus and hypertension were observed more frequently among women, whereas a history of atrial fibrillation was observed more frequently among men. Among patients with ICM, the number of years that had elapsed since the first MI was greater for men than for women, although the durations of clinical HF and other historic variables were not significantly different. Medication use at the time of transplantation did not differ

Table 2. Cardiac and Myocyte Morphology Data Grouped by Etiology and Gender

	IDC Patients			ICM Patients		
	Male (n = 35)	Female (n = 15)	p Value	Male (n = 37)	Female (n = 13)	p Value
Heart weight index, g/m ²	291 ± 12	295 ± 28	0.863	290 ± 9	249 ± 11	0.018
Echocardiographic data						
LV mass index, g/m ²	180 ± 12	170 ± 20	0.649	169 ± 8	139 ± 10	0.060
LV EDD index, cm/m ²	3.9 ± 0.1	4.2 ± 0.3	0.273	3.9 ± 0.1	3.7 ± 0.1	0.554
LV ESD index, cm/m ²	3.4 ± 0.2	3.7 ± 0.3	0.209	3.2 ± 0.1	3.0 ± 0.1	0.273
Septal wall thickness, cm	0.93 ± 0.03	0.83 ± 0.05	0.057	0.90 ± 0.03	0.86 ± 0.06	0.524
Posterior wall thickness, cm	0.92 ± 0.02	0.87 ± 0.05	0.271	0.91 ± 0.03	0.90 ± 0.04	0.798
Relative wall thickness	0.26 ± 0.02	0.25 ± 0.02	0.630	0.25 ± 0.01	0.28 ± 0.02	0.069
Cellular data						
Myocyte volume, 1,000 × μm ³	48.5 ± 2.2	47.4 ± 3.4	0.780	52.0 ± 2.5	38.2 ± 2.3	0.003
Myocyte length, μm	219 ± 6	208 ± 6	0.284	199 ± 5	174 ± 7	0.010
Myocyte width, μm	32 ± 1	31 ± 1	0.928	32 ± 1	30 ± 1	0.176
Myocyte CSA, μm ²	223 ± 10	234 ± 22	0.626	263 ± 13	223 ± 14	0.099

Data for continuous variables are expressed as mean ± SEM.

CSA = cross-sectional area; EDD = end-diastolic diameter; ESD = end-systolic diameter; ICM = ischemic cardiomyopathy; IDC = idiopathic dilated cardiomyopathy; LV = left ventricular.

between men and women with idiopathic CM, but among patients with ICM, there was greater use of diuretics among women and greater use of antiarrhythmics among men.

MENOPAUSAL STATUS. Eight of 15 women with idiopathic CM and nine of 13 patients with ICM were post-menopausal ($p = ns$). When HRT was taken into account, only 7 of 13 women with ICM and 4 of 15 women with idiopathic CM were post-menopausal and without estrogen supplementation ($p = ns$). When known, the age at the time of menopause was similar regardless of the etiology of HF: idiopathic vs. ICM (46.1 ± 1.7 years vs. 48.9 ± 1.3 years) ($p = ns$). There were no significant differences observed in any of the cellular indices measured between HRT users and nonusers.

Cardiac morphology. Data describing cardiac and cell morphology in each of the etiologic subgroups are presented in Table 2. Among patients with idiopathic CM requiring cardiac transplantation, hearts from men and women exhibited remarkable similarity for all organ and cellular morphologic variables assessed. Of note, significant gender differences in raw values for heart weight, LV mass, LVEDD, and LVEDS (data not shown) all became equivalent after these variables were normalized for body surface area. For patients with ICM, several important differences in cardiac morphology were observed. Specifically, the heart weight index was significantly greater in men ($p = 0.018$), and there was a strong trend toward an increased LV mass index as well. In addition, although there were no gender differences in indexed chamber dimensions or wall thickness, relative wall thickness tended to be higher in women with ICM compared with their male counterparts.

