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The Aging Process of the Heart: Obesity Is the Main Risk Factor for Left Atrial Enlargement During Aging

The MONICA/KORA (Monitoring of Trends and Determinations in Cardiovascular Disease/ Cooperative Research in the Region of Augsburg) Study

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Objectives This prospective study evaluated the association of obesity and hypertension with left atrial (LA) volume over 10 years.

Background Although left atrial enlargement (LAE) is an independent risk factor for atrial fibrillation, stroke, and death, little information is available about determinants of LA size in the general population.

Methods Participants (1,212 men and women, age 25 to 74 years) originated from a sex- and age-stratified random sample of German residents of the Augsburg area (MONICA S3). Left atrial volume was determined by standardized echocardiography at baseline and again after 10 years. Left atrial volume was indexed to body height (iLA). Left atrial enlargement was defined as iLA ≥35.7 and ≥33.7 ml/m in men and women, respectively.

Results At baseline, the prevalence of LAE was 9.8%. Both obesity and hypertension were independent predictors of LAE, obesity (odds ratio [OR]: 2.4; $p < 0.001$) being numerically stronger than hypertension (OR: 2.2; $p < 0.001$). Adjusted mean values for iLA were significantly lower in normal-weight hypertensive patients (25.4 ml/m) than in obese normotensive individuals (27.3 ml/m; $p = 0.016$). The highest iLA was found in the obese hypertensive subgroup (30.0 ml/m; $p < 0.001$ vs. all other groups). This group also presented with the highest increase in iLA (+6.0 ml/m) and the highest incidence (31.6%) of LAE upon follow-up.

Conclusions In the general population, obesity appears to be the most important risk factor for LAE. Given the increasing prevalence of obesity, early interventions, especially in young obese individuals, are essential to prevent premature onset of cardiac remodeling at the atrial level. (J Am Coll Cardiol 2009;54:1982–9) © 2009 by the American College of Cardiology Foundation

At an individual level, the combination of excessive caloric intake, lack of physical activity, and genetic susceptibility has resulted in a dramatic increase in the prevalence of obesity worldwide (1,2).

Obesity (3–5) and arterial hypertension (6,7) cause a variety of structural and functional cardiac changes that may affect left atrial (LA) size. Cardiac adaptation to obesity mainly consists of left ventricular (LV) dilation associated

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with an increased LV mass with the pattern of eccentric hypertrophy. Essential hypertension, by contrast, results most frequently in a concentric increase of LV mass. Eccentric and concentric hypertrophy both impair ventricular filling and thus facilitate the development of diastolic dysfunction (8), ultimately leading to left atrial enlargement (LAE) (9). In fact, LAE is known as a sensitive indicator of LV pre-load (10). Chronic volume overload related to obesity or chronic pressure overload related to hypertension may therefore both result in LAE.

Hemodynamically, the left atrium has 3 major functions. It serves as: 1) a reservoir that collects pulmonary venous return during ventricular systole; 2) a conduit for the passage of blood from the left atrium to the left ventricle during early ventricular diastole; and 3) a contractile pump that enhances LV filling in late diastole (11). Consequently, LV filling and performance may also be influenced by LAE.

This study evaluated the aforementioned association between obesity and arterial hypertension with LAE. In the first step, we investigated the association of different cardiovascular risk factors with LA size. In the second step, we delineated the influence of obesity and hypertension on LA size and the prevalence of LAE. Finally, we evaluated the effects of obesity and arterial hypertension on changes of LA volume during 10 years of follow-up and incidental development of LAE in a well-characterized population-based sample.

Methods

Study sample. Between October 1994 and June 1995, baseline data were obtained from the third survey (S3) of the population-based MONICA (Monitoring of Trends and Determinations in Cardiovascular Disease) & Augsburg/KORA (Cooperative Research in the Region of Augsburg) study. Only participants age 25 to 74 years at baseline who displayed echocardiographic M-mode tracings with sufficient quality for quantitative measurements at baseline were also eligible for an echocardiographic investigation at follow-up (F3) that was conducted between March 2004 and May 2005. The MONICA Augsburg project was part of the international collaborative World Health Organization MONICA project (12) and investigated the cardiovascular risk factor profile of randomly selected subjects of the resident population in cross-sectional surveys (13). The study design, sampling frame, and data collection have been described in detail elsewhere (12,13).

