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Gender-specific differences of cardiac remodeling in subjects with left ventricular dysfunction: a population-based study

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Abstract

Background: Recent studies suggest that female gender is associated with a lower prevalence and a more benign prognosis of heart failure. In the current population-based study, it was our objective to evaluate the implications of gender on the association between impaired left ventricular (LV) function and mass as well as neurohumoral activation. **Methods and results:** A total of 1883 subjects (992 female, 891 male) of two MONICA surveys in Augsburg, Germany, were analyzed. Participants of one of these surveys were additionally characterized with respect to neurohormonal activation. As compared to men, women were characterized by a slightly higher LV ejection fraction (EF, Teichholz-Method, 65.4±0.3% vs. 63.4±0.3, $P<0.01$) and a markedly lower LV mass index (LVMI 81±1 g/m^2 vs. 96±1, $P<0.01$). As compared to men with normal LV function, those with LV dysfunction (EF below mean minus two standard deviations, S.D.) were characterized by significantly increased LV mass (LVMI +48%, $P<0.01$), plasma BNP (+373%, $P<0.01$) and ANP (+57%, $P<0.01$), while no significant changes were observed in women (LVMI +3%, BNP +48%, ANP +27%, all P=n.s). Only a small subgroup of women with severe LVD (EF below mean — 3 S.D.) was characterized by significantly increased LV mass (LVMI +23%, $P<0.05$ vs. control and LVD), however, this increase was less pronounced as compared to men with severe LVD (LVMI +46%, $P<0.01$ vs. control). Gender-specific differences between LV function and structure were also confirmed by multivariate analysis. While LVMI was independently and significantly correlated with EF in male subjects in addition to systolic blood pressure, age, and body mass index (all $P<0.01$), these parameters displaced EF as a predictor of LVMI in female subjects. **Conclusions:** Men with moderate or severe LV dysfunction are characterized by an increase in both LV mass and cardiac natriuretic peptide plasma concentrations. In contrast, LV mass and natriuretic peptide concentrations increase to a lesser extent and only with severe LV dysfunction in women. These observational data suggest gender-specific control of myocardial adaptations to hemodynamic overload and a more rapid induction of LV hypertrophy during myocardial dysfunction in male subjects.

Keywords: Epidemiology; Gender; Hypertrophy; Hypertension; Heart failure; Natriuretic peptide; Ultrasound

1. Introduction

A growing awareness for potential gender-differences in subjects with heart failure has been fueled by evidence from studies which have addressed diagnosis [1], epidemiology [2–4], response to treatment [5], and outcome [2,3,6–8] of this disease. In general, these studies suggested a lesser susceptibility of middle-aged women to heart failure, a more favorable clinical course of disease, and even a potentially better survival. Due to potential methodological limitations in these studies, however, the notion of true gender-specific differences in the pathophysiology and progression of heart failure still remains

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weak. For example, heart failure was often defined clinically and without assessment of left ventricular performance [2,3]. The clinical diagnosis of heart failure, however, may be less accurate in women as compared to men since it is less closely associated with systolic LV dysfunction [1]. A further problem arises from the fact that women are often underrepresented in clinical studies.

Nevertheless, gender-specific differences have also been suggested with respect to pathophysiological and biochemical mechanisms of heart failure in a number of experimental studies. The majority of these studies have again suggested that female gender is associated with more favorable myocardial adaptations to hemodynamic overload, including a better preserved contractile response [9,10] and a greater adaptive hypertrophic reserve [11].

Given the mounting evidence for a genuine gender-specific effect, it was our objective to evaluate the effect of gender upon the relationship between impaired left ventricular function and left ventricular remodeling and neurohumoral activation in a setting without bias towards clinically severe cases. We therefore assessed left ventricular function and structure as well as circulating neurohormones in a large population-based sample. Based upon previous clinical and experimental evidence, we hypothesized that male gender would be associated with a more pronounced hypertrophic response and neurohumoral activation in subjects with left ventricular dysfunction.