For patients with ICM, gender differences in cardiac and LV mass were paralleled by marked gender differences in myocyte volume such that average myocyte volume was 36% greater in men than in women. Further morphologic anal-

ysis revealed that the greater cell volume among men was a reflection of a significantly greater (14%) average cell length and a nonsignificantly greater (18%) myocyte cross-sectional area. The average values for median cell volume among women and men with ICM are compared with historical data from nonfailing nonhypertensive controls in Figure 1 (16). Although the time between first MI and time to transplantation was shorter among women compared to men, this difference did not correlate with cellular remodeling indices such as cell volume, using simple linear regression for analysis, as shown in Figure 2.

Analysis of potential confounding factors. Based on the three-factor analysis of variance (using Bonferroni adjustment, 28 comparisons), the gender difference in cellular remodeling among patients with ICM could not be attributed to differences in the proportion of patients with diabetes or hypertension ($p = 1.0$). Similarly, differences in pharmacologic inhibition of renin-angiotensin system by angiotensin II receptor blocker ($p = 1.0$) or angiotensin-converting enzyme inhibitors ($p = 0.27$) could not account for the observed gender differences in cardiac myocyte morphology among patients with ICM. In addition, when cell volume data were adjusted for either age ($p = 0.01$) or heart weight index ($p = 0.049$), analysis of covariance (using 6 comparisons) confirmed a gender difference in myocyte volume that was limited to those patients with ICM.

Cardiac function. Analysis of hemodynamic and function data was performed. With the exception of a somewhat higher right atrial pressure among women with idiopathic CM, cardiac hemodynamic measurements were equivalent among men and women in the two etiologic groups. Within both the ischemic and idiopathic groups, we observed no gender differences in isolated myocyte fractional shortening or time to 50% relaxation (data not shown).

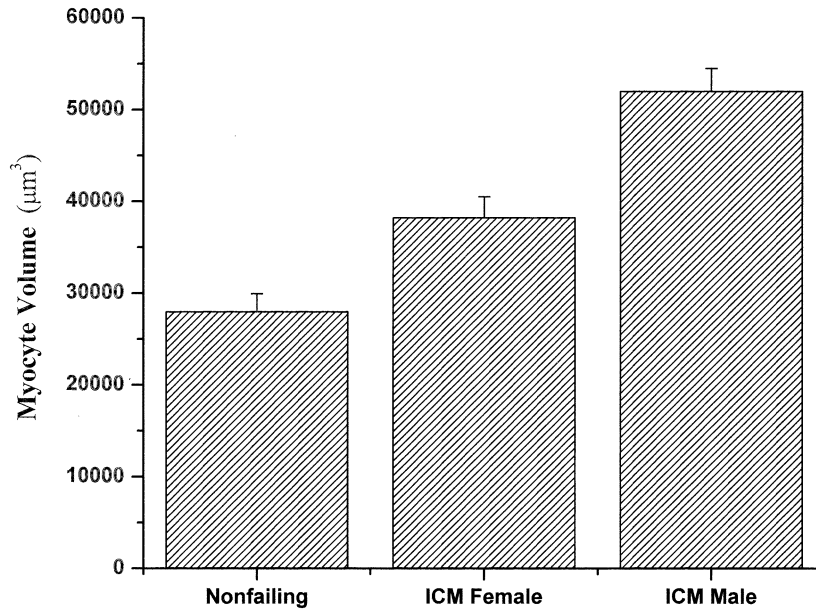


Figure 1. Average myocyte volume for nonhypertensive, nonfailing hearts (n = 8), and ischemic cardiomyopathy (ICM) hearts from men (n = 37), and women (n = 13). The data for the nonfailing hearts is an historical control group previously reported in reference 16. Data are mean ± SEM. p < 0.05 for both ICM males and females.