From a total of 1,675 participants in S3, 1,417 displayed sufficient echocardiographic M-mode tracings. However, a number of these participants were inaccessible or ineligible for the F3 follow-up examination because of death (58), interdiction of re-contact (63), migration (41), or severe illness (7). From the remaining 1,248 individuals who were invited to the re-examination, 1,005 participated in the follow-up study (net response 80.5%). For these particular analyses only, data derived from individuals with adequate echocardiographic images of the 4-chamber view were used (S3 = 1,212 individuals; F3 = 914 individuals). Compared with the entire sample, these individuals were significantly younger and presented with lower body mass index (BMI) and systolic blood pressure levels.

Abbreviations and Acronyms

BMI = body mass index
BSA = body surface area
iLA = indexed left atrial volume
LA = left atrial
LAE = left atrial enlargement
LV = left ventricular
SV = stroke volume

Interview and medical examination. On both occasions, all participants underwent an interview related to personal medical history, lifestyle, and health behavior. Obesity was defined according to the National Institutes of Health Consensus Development Panel criteria (14) as BMI ≥27.3 kg/m^2 in men and ≥27.8 kg/m^2 in women. Resting blood pressure was measured under strictly standardized conditions. Arterial hypertension was considered at a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg or current intake of antihypertensive medication. In addition, participants underwent standardized medical examinations including collection of a nonfasting venous blood sample. Diabetes mellitus was defined by the patient's self-report. Hypercholesterolemia was defined as a low-density lipoprotein cholesterol level ≥130 mg/dl. Cardiovascular disease was defined as stroke or myocardial infarction reported by standard questionnaire.

Echocardiography. Echocardiograms were performed using commercially available echocardiographs (in S3 Sonos 1500 and in F3 Sonos 4500, Philips Electronics, Eindhoven, the Netherlands). To reduce interobserver variability, all tracings were analyzed by a single cardiologist at each examination. Echocardiographic measurements were corrected for observer- and device-related differences between the 2 examinations. All echocardiographic investigations and reading procedures were performed following a standardized protocol. The quality of the echocardiographic investigations was assessed as previously described by the SHIP (Study of Health in Pomerania) study group (15).

Assessment of LA volume. Measurements of the LA volume were performed at end-systole of the left ventricle in the apical 4-chamber view by planimetry (Fig. 1). As superior border of the atrial outline, a straight line connecting both sides of mitral valve attachment points to the valve ring was taken. Both the atrial appendage and the pulmonary veins, when visualized, were carefully excluded (16). Left atrial volume was then calculated using the methods of discs (the Simpson rule).

Assessment of LA pressure and volume load. Pulmonary venous flows were used to assess mean LA pressure (17). Pulmonary vein Doppler was obtained by placing a color flow-guided 3- to 4-mm sample volume 1- to 3-cm deep within the pulmonary vein. Left atrial pressure load was estimated by calculation of S/D ratio.

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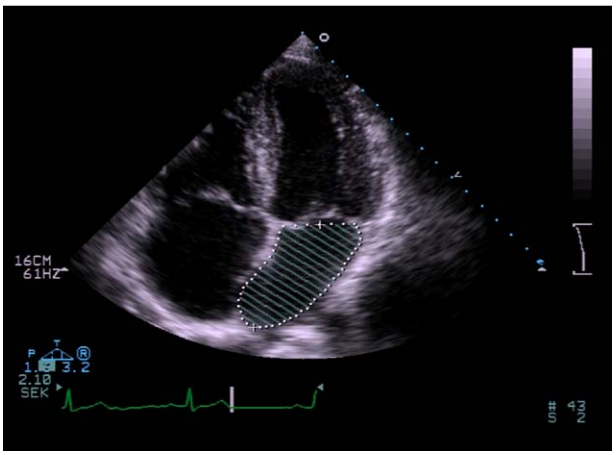

Figure 1 **Measurements of Left Atrial Volume**

Measurements were performed at end systole in the apical 4-chamber view by planimetry. As the superior border of the atrial outline, a straight line connecting both sides of the mitral valve attachment points to the valve ring was taken. Both the atrial appendage and the pulmonary veins, when visualized, were carefully excluded. Left atrial volume was calculated using the methods of discs (the Simpson rule).

