Age is an independent risk factor for left atrial dysfunction: results from an observational study

M.A.M. Ploumen, L.H.B. Baur, M.J. Streppel, C.L.B. Lodewijks-van der Bolt, B. Winkens, R.A.G. Winkens, H. E.J.H. Stoffers

Introduction. The degenerative changes of myocardial tissue are thought to influence left atrial (LA) function. Changes of left atrial function are generally due to changes in left ventricle (LV) compliance. But valvular dysfunction and hypertension as comorbidity cannot be ignored. Women have a different clinical profile compared with men concerning the risk of heart failure. We investigated the influence of increasing age and gender corrected for comorbidity, on left atrial function.

Methods. Using an open access echocardiography database, supplemented with additional LA function measurements, we defined three different LA function parameters. Odds ratios (OR) were calculated to reproduce the relation between age, gender and LA function. The association between age, gender and LA function was estimated, and corrected for comorbid conditions as valve disease, high blood pressure and LV dysfunction, using logistic regression.

Results. Higher age was positively correlated with increased LA volume, decreased ejection fraction and increased LA kinetic energy. Age per decade increase, corrected for comorbidity,

resulted in an increased risk of LA dysfunction (OR between 1.5 and 1.9). Gender had little influence on LA function parameters except for LA maximal volume. Men had a significantly larger LA maximal volume compared with women.

Conclusions. In this open access echocardiography database, increasing age was correlated with LA dysfunction. Age per decade increase, corrected for comorbid conditions such as mitral and aortic valve disease, hypertension and heart failure, is an independent risk factor for LA dysfunction. The gender influence on LA dysfunction seems to be limited. (Neth Heart J 2010;18:243-7.)

Keywords: Age Factors; Atrial Function; Female; Male; Comorbidity

The risk of developing heart failure increases with age. As a result the overall likelihood of developing heart failure in a lifetime is 20% at all ages above 40.¹

Recently, it was shown that women have a different clinical profile compared with men concerning the risk of hypertension and heart failure. The results from the European Heart Survey on Heart Failure and the BEST study showed that in a population of patients with New York Heart Association class III/IV and LVEF <35%, women are older, more often have hypertension, diabetes, cerebrovascular disease and valvular disease, but have a lower prevalence of left ventricular systolic dysfunction.²⁻⁴

Many studies have investigated the influence of normal ageing on atrial volume and function, especially since the large proportion of diastolic heart failure - up to 54% of the total number of heart failure - is known.⁵ Early identification of LA dysfunction is important because of the increased risk of thrombogenesis resulting in infarction and stroke.

There is some evidence found that there is a gender difference in left atrial size. A limitation of these studies is the exclusion of patients with comorbidity: patients with known hypertension, left

M.A.M. Ploumen

M.J. Streppel

B. Winkens

R.A.G. Winkens

University of Maastricht, Maastricht, the Netherlands

L.H.B. Baur

Department of Cardiology, Atrium Medical Centre Parkstad, Heerlen and University of Maastricht, Maastricht, the Netherlands

C.L.B. Lodewijks-van der Bolt

Department of Cardiology, Atrium Medical Centre Parkstad, Heerlen, the Netherlands

H. E.J.H. Stoffers

Care and Public Health Research Institute (CAPHRI), University of Maastricht, Maastricht, the Netherlands

Correspondence to: L.H.B. Baur

Department of Cardiology, Atrium Medical Centre Parkstad, PO Box 4446, 6401 CX Heerlen, the Netherlands
E-mail: l.baur@atriummc.nl

ventricle dysfunction and valve disease were often excluded. Especially hypertension has a high incidence in the elderly (38% male and 42% female in the age group 65-85 years).⁶ Excluding these patients leads to under representation of elderly patients in these studies.

The aim of the present study is to investigate the influence of ageing and gender on LA function and the effect of relevant comorbidity on this association.

In this study comorbidity is defined as high blood pressure, valve disease and finally systolic and diastolic LV dysfunction. Data from an open access echocardiography service were used.

Methods

The open access service

In 2002 an open access echocardiography service was started in Parkstad, Limburg, the Netherlands.^{7,8} All general practitioners (GPs) were able to order an echocardiogram, without referring the patient to a cardiologist. GPs had to provide the indication for ordering an echocardiogram, current medication, relevant medical history and findings of the physical examination on a special request form. The GPs were encouraged to fill out the forms completely. In all patients a routine echocardiography examination was performed by an experienced cardiologist or a fellow in cardiology under supervision. M-mode, two-dimensional and Doppler echocardiography were performed on a Philips SONOS 5500® system and filed on the ENCONCERT® digital storage and retrieval system. Afterwards, the results were interpreted according to the criteria of the American Societies of Echocardiography, by a cardiologist with much experience in echocardiographic imaging.⁹ The summarised results were sent to the GP. In case of possible abnormalities (e.g. significant valve disease, significant LV dysfunction and significant pulmonary hypertension) the GP was advised to refer the patient to the cardiologist or another specialist, to change or start medication, to repeat the echocardiogram after some time or to consider endocarditis prophylaxis.

Study population

As mentioned above, baseline details and the results of the echocardiographic examinations from the open access service were collected in a database, which is the basis for the present study. All subjects were included by GPs whenever they considered an echocardiogram necessary. From the beginning of the project in 2002 until the start of the analyses presented in this paper (January 2009), 1001 patients were included in the database.