2. Methods

2.1. Study population

A total of 2363 subjects participated either in the echocardiographic substudy of the third MONICA Augsburg survey in 1995 and 1996 ($n=1678$) or in the second follow-up examination of the first MONICA Augsburg survey in 1994 ($n=685$) [12–14]. Subjects originate from a sex-age-stratified random sample of all German residents of the Augsburg study area. All subjects responded to a questionnaire on medical history, physical activities, medication, and personal habits. Body height and weight were recorded with subjects wearing light clothing and body mass index was computed as weight in kilograms divided by height in square-meters (kg/m^2). A 12-lead electrocardiogram was recorded and resting blood pressure was measured after subjects had been in a sitting position for a minimum of 30 min. Blood pressure was measured at the right arm three times. Hypertension was defined as systolic blood pressure >160 mmHg or diastolic blood pressure >95 mmHg or intake of anti-hypertensive medication. An echocardiogram was performed on each subject and could be analyzed in a total of 1883 subjects with respect to left ventricular function and mass. Additional neurohormonal analyses were carried out in participants of the smaller survey.

2.2. Echocardiography

A two-dimensionally guided M-mode echocardiogram was performed by an expert sonographer (Sonos 1500, Hewlett Packard) but only subjects with optimal visualization of left ventricular interfaces were used for assessment of left ventricular function and mass.

M-mode tracings were recorded on strip-chart paper at 50 mm/s. To reduce inter-observer variability, all M-mode tracings were analyzed by a single cardiologist who was blinded for the clinical and biochemical data. Measurements for M-mode guided calculation of left ventricular mass were taken just below the tip of the mitral valve. Left ventricular internal end-diastolic (EDD) and end-systolic diameters (ESD) and septal (Swth) and posterior wall thickness (Pwth) were measured according to the guidelines of the American Society of Echocardiography [15]. Left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated according to the formula by Teichholz et al. [16]:

$$\mathrm{EDV\ (ml)} = (7/(2.4 + \mathrm{EDD})) \cdot \mathrm{EDD}^3 \text{ and}$$

$$\mathrm{ESV\ (ml)} = (7/(2.4 + \mathrm{ESD})) \cdot \mathrm{ESD}^3,$$

and left ventricular ejection fraction (EF) as:

$$\mathrm{EF\ (\%)} = ((\mathrm{LVEDV} - \mathrm{LVESV})/\mathrm{LVEDV}) \cdot 100$$

Left ventricular systolic dysfunction was considered when ejection fraction was two standard deviations or more below the mean of the respective gender group, i.e. equal or below 46% in men and 49% in women. Severe left ventricular dysfunction was considered when ejection fraction was three standard deviations or more below the mean of the respective gender group, i.e. equal or below 38% in men and 41% in women.

Left ventricular mass (LVM) in grams (g) was calculated according to the formula described by Devereux et al. [17] as:

$$\mathrm{LVM\ (g)} = 0.8 \cdot (1.04 \cdot (\mathrm{EDD} + \mathrm{Swth} + \mathrm{Pwth})^3 - \mathrm{EDD}^3) + 0.6\ \mathrm{g}$$

LVM was indexed to body surface area as left ventricular mass index (LVMI) in g/m^2 body surface area. Left ventricular hypertrophy was considered when LVMI was greater than two standard deviations above the mean of the respective gender group, i.e. equal or greater 147 g/m^2 body surface area in men and 127 g/m^2 body surface area in women.