Because all individuals with significant valvular disease were excluded, LV stroke volume (SV) should be equal to LA volume load. Left ventricular SV (ml) was calculated as:

$$VTI_{LVOT} \times (0.5 \times LVOT)^2 \times \pi$$

(18) where VTI represents the velocity time integral, and LVOT represents LV outflow tract. Both parameters were only available for the F3 follow-up study.

Statistical analysis. Blood pressure measurements and echocardiography had to be carried out with different methods in S3 and F3 because observers had changed after 10 years and the devices had been replaced, reflecting technologic progress. Systematic differences between surveys owing to different measurement methods were assessed by using data from all 1,005 individuals examined on both occasions using a mixed regression model. We specified a linear model with an individual random intercept for each participant. The variance of this intercept and thus the correlation between the 2 measurements of each individual were assumed to be equal for all participants. The model also included age, sex, BMI, and antihypertensive medication as covariates. An interaction term between sex and study was included to allow for statistically significant effects of measurement devices in men and women. Systematic differences estimated from these models were used to derive correction values that were applied to all values recorded in the baseline survey of 1994 to 1995.

To assess the relations between indexed left atrial volume (iLA) (dependent variable) and age, sex, cardiovascular disease, and cardiovascular risk factors, age, sex, S/D ratio, and SV standardized regression coefficients (β) and respective p values were calculated using linear regression models.

Because there are no generally accepted reference values published to define LAE based on iLA, partition values (derived as mean value + 2 SDs) were generated within a healthy reference group excluding all participants with evidence of mitral regurgitation, hypertension, obesity, diabetes, or cardiovascular disease. Prevalence and incidence odds ratios (ORs) for LAE were calculated using a logistic regression model with arterial hypertension and obesity as the predictors of interest adjusted for age and sex. To estimate the relative impact of predictors on LAE, we calculated the population-attributable risk percent (19). Population-attributable risk percent expresses the proportion of LAE in the study population that is attributable to the exposure of predisposing factors and that theoretically could be eliminated if the exposure was eliminated. It was calculated using the formula:

$$PAR\% = (P_e[POR - 1] / [P_e(POR - 1) + 1]) \times 100$$

where PAR% indicates the population-attributable risk percent, P_e represents the proportion of the population exposed to the risk factor, and POR indicates the adjusted prevalence OR. Finally, adjusted means for iLA and for absolute changes of iLA comparing baseline and follow-up measurements were estimated for groups with single or concurrent presence of hypertension and obesity using analyses of variance adjusted for age and sex. All analyses

Table 1 **Characteristics of the Total Study Sample and Healthy Reference Group**

	Healthy Reference Group (n = 433)	Total Study Sample (n = 1,212)
Age (yrs)	42.1 ± 11.4	48.5 ± 13.7
Male sex	40.2	48.0
BMI (kg/m^2)	23.8 ± 2.3	26.2 ± 3.9
SBP (mm Hg)	114 ± 12	125 ± 19
DBP (mm Hg)	75 ± 8	81 ± 11
Obese	—	34.2
Hypertensive	—	36.4
Current smoker	28.9	28.1
Hypercholesterolemia	68.7	76.7
Atrial fibrillation	—	0.8
Cardiovascular disease	—	1.2
Diabetes mellitus	—	2.1
LV mass (g)	137 ± 35	160 ± 48
e/a ratio	1.51 ± 0.53	1.28 ± 0.50
LA (M-mode) (mm)	34 ± 4	37 ± 5
LA volume (ml)	39 ± 10	43 ± 14
LA volume/BSA (ml/m^2)	22 ± 5	23 ± 7
LA volume/height (ml/m)	23 ± 6	26 ± 8

Values are mean ± SD or %.