DISCUSSION

The present study examined whether there are gender differences in cardiac remodeling among humans with end-stage HF. Among patients with advanced idiopathic CM, we observed equivalent degrees of eccentric cardiac hypertrophy among men and women, with an overall pattern similar to that previously reported in animal models of advanced HF due to pressure overload. In contrast,

among patients with ICM, we observed a significant gender difference in the magnitude of cardiac hypertrophy that has not been previously reported. By employing human cardiac myocyte isolation and morphologic analysis (16), our studies further demonstrate that gender differences in cardiac remodeling in ICM are largely related to fundamental differences in cellular remodeling rather than simply differences in infarct size or expansion. Furthermore, the distinctions

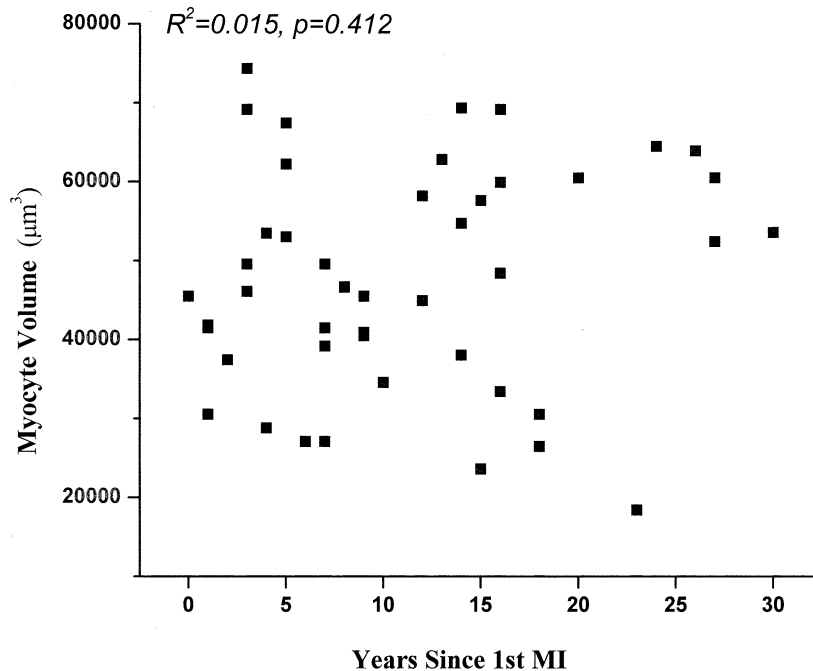


Figure 2. Scatterplot depicting the relationship between myocyte volume and number of year since the first myocardial infarction (MI) among patients with ischemic cardiomyopathy (n = 50). As indicated numerically within the plot, simple linear regression analysis revealed no significant relationship between these variables.

observed between advanced idiopathic CM and advanced ICM suggest that local myocardial responses to injury may contribute to the gender differences observed among patients with ICM.

Among patients with inotrope-dependent idiopathic CM, we observed no qualitative or quantitative gender differences in cardiac hypertrophy. This morphologic equivalence among men and women with idiopathic CM was observed using four separate types of analytic techniques: 1) direct measurement of heart weight, 2) echocardiographic estimation of LV mass, 3) Coulter Channelyzer determination of median cell volume, and 4) direct morphologic analysis of isolated cardiac myocytes. Our decision to index organ level parameters to body size is supported by this multilevel morphologic equivalence and by conventions established in previous reports (15,20). Of note, the nearly identical degrees of organ and cellular eccentric hypertrophy occurred despite a higher prevalence of hypertension and diabetes among females with idiopathic CM. Although we are aware of no similar analysis in humans, prior studies in animal models of chronic pressure overload suggest some similarities. Specifically, in spontaneously hypertensive rats developing HF and eccentric hypertrophy, Tamura *et al.* (15) reported equivalent chamber dilation, cardiac hypertrophy, and cellular hypertrophy in male and female animals. Although significant gender differences were observed at earlier time points before HF developed, in this and other studies (13,15), the morphologic equivalence once decompensated HF developed is quite similar to our findings in idiopathic CM at both the organ and cellular levels.