2.3. Biochemical measurements

Neurohumoral analysis was available from subjects of the second follow-up examination of the first MONICA Augsburg survey. In these subjects, blood was drawn in a supine resting position, chilled, centrifuged and plasma stored at $-80°C$ until measurement. ANP, BNP, and

cGMP were measured by standard radioimmunoassay technique and all determinations were carried out in duplicate. For measurement of ANP, plasma was pre-acidified with acetic acid, extracted on pre-washed C18 columns (Sep-Pak, Waters), washed with Tris–HCl, eluted with acetonitril/ammonium acid, and measured with a commercially available antibody (Amersham). BNP was measured with a commercially available RIA-kit (Shionogi) without cross-reactivity to ANP and a lower limit of detection of 2.0 pg/ml [18]. cGMP was measured after methanol extraction by a commercially available kit (NEN). Immunoreactive renin was measured in a 200 μl plasma sample by immunoradiometric assay kit (Nichols Institute), according to the methods proposed by Derkx et al. [19]. A complete data set including echocardiographic and neurohumoral characterization was available in 514 subjects for PRA, 513 for ANP, 497 for cGMP, and 479 for BNP, respectively.

2.4. Statistics

Anthropometric, hemodynamic and neurohumoral data except BNP concentrations were tested for statistically significant differences by Student's *t*-test. Differences between BNP concentrations were tested by Mann Whitney *U*-test, since the distribution of BNP was markedly skewed. Differences between groups with categorical data were compared by chi-square test. Together with multivariate regression analysis of univariate predictors of left ventricular mass index, the corresponding beta coefficients were computed. Beta coefficients are an adjusted measure for the increase or decrease in left ventricular mass index that can be attributed to a given change of the corresponding independent variable. *P*-values below 0.05 were defined as statistically significant and *P*-values below 0.01 as highly significant.

3. Results

3.1. Study population

Anthropometric data are depicted in Table 1. As compared to women, men had a higher body mass index ($P<0.05$), a higher incidence of previous myocardial infarction ($P<0.05$), a higher likelihood for evidence of left ventricular hypertrophy in their electrocardiograms ($P<0.01$), a lower heart rate ($P<0.01$), and a higher diastolic blood pressure ($P<0.01$).

Women presented with a significantly higher mean ejection fraction as compared to men ($P<0.01$) and 2.6% men and 2.5% women were designated to have left ventricular dysfunction as defined by an ejection fraction of two standard deviations ore more below the mean of the respective gender group.

As compared to men with normal ejection fraction, men with left ventricular dysfunction were older ($P<0.01$), had a higher incidence of previous myocardial infarction ($P<0.05$), were treated more often with ACE inhibitors, diuretics, or beta blockers ($P<0.01$), and had a higher heart rate ($P<0.01$) (Table 1). The same relative changes were observed in women with left ventricular dysfunction, but did not reach statistical significance. Both, men and women with left ventricular dysfunction had a tendency towards increased body mass index and towards hypertensive blood pressures as compared to subjects with normal ejection fraction.

Table 1
Characterization of study population

	Male		Female	
	EF normal ($n=868$)	LVD ($n=23$)	EF normal ($n=967$)	LVD ($n=25$)
Age (yrs)	51.8±0.4	59.3±2.5**	52.3±0.4	54.0±2.3
BMI (kg/m^2)	26.8±0.1	27.9±0.7	26.5±0.1†	27.1±0.9
Hypertensive BP	41.7	47.8	39.0	42.3
MI-ECG (%)	3.9	12.5*	2.4†	7.7
LVH-ECG (%)	14.0	27.3	2.8‡	0.0†
Diuretic (%)	3.9	29.2**	7.1‡	19.2*
Heart rate (min^{-1})	68.5±0.4	76.8±3.5**	70.3±0.4‡	71.3±2.4
Sys BP (mmHg)	147.2±0.7	149.4±4.9	146.0±0.8	145.8±4.6
Dia BP (mmHg)	89.6±0.4	91.4±2.7	87.5±0.4‡	89.0±2.7
EF (%)	64.1±0.2	36.9±1.6**	65.9±0.2‡	43.2±1.3**,†
LVEDD (mm)	50.1±0.2	57.7±1.8**	46.1±0.1‡	46.9±1.1‡
SWth (mm)	11.2±0.2	12.7±0.6**	10.0±0.1‡	10.3±0.5†
PWth (mm)	9.3±0.1	10.1±0.4*	8.3±0.05‡	8.3±0.3‡