BMI = body mass index; BSA = body surface area; DBP = diastolic blood pressure; e/a ratio = ratio of early to late transmitral flow velocities; LA = left atrial; LA (M-mode) = anteroposterior diameter of left atrium in parasternal long axis view; LA volume = volume of left atrium obtained in apical 4-chamber view; LV = left ventricular; SBP = systolic blood pressure.

were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, Illinois).

Results

Relation of cardiovascular risk factors to LA volume. Clinical characteristics and echocardiographic parameters of the entire study sample and a healthy subgroup are shown in Table 1. As compared with the entire sample, the healthy reference group was substantially younger and presented with lower systolic and diastolic blood pressure levels, better diastolic function (as indicated by a higher e/a ratio), lower average values for BMI and LV mass, and smaller LA size.

Left atrial volume was normalized to body height (iLA) in the remainder of the study because such indexing results in better discrimination of the effects related to obesity (20,21).

To evaluate the influence of different cardiovascular risk factors on LA size, several linear regression analyses were performed (Table 2). Strong associations with LA size were observed for obesity, arterial hypertension, and age. When the standardized regression coefficients (β) were compared, the effect of obesity was almost twice the effect of hypertension. Of note, when the relation of cardiovascular risk factors to absolute changes of iLA volume during 10 years of follow-up was analyzed (Table 2, model 3), there was no significant effect of hypertension detectable. Similar results were found after replacing categoric variables by their continuous counterparts (e.g., replacing arterial hypertension [y/n] by systolic blood pressure [mm Hg]; data not shown). In this particular study, no association of LA size with diabetes and hypercholesterolemia was observed. A "protective effect" of smoking was likely caused by colinearity to age owing to the high number of young smokers.

Prevalence of LAE. Partition values for the definition of LAE were calculated within a healthy reference group (Table 3). Left atrial enlargement was defined as iLA ≥35.7 ml/m in men and ≥33.7 ml/m in women.

The crude prevalence of LAE in the total study sample was 9.6% for men and 10.0% for women ($p = 0.825$ for the difference between the sexes). In the normal-weight normotensive subgroup, the prevalence was lowest (2.5% for men and 3.2% for women), with no significant difference between the sexes ($p = 0.646$) (Table 4). In comparison, individuals with hypertension but without obesity presented with significantly higher prevalence of LAE (15.2%; $p < 0.001$ for men and 11.0%; $p = 0.001$ for women). Obese normotensive individuals also presented with a significantly increased prevalence of LAE (12.2%; $p < 0.001$ for men and 13.6%; $p < 0.001$ for women). Comparing the crude prevalences separately for both sexes showed no statistically significant difference between normal-weight hypertensive patients and obese normotensive individuals. The highest prevalence of LAE was seen in the obese hypertensive subgroup (15.7%, $p < 0.001$ for men; 30.5%, $p < 0.001$ for women). Of note, the latter values significantly differed from all other subgroups (Table 4). In adjusted logistic regression models (Fig. 2), both hypertension and obesity were significant independent predictors of LAE. Obesity (OR: 2.4; 95% confidence interval [CI]: 1.6 to 3.7; $p < 0.001$) was numerically a stronger predictor than hypertension (OR: 2.2; 95% CI: 1.4 to 3.4; $p < 0.001$).

As estimated by the population-attributable risk, obesity accounted for 32.4% (hypertension 30.4%) of LAE observed at baseline in the entire population. Interestingly, with a traditional partition value for LAE (LA volume indexed by

Table 3 Partition Values for Different Indexing of Left Atrial Volume

	Mean	SD	Mean + 2SD	Rel Dev
Men				
LA (ml)	42.5	10.5	63.5	0.13
LA/BSA (ml/m^2)	22.1	5.2	32.5	−0.01
LA/height (ml/m)	24.1	5.8	35.7	0.05
Women				
LA (ml)	36.3	9.6	55.5	
LA/BSA (ml/m^2)	21.7	5.5	32.8	
LA/height (ml/m)	22.2	5.8	33.7	

BSA = body surface area; LA = volume of left atrium obtained in apical 4-chamber view; Rel Dev = relative deviation of partition values (PV) men versus women as calculated: $(PV_{men} - PV_{women})/([PV_{men} + PV_{women}]/2)$.