In contrast, we report for the first time a striking gender difference in post-infarction cardiac remodeling among patients with advanced, inotrope-dependent ICM. Using the same body size normalization that was applied to patients with idiopathic CM, we observed a significantly greater heart weight index among men with ICM. Moreover, LV mass index derived using different methodology suggested a gender difference of similar magnitude. A recent population-based analysis of gender-specific differences in cardiac remodeling in patients with LV dysfunction, demonstrated an attenuated degree of hypertrophy among female subjects (21). Our cellular morphology data support and extend the gender differences observed at the organ level among patients with ICM. Specifically, the degree of post-infarction cellular hypertrophy among men was nearly twice that observed among women on the basis of cell volume analysis and comparison to myocytes from nonfailing, nonhypertensive controls. Although the time since the first MI was longer for men in our study, even among women the average interval was 6.6 years. Moreover, regression analysis did not support any significant relationship between indices of cellular hypertrophy and the time since the first infarction. From a mechanistic standpoint, these differences in cellular remodeling suggest that the gender differences in organ mass and morphology reflect fundamental differences in cellular remodeling in the noninfarcted

myocardium rather than differences in the remodeling of infarcted tissue or the peri-infarct zone.

The contrast between the gender differences in post-infarction hypertrophy and the lack of such differences among patients with idiopathic CM is an intriguing aspect of these studies. Neither clinical variables nor hemodynamic data obtained at the time of transplantation suggest any extracardiac explanation for this etiologic distinction. Alternatively, it seems more likely that local myocardial factors such as responses to injury, chronic ischemia, or paracrine effects of interstitial or infarcted myocardium could contribute to the apparent interaction between etiology and gender in these studies. This speculation is based on the established ability of interstitial cells to generate cytokines and growth factors such as angiotensin II and endothelin that modulate myocyte growth *in vitro*. From this perspective, the etiology-based gender differences we observed could indirectly reflect gender differences in myocyte responses to myocardial growth modulators.

Our findings do not necessarily support an estrogen-mediated difference in post-infarction remodeling. Although there are estrogen receptors in the heart (22), most of the women in the ICM group were post-menopausal, and the proportion receiving HRT was equivalent to the proportion observed among the women with idiopathic CM. The lack of a relationship between menopausal status or HRT and the observed differences in cellular hypertrophy in patients with ICM is consistent with the interpretation that gender differences in cardiac remodeling may not be estrogen-dependent. Indeed, recent clinical trials show no benefit from HRT in the progression of cardiovascular disease (23–25), yet a survival benefit has been consistently reported for women with HF compared with men (26,27). The estimated age of menopause for women in this cohort of patients with advanced HF was less than the median age reported in the U.S. (17,28), but the significance of this finding is unclear.

Despite the novelty of our findings, several limitations of this research deserve mention. First, the remodeling patterns observed among the most severely myopathic patients who require transplantation may not be representative of the remodeling that occurs in patients with less severe disease. Second, the observed differences in end-stage CM offer no insight on the evolution of the remodeling patterns observed. For example, it is possible that significant gender differences exist in idiopathic CM before the development of end-stage HF, as has been reported in genetically hypertensive rats (15). Finally, although men and women in each etiologic subgroup had similar medications and hemodynamics at the time of transplantation, this does not exclude possible differences in these variables during the years of evolving CM.

In conclusion, the present studies demonstrate significant gender-related differences in cardiac and cellular remodeling among patients with end-stage ICM. Our findings support the general hypothesis that gender-based differences in

myocardial biology contribute to recently reported gender differences in clinical outcomes and therapeutic responses following MI. Further studies are required to more completely explore the evolution of post-infarction remodeling and to identify the mechanisms through which gender modulates myocardial remodeling.

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