Mean±S.E.M. LVD, LV dysfunction; BMI, body mass index; BP, blood pressure; MI-ECG, electrocardiogram with evidence for previous myocardial infarction; LVH-ECG, electrocardiogram with evidence for LV hypertrophy; sys BP, systolic blood pressure; dia BP, diastolic blood pressure; LVEDD, LV end-diastolic diameter; SWth, septal wall thickness; PWth, posterior wall thickness. *: $P<0.05$ vs. normal EF; **: $P<0.01$ vs. normal EF; †: $P<0.05$ vs. male; ‡: $P<0.01$ vs. male; *t*-test for continuous data, chi-square test for categorical data.

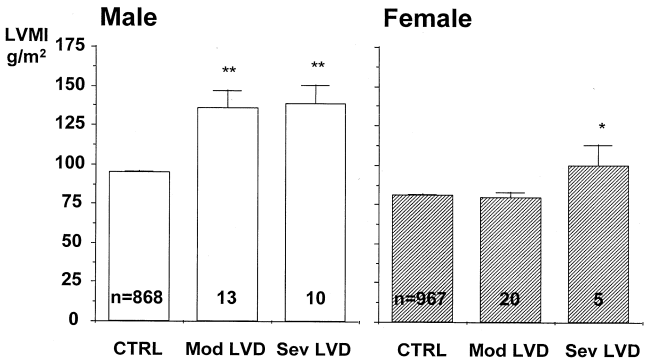

Fig. 1. LV mass index (LVMI) in male (open bars) and female (dashed bars) subjects with normal LV function (control, CTRL), moderate LV dysfunction (mod LVD), and severe LV dysfunction (sev LVD). *: $P<0.05$ vs. CTRL, **: $P<0.01$ vs. CTRL.

3.2. Left ventricular function, mass and cardiac structural parameters (Fig. 1, Table 1)

The prevalence of left ventricular hypertrophy was 26% in male subjects with left ventricular dysfunction as compared to 8% in female subjects with left ventricular dysfunction.

Left ventricular mass index was significantly increased only in men with left ventricular dysfunction (137.0±8.0 g/m^2, $n=23$ vs. 95.0±0.8 g/m^2, $n=868$, $P<0.01$). In contrast, women with left ventricular dysfunction were characterized by unchanged left ventricular mass index (83.3±4.3 g/m^2, $n=25$ vs. 81.1±0.6 g/m^2, $n=967$, $P=$ n.s.). The same results were obtained when the male cutoff criterion for left ventricular dysfunction (EF$<=$46%) was applied to women (87.5±5.4 g/m^2, $n=18$ vs. 81.0±0.6 g/m^2, $n=974$, $P=$n.s.) and when the female cutoff criterion for left ventricular dysfunction (EF$<=$49%) was applied to men (124.9±6.4 g/m^2, $n=36$, vs. 94.9±0.8 g/m^2, $n=855$, $P<0.01$).

Further subgroup analysis demonstrated that women with severe left ventricular dysfunction (as defined by an ejection fraction of three standard deviations or more below the mean) were characterized by increased left ventricular mass index (Fig. 1). However, the relative increase of left ventricular mass index in this group (+23% vs. control, $P<0.05$) was substantially smaller as compared to that in men with severe left ventricular dysfunction (+46% vs. control, $P<0.01$).

The same gender-specific pattern of increased left ventricular mass index in subjects with left ventricular dysfunction was observed after exclusion of subjects with a history of myocardial infarction. Specifically, men without previous myocardial infarction were characterized by increased left ventricular mass index in the presence of moderate and severe left ventricular dysfunction (severe: 130.4±9.4 g/m^2, $n=9$, moderate: 134.3±13.3 g/m^2, $n=$ 11, both $P<0.01$ vs. control 94.2±0.8 g/m^2, $n=834$) while women were characterized by increased left ventricular mass index exclusively in the presence of severe left ventricular dysfunction (99.9±13.4 g/m^2, $n=5$, $P<$ 0.05 vs. moderate 77.3±4.0 g/m^2, $n=18$, and control 80.9±0.7 g/m^2, $n=944$).