Table 2 Relation of Cardiovascular Risk Factors to iLA

	Model 1 iLA		Model 2 iLA		Model 3 ΔiLA	
Dependent Variable	β	p Value	β	p Value	β	p Value
Age (yrs)	0.085	0.026	0.111	0.002	0.135	<0.001
Female sex	−0.040	0.234	−0.035	0.284	0.000	0.992
Obesity (y/n)	0.222	<0.001	0.215	<0.001	0.173	<0.001
Hypertension (y/n)	0.121	0.001	0.123	<0.001	0.064	0.077
Current smoker (y/n)	−0.088	0.009	—	—	—	—
Hypercholesterolemia (y/n)	−0.028	0.424	—	—	—	—
Diabetes mellitus (y/n)	0.001	0.965	—	—	—	—
Cardiovascular disease (y/n)	0.056	0.086	0.057	0.080	0.077	0.021

Relation of cardiovascular risk factors to iLA (models 1 and 2) at baseline investigation and ΔiLA (model 3) during 10 years of follow-up. Regression coefficients (β) and respective p values for regression models including age, sex, cardiovascular disease, and all cardiovascular risk factors (model 1; $R^2 = 0.16$); age, sex, obesity, hypertension, and cardiovascular disease (model 2; $R^2 = 0.12$); and age, sex, obesity, hypertension, cardiovascular disease, and the baseline measurement of iLA (model 3; $R^2 = 0.09$).
iLA = indexed left atrial volume.

Table 4 Crude Prevalence of LAE

	Men				Women			
	n	Prevalence	OR (95% CI)	p Value	n	Prevalence	OR (95% CI)	p Value
Total population	582	9.6% (8.2%)*	—	—	630	10.0% (7.8%)*	—	—
Normal weight normotensive	238	2.5% (2.5%)*	—	—	347	3.2% (2.9%)*	—	—
Normal weight hypertensive	112	15.2% (13.4%)*	6.9 (2.6–18.1)	<0.001	100	11.0% (11.0%)*	3.8 (1.6–9.0)	0.001
Obese normotensive	98	12.2% (10.2%)*	5.4 (2.0–14.8)	<0.001	88	13.6% (10.2%)*	4.8 (2.1–11.3)	<0.001
Obese hypertensive	134	15.7% (12.7%)*	7.2 (2.8–18.3)	<0.001†	95	30.5% (20.0%)*	13.4 (6.4–28.2)	<0.001†

Crude prevalence of LAE based on internal MONICA-Augsburg partition value (men iLA ≥35.7 ml/m; women iLA ≥33.7 ml/m) among normal-weight normotensive (men BMI <27.3 kg/m^2; women BMI <27.8 kg/m^2), normal-weight hypertensive (systolic/diastolic blood pressure ≥140/90 mm Hg or drugs), obese normotensive individuals, and obese hypertensive men and women. p values were calculated with chi-square tests (vs. normal-weight normotensive individuals). *Crude prevalence using a traditional partition value for LAE (LA volume indexed by BSA ≥33 ml/m^2). †Versus normal-weight hypertensive individuals; men: OR: 1.0 (95% CI: 0.5 to 2.1), p = 0.915; women: OR: 3.6 (95% CI: 1.7 to 7.6), p = 0.001; versus obese normotensive individuals; men: OR: 1.3 (95% CI: 0.6 to 2.9), p = 0.460; women: OR: 2.9 (95% CI: 1.3 to 5.9), p = 0.006.

BMI = body mass index; BSA = body surface area; CI = confidence interval; iLA = indexed left atrial volume; LA = left atrial; LAE = left atrial enlargement; OR = odds ratio.

body surface area [BSA] ≥33.0 ml/m^2 for both sexes), the crude prevalence of LAE was lower, especially in the obese subgroups (Table 4).

Incidence of LAE. The crude incidence of LAE in the entire study sample after 10 years of follow-up was 18.7% for men and 21.1% for women (p = 0.397 between sexes). In the normal-weight normotensive subgroup, the incidence was lowest (men 10.9% and women 11.6%; p = 0.828). As compared with respective male and female normal-weight normotensive subgroups, a higher incidence of LAE was found in nonobese women with hypertension (30.0%; p < 0.001) but not in respective men (14.3%; p = 0.496). In contrast, compared with the normal-weight normotensive subgroups, obese normotensive individuals displayed a significantly higher incidence of LAE in both sexes (women 34.8%, p < 0.001; men 38.2%, p < 0.001). A similar incidence of LAE was seen in the obese hypertensive subgroup (women 25.0%, p = 0.004; men 44.7%, p < 0.001). In adjusted logistic regression models (Fig. 3), only obesity was a significant independent predictor of incident LAE (obesity OR: 2.7; 95% CI: 1.8 to 4.1; p < 0.001; hypertension OR: 1.1; 95% CI: 0.7 to 1.7; p = 0.564).

Relation of LA pressure and volume load to LA size. To evaluate the influence of LA pressure and volume load on LA size, linear regression analyses were performed (Table 5). A significant association of LA pressure load (as estimated by the S/D ratio) with LA size was only found in hypertensive subgroups. In contrast, a significant association between LA volume load (as estimated by the SV) and LA size was found in the obese and normal-weight normotensive subgroups.

Adjusted mean values of iLA. To further delineate the influence of obesity and hypertension on LA volume, we calculated adjusted mean iLA values (Fig. 4). The iLA in the normal-weight hypertensive group was significantly higher than in the normal-weight normotensive group. Obesity alone was associated with a significantly stronger increase in LA size than hypertension. The largest LA size was found in the obese hypertensive subgroup. Additionally, we evaluated the effect of obesity and hypertension on changes in iLA during aging of 10 years (Fig. 5). Except for the normal-weight normotensive subgroup, there was a significant increase in iLA detectable in all other groups. The highest increase in iLA was found in the obese normotensive and in the obese hypertensive patients.

Discussion

To our knowledge, this is the first evaluation of factors affecting LA remodeling during aging over 10 years. Both hypertension and obesity were identified as independent predictors of LAE. Besides aging itself, obesity was the strongest risk factor for incident LAE studied. Furthermore, our results suggested that LAE in obese and in hypertensive individuals may be caused by different pathophysiologic mechanisms.

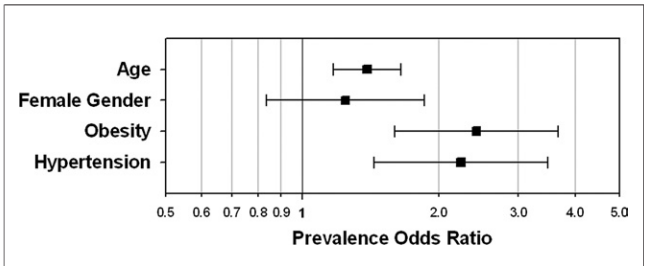

Figure 2 Prevalence Odds Ratios for Left Atrial Enlargement

Odds ratios with 95% confidence intervals; results of logistic regression model, adjusted for age (risk per decade) and sex.

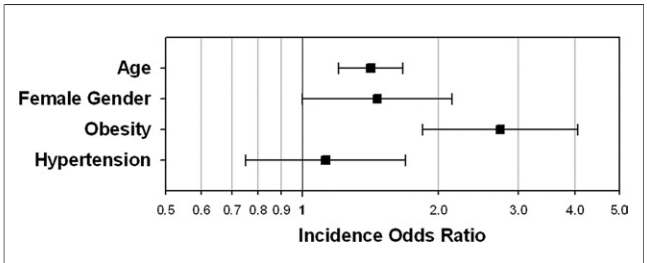

Figure 3 Incidence Odds Ratios for Left Atrial Enlargement

Odds ratios with 95% confidence intervals; results of logistic regression model, adjusted for age (risk per decade) and sex.

Table 5 Relation of Volume and Pressure Load to Indexed Left Atrial Volume

	S/D Ratio (Pressure Load)		Stroke Volume (Volume Load)	
	β	p Value	β	p Value
Normal weight normotensive	−0.005	0.939	0.389	<0.001
Normal weight hypertensive	−0.351	<0.001	0.063	0.361
Obese normotensive	−0.136	0.171	0.306	0.002
Obese hypertensive	−0.168	0.010	0.292	<0.001

Regression coefficients (β) and respective p values for regression models including S/D ratio, stroke volume, and age and sex (data not shown). Data derived from the follow-up investigation.