A similar pattern was observed with respect to left ventricular dimensions and wall thickness. Specifically, men with left ventricular dysfunction presented with significantly greater left ventricular end-diastolic diameter and greater septal and posterior wall thickness as compared to men with normal left ventricular function (all $P<0.05$, Table 1). In women, the respective adaptations to left ventricular dysfunction were less pronounced and statistically not significant. Again, only women with severe left ventricular dysfunction were characterized by significant increases in septal (12.2±1.6 mm vs. control 10.0±0.1, $P<0.05$) and posterior wall thickness (9.6±1.1 mm vs. control 8.3±0.05, $P<0.05$) and a tendency towards increased left ventricular end-diastolic diameter (48.0±3.8 mm vs. control 46.1±0.1, $P=$n.s.).

3.3. Uni- and multivariate regression analysis (Table 2, Fig. 2)

In univariate regression analysis, left ventricular mass index was significantly correlated with EF as well as age, body mass index, and systolic and diastolic blood pressure in both genders (all $P<0.01$, Table 2). However, in

Table 2
Univariate and multivariate predictors of LV mass index

	Male		Female	
	univariate (P-value/r-value)	multivariate (P-value/β-coeff.)	univariate (P-value/r-value)	multivariate (P-value/β-coeff.)
EF (%)	0.0001/0.14	0.0001/−54.0	0.0006/0.11	NS/5.7
Age (yrs)	0.0001/0.34	0.0001/0.5	0.0001/0.42	0.0001/0.4
BMI (kg/m^2)	0.0001/0.30	0.0001/1.1	0.0001/0.39	0.0001/0.8
Sys BP (mmHg)	0.0001/0.36	0.0001/0.2	0.0001/0.45	0.0005/0.1
Dia BP (mmHg)	0.0001/0.30	NS/0.1	0.0001/0.38	NS/0.1

Coeff., coefficient; EF, left ventricular ejection fraction, NS, not significant, yrs., years; BMI, body mass index; sys BP, systolic blood pressure; dia BP, diastolic blood pressure.

multivariate regression analysis, EF was confirmed as significant and independent statistical predictor of left ventricular mass index only in male subjects ($P<0.01$). In contrast, EF was no independent predictor of left ventricular mass index in female subjects after adjustment for age, body mass index, and systolic blood pressure (Table 2). Also, there was no significant independent effect upon LVMI when estrogen replacement therapy was included into the multivariate model. The adjusted increases in left ventricular mass index which can be attributed to given changes in EF, age, body mass index, and blood pressure are depicted in Fig. 2.

3.4. Neurohumoral activation (Figs. 3, 4)

In subjects with additional neurohumoral characterization, men with normal ejection fraction were characterized by significantly lower ANP (51.2±1.9 pg/ml vs. 63.1±2.1, $P<0.01$), BNP (15.3±1.2 pg/ml vs. 21.3±1.6, $P<0.01$), and cGMP (3.3±0.1 pmol/ml vs. 3.5±0.1, $P<0.01$), as well as significantly higher renin (20.5±2.1 mU/l vs. 14.9±0.7, $P<0.01$) as compared to women.

In male subjects with left ventricular dysfunction, ANP (79.9±9.3 pg/ml, $P<0.05$) and BNP (70.9±19.7 pg/ml, $P<0.05$) were significantly increased (Fig. 3) and accompanied by a significant increase in their second messenger, cGMP (4.9±1.0 pmol/ml vs. 3.3±0.1, $P<0.01$; Fig. 4). In contrast, women with left ventricular dysfunction were characterized by an attenuated and statistically not significant increase in ANP (80.0±15.5 pg/ml, $P=$n.s.) and BNP (31.0±7.2 pg/ml, $P=$n.s.) as well as a blunted increase in cGMP (3.9±0.6 pmol/ml vs. 3.5±0.1, $P=$n.s.). No significant differences in renin were observed in men (17.3±3.1 mU/l vs. 20.5, $P=$n.s.) and women (16.3±2.5 mU/l vs. 14.9±0.7, $P=$n.s) with left ventricular dysfunction as compared to control.