Obesity is the main risk factor for LAE. Several studies have identified BMI as an independent predictor of LA size in adults (22,23). Our data confirmed this strong relation in a large population-based sample. Particularly, we found strong associations of obesity, arterial hypertension, and age with LA size. In linear regression models, the effect of obesity was almost twice the effect of hypertension. We also assessed the impact of the concurrence of obesity and hypertension on LA volume index. After adjustment for age and sex, obesity resulted in higher iLA than hypertension.

Wang et al. (24) found obesity to be an important risk factor for new-onset atrial fibrillation. The increased risk for atrial fibrillation associated with obesity appeared to be mediated by LA dilation. Interestingly, in their multivariate regression models, the association between BMI and risk of atrial fibrillation was not significantly influenced by systolic blood pressure. This is in line with our observations, which revealed obesity to be the main risk factor for LAE during aging.

With regard to the increasing prevalence of obesity in industrialized countries, development of effective primary prevention strategies are essential to avoid premature cardiovascular remodeling. It remains unclear, however, to what extent weight maintenance or moderate weight loss has beneficial effects, resulting in regression of LAE. Evidence in this field is limited. There are only a few studies available investigating the effect of substantial weight loss in morbid obese individuals (25). Whether these results can be applied to the general population needs further investigation.

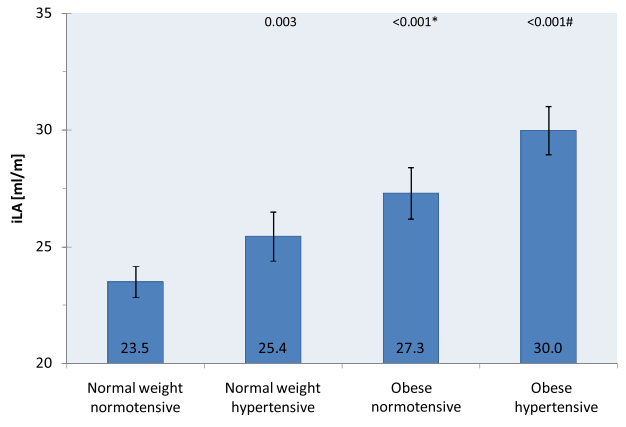

Figure 4 Adjusted Mean Values for iLA

Adjusted mean values with 95% confidence intervals as estimated with univariate variance analysis, adjusted for age and sex; p values for comparison with normal-weight normotensive individuals: *p = 0.016 versus normal-weight hypertensive patients; #p < 0.001 versus normal-weight hypertensive patients; p < 0.001 versus obese normotensive individuals. iLA = indexed left atrial volume.

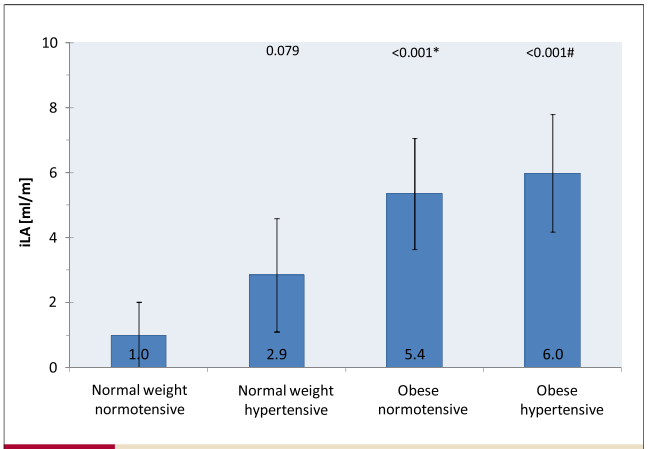

Figure 5 Adjusted Mean Values for Absolute Changes of iLA

Adjusted mean values with 95% confidence intervals as estimated with univariate variance analysis, adjusted for age, sex, and the baseline measurement of left atrial volume; p values for comparison with normal-weight normotensive individuals: *p = 0.042 versus normal-weight hypertensive patients; #p = 0.012 versus normal-weight hypertensive patients; p = 0.607 versus obese normotensive individuals. iLA = indexed left atrial volume.