Similarly, when the male cutoff criterion for left ventricular dysfunction (EF<=46%) was applied to women (selecting towards greater functional impairment and fewer index cases) BNP and cGMP only had a tendency to increase by 71% (36.4±8.9 pg/ml vs. 21.4±1.6, $P=$n.s) and 32% (4.6±0.6 pmol/ml vs. 3.5±0.1, $P=$n.s.) and ANP increased by 51% (95.0±16.4 pg/ml vs. 62.9±2.1, $P<0.05$). In contrast, when the female cutoff criterion for left ventricular dysfunction (EF<=49%) was applied to

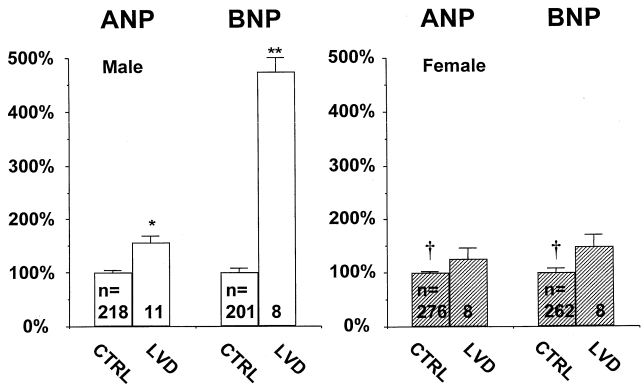

Fig. 3. Relative increases in plasma atrial natriuretic peptide (ANP, left) and brain natriuretic peptide (BNP, right) in male (open bars) and female (dashed bars) subjects with LV dysfunction (LVD) relative to subjects with normal LV function (control, CTRL, 100%). *: $P<0.05$ vs. CTRL, **: $P<0.01$ vs. CTRL, †: $P<0.05$ vs. male.

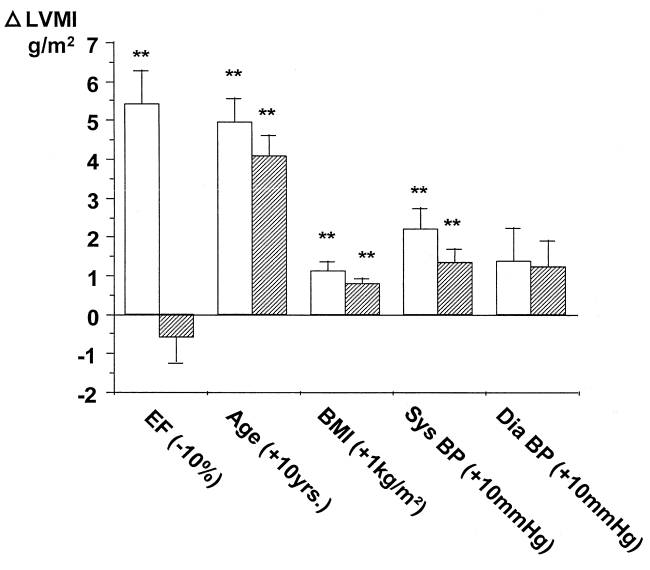

Fig. 2. Changes in LV mass index (LVMI) in relation to given changes of ejection fraction (EF), age, body mass index (BMI), systolic blood pressure (sys BP), and diastolic blood pressure (dia BP): adjusted results from multivariate regression analysis for male (open bars) and female (dashed bars) subjects. **: $P<0.01$.

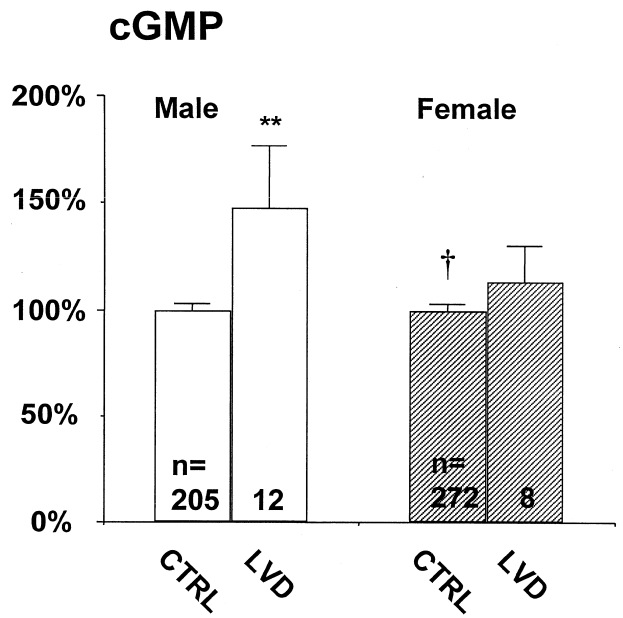

Fig. 4. Relative increases in plasma cGMP in male (open bars) and female (dashed bars) subjects with LV dysfunction (LVD) relative to subjects with normal LV function (control, CTRL, 100%). **: $P<0.01$ vs. CTRL, †: $P<0.05$ vs. male.

men (selecting towards lesser functional impairment and more index cases), statistically significant increases were still present for ANP, BNP, and cGMP with 50% (71.6±8.5 pg/ml vs. 51.4±1.9, $P<0.01$), 259% (55.1±16.3 pg/ml vs. 15.3±1.2, $P<0.01$), and 32% (4.4±0.8 pmol/ml vs. 3.3±0.1, $P<0.01$) respectively.

4. Discussion

The objective of this population-based study was to investigate gender-related patterns of left ventricular structure and neurohumoral activation associated with left ventricular dysfunction. On average, male subjects were characterized by a slightly lower ejection fraction, greater left ventricular mass, higher renin, and lower ANP and BNP as compared to female subjects. In the presence of left ventricular dysfunction, a marked increase in left ventricular mass was observed in male subjects with either moderate or severe left ventricular dysfunction. In contrast, only a small subgroup of female subjects with severe left ventricular dysfunction was characterized by a mild increase in left ventricular mass that was, however, attenuated in comparison to respective male subjects. Similarly, increases in left ventricular dimensions, wall thickness, and activation of the cardiac natriuretic peptides were markedly attenuated in female subjects with left ventricular dysfunction. The current study thus provides observational evidence for gender-specific control of left ventricular remodeling with left ventricular dysfunction.

Similarly to the current study, relatively smaller left ventricular dimensions in association with higher left ventricular ejection fraction have been reported in women as compared to men in a recent clinical study [20]. Moreover, it has been suggested in clinical and epidemiological studies that women are characterized by smaller left ventricular end-diastolic volumes in the presence of elevated filling pressures [20], smaller left ventricles with enhanced performance in the presence of mild arterial hypertension [21], less eccentric left ventricular remodeling in isolated systolic hypertension [22], and less eccentric left ventricular remodeling, less left ventricular mass, and better preserved contractile response in aortic stenosis [23]. These studies have been complemented by experimental investigations which have reported an attenuated hypertrophic response in female sinu-aortic denervated rats [24], a better preserved contractile function in female rats with pressure hypertrophy induced by aortic banding [9] and aged female transgenic mice with hypertrophic cardiomyopathy [10], and a greater hypertrophic reserve in association with better preserved contractile function in female spontaneously hypertensive rats [11]. Our current study extends these findings and suggests that human female myocardium also has a greater capability to preserve left ventricular geometry during hemodynamic overload associated with left ventricular dysfunction [25].