Varying methods and partition values exert a prominent influence on the proportion of patients identified as having LAE. Currently the recommended and most frequently used parameter for normalization of LA volume measurements is BSA (26). However, because BSA is calculated using body height and weight, indexing of LA volume by BSA may lead to an underestimation of LA remodeling, especially in obese individuals (20,21). Therefore, the best method for normalization of LA volume measurements is still being debated. For example, normalization of LV mass to the power of its allometric or growth relation with height (height$^{2.7}$) enhanced the ability to detect LV hypertrophy related to obesity (27). Consequently, we suggest a body weight–independent indexing of LA volume. As demonstrated in this paper, indexing of LA volume by body height enhanced the ability to detect LAE related to obesity.

Hypertension and LAE. A direct relation between systolic blood pressure and LA size has been demonstrated in several population-based studies (7,28,29). Furthermore, in patients with essential hypertension, LAE is a common echocardiographic finding with a significant relation to LV mass (4). In hypertensive individuals, cardiac adaptations may be due to pressure overload of the LA that is primarily related to impaired filling secondary to concentric hypertro-

phy (5,30). Impaired LV filling may lead to an increased LA pressure, ultimately resulting in LAE.

By contrast, the mechanisms by which obesity may promote LAE are more complex (30). Obese patients may undergo LA dilation resulting from hemodynamic alterations like increased intravascular volume and increased cardiac output (3,30). Subsequently, these alterations may lead to LA volume overload (31).

Within this study a significant association of LA size to indirectly estimated LA pressure was only found in individuals presenting with hypertension. By contrast, in obese individuals, a significant relation between LA size and LA volume load was detectable. These findings strengthen the notion that LAE in obese and in hypertensive individuals may be caused by different pathophysiologic mechanisms. Furthermore, our data suggest that LA pressure load in hypertensive individuals resulted in an increase in LA size early after occurrence of the disease (i.e., the association with prevalent LAE was relatively strong). However, further LAE during follow-up was observed to a much lesser extent, resulting in low incidence of LA dilation in hypertensive individuals. In contrast, chronic LA volume load within the obese may result in a continuous enlargement of the left atrium as indicated by significant associations with both prevalent and incident LAE. Comparing the relation of obesity and hypertension with LAE, this observation may partly explain the stronger role of obesity.

The left atrium: underestimated prognostic factor? The current study contributes to the mounting evidence that obesity (22,23) and hypertension (9,20) lead to LAE. As a result, the incidence of atrial fibrillation, with its subsequent risks of stroke and heart failure, rises in obese (24,32) and in hypertensive individuals (32,33). Because of the higher prevalence of hypertension in the general population, more cases of atrial fibrillation are related to this condition than to any other cardiovascular risk factor (34). However, with regard to the increasing prevalence of severe obesity in developed countries, its importance in the development of atrial fibrillation will increase and may replace arterial hypertension as the main risk factor.

Study limitations. We report an association in a rather complex biologic system with multiple interactions. Thus, it is difficult to establish causal relationships using the present cross-sectional study design. In this study, definition of diabetes was limited (e.g., there was no fasting glucose level available) and the number of diabetic patients was relatively small. As a result, the relation of diabetes and LA size still remains unclear and needs further investigation. Moreover, we had to rely on 2 single measurements to represent a period of 10 years. Thus, fluctuations of blood pressure, glucose levels, or other risk factors or the effects of intermittent medications were not included in our analyses. Finally, the prevalence of atrial fibrillation within this cohort was low (0.8%). It was therefore not possible to draw any firm conclusion about the determinants of atrial fibrillation.

Conclusions

Both obesity and hypertension were found to be independent risk factors for LAE and are probably acting through different pathophysiologic mechanisms. However, in the general population, obesity appears to be the most important risk factor. With regard to the increasing prevalence of excess obesity in developed countries, early interventions, especially in young obese individuals, are essential for the prevention of premature onset of cardiac remodeling.

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