To date, experimental studies investigating the underlying mechanisms for potential gender-related differences are still sparse. However, the more favorable adaptations to pressure overload in female rats have been linked to an attenuated increase in beta-myosin heavy chain and ANP mRNA and a blunted decrease in sarcoplasmic reticulum Ca–ATPase mRNA as compared to male rats [9]. Another study in aged monkeys has suggested gender differences in myocardial beta-adrenergic receptor signaling with a depressed contractile response to beta-adrenergic agonists selectively in male monkeys [26]. Although our current data do not allow to address the effects of estrogen, a protective role has been suggested for this hormone [27] and is has been demonstrated that estrogen inhibits (and testosterone facilitates) the development of left ventricular hypertrophy in sinu-aortic denervated rats [24]. In this respect, our current finding of gender-specific regulation of the opposing natriuretic peptide and renin-angiotensin systems may also be of interest. It is tempting to speculate that the greater basal activation of the antimitogenic natriuretic peptide system [28–30] in women with normal left ventricular function may help to preserve cardiac structure and delay activation of the renin–angiotensin system during increased cardiac load [31]. Furthermore, the current finding of a markedly attenuated increase of the cardiac natriuretic peptides ANP and BNP as well as their second messenger cGMP in women with left ventricular dysfunction corroborates our findings with respect to left ventricular mass. Since ventricular re-expression and secretion of the natriuretic peptides has previously been shown to be closely associated with hypertrophic left ventricular remodeling [32,33], the current neurohormonal observation supports attenuated or blunted increases in left ventricular mass in female subjects with left ventricular dysfunction independently from measurements of left ventricular mass by echocardiography. A differential gender-effect is further supported by lacking signs of hypertrophy upon ECG in female subjects with left ventricular dysfunction while such signs were present in a significant number of corresponding male subjects.

The current study harbors a potential for bias due to the choice of gender-specific cut-off values in the definition of left ventricular dysfunction. Because women were, on average, characterized by a higher ejection fraction, the cut-off value for ventricular dysfunction was higher as compared to men. It might therefore appear that — by definition — women were designated to have left ventricular dysfunction at less functional impairment. However, the observation of a blunted increase in left ventricular mass in female subjects was confirmed even if the male cut-off criteria for left ventricular dysfunction were employed. Vice-versa, the observation of a marked increase in left ventricular mass in male subjects with left ventricular dysfunction was confirmed even if the female cut-off criteria were employed. A higher prevalence of myocardial infarction in men might offer another potential explanation

for the gender-specific adaptation to left ventricular dysfunction due to inaccurate assessment of left ventricular function and mass by echocardiography in these patients. However, when patients with previous myocardial infarction were excluded from analyses, the observed effect was robust and gender-specific left ventricular remodeling during left ventricular dysfunction was confirmed. In fact, the relatively higher proportion of men with ACE inhibitors and beta-blockers, i.e. medications that may regress LV hypertrophy, may even lead to an underestimation of the gender-related effects on LV mass. The higher proportion of men with heart failure medication may also suggest that symptoms of the disease were more prevalent in this group. Unfortunately, our questionnaire and physical examinations do not provide precise information in this respect. Nevertheless, the current association should also be studied by enhanced methodology including prospective follow-up examinations or very accurate measurements of left ventricular mass, such as cardiac magnetic resonance imaging. Recent studies which have utilized this method could already corroborate that LV mass needs to be stratified for age and gender [34].

In conclusion, this observational study provides important new insight into gender-specific differences in left ventricular remodeling. It strongly suggests gender-specific control of myocardial adaptations to hemodynamic overload with a greater tendency towards left ventricular dilatation and hypertrophy during left ventricular dysfunction in male subjects. While the clinical importance of the current observation for the syndrome of heart failure remains to be established, it is tempting to speculate that the more favorable left ventricular remodeling associated with left ventricular dysfunction in women might have a role in disease-progression and may ultimately contribute to better survival of women with heart failure.

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