Echocardiographic measurements

To study LA function, more than routine echocardiographic variables were needed. Using the

Table 1. Definitions of additional echocardiography measurement

Measurement	Definition	Calculation
LA max volume	Volume before mitral valve opening	Volume at the onset of the P wave
LA ejection fraction	% LA content ejected in LV	LA emptying volume / LA maximal volume
LA kinetic energy	Energy of the blood flow particles across the mitral valve by atrial contraction	$0.5 \cdot \text{LA emptying volume} \cdot \rho \cdot A^2$ / 1000

LA=left atrial, LV=left ventricle, ρ =blood density=1.06 gm/cm³, A=late diastolic transmitral flow velocity (cm/s), LA emptying volume = maximal LA volume – minimal LA volume.

ENCONCERT^a analysis system, the following additional measurements were done: late diastolic transmitral flow velocity (cm/s), left atrial maximal volume (cm³), left atrial minimal volume (cm³) and pre-atrial contraction volume (onset P wave) (cm³). LA maximal volume was measured just before mitral valve opening and minimal volume at the point of mitral valve closure. Volume at the onset of the P wave in the electrocardiogram taken simultaneously was considered to be the LA volume at the onset of LA systole. The mentioned measurements were performed by Marjolein Streppel under the supervision of experienced cardiologists. These data were used for calculation of LA ejection fraction (%) and LA kinetic energy (Kerg).^{10,11} The definitions of these variables are listed in table 1.

In accordance with previous studies the calculated variables plus the LA maximal volume were used as variables representing LA function or diastolic heart function. LA maximal volume is proposed to be a marker of diastolic heart failure because of the direct exposure to the LV through the open mitral valve.^{5,12}

Definitions of comorbidity

High blood pressure was defined as a systolic blood pressure >140 mmHg and/or a diastolic blood pressure >90 mmHg, following the guidelines of the Dutch College of General Practitioners and the European and American Societies of Hypertension and Cardiology.^{13,14}

Systolic left ventricular dysfunction was defined as a left ventricular ejection fraction <40%, because of the well-recognised clinical significance of this cut-off point.

Table 2. Study population.

		All (n=975)	Male (n=409)	Female (n=566)	P value
Population characteristics					
Age, years (mean, SD)		59.8±18.6	58.3±17.6	60.9±19.2	0.03*
High blood pressure, n, (%)†		478 (49.0)	192 (40.2)	286 (59.8)	0.27
Left valve disease (n, %)†		161 (16.5)	65 (40.4)	96 (59.6)	0.66
LV dysfunction (systolic & diastolic) (n, %)†		396 (40.6)	183 (46.2)	213 (35.8)	0.03*
Echocardiographic outcome variables n (%) n (%)					
LA max volume (mean, SD)†	874 (89.6%)	51.8±24.2	55.2±26.4	49.4±22.2	0.00*
LA EF (mean, SD)†	874 (89.6%)	0.6±0.17	0.6±0.2	0.6±0.2	0.18
LA kinetic energy (mean, SD)†	797 (81.7%)	131.6±109.95	120.8±106.2	139.2±112.0	0.21

LA=left atrial, LV=left ventricle, * significance $p<0.05$, † see text for definition.

Diastolic dysfunction of the LV was first estimated based on the peak velocity E/A ratios. Because of its age dependence, patients were divided into different age categories and age specific cut-off points were used for deviated peak velocity E/A ratios.¹⁵ For patients younger than 20 years, there are no reliable cut-off points described. For that reason we made the most truthful assumption that these young persons had no diastolic dysfunction.

Left valve disease was defined as insufficiency or stenosis of the mitral valve or aortic valve, measured by leakages or grade 2 or more, respectively, and valvular gradients on Doppler echocardiography. Isolated aortic valve disease included stenosis and insufficiency. The presence of valve stenosis was scored for aortic valve and mitral valve by measuring gradients as already stated. Stenosis was present when maximal gradients exceeded 30, 10 and 15 mmHg, respectively. Aortic stenosis was in addition to the maximal gradient, also dependent on the mean gradient, with 20 mmHg as a cut-off point.

Statistical analysis

The cut-off points for normal versus abnormal LA function were calculated for all LA variables according a normal distribution with 95% confidence interval (mean $\pm 2SD$), using the mean value of all patients with good cardiac health.¹⁶ Good cardiac health was defined as not having hypertension and not having any significant disease detected by echocardiography. This resulted in a total cardiac healthy population of 163 patients, including patients for whom blood pressure values were missing. This decision was made based on the assumption that GPs would usually have mentioned blood pressure values that were significantly raised.

Statistical analyses were performed with SPSS

statistical software (SPSS 15.0). Odds ratios with 95% confidence intervals were used to examine the influence of age and gender on LA function. The association between age, gender and LA function was corrected for comorbidity conditions that turned out to be significant risks for LA dysfunction, using logistic regression.

T tests were performed to analyse significance in differences between male and female characteristics.

Results

Population characteristics

Of the 1001 subjects included in the database at the start of the analysis, 975 could be used in our study. The data of 12 patients were lost to follow-up because the computer system failed to extract the echocardiography images of these patients. Possible explanations are inaccurate saving at the time, incorrect identification numbers or errors in the storage system. In 14 patients the quality of the images had shortcomings in such a way that they were unusable in our study.

The characteristics of the remaining 975 subjects are listed in table 2. More women than men were included in our study. The mean age of the study population was 59.8 years (range 5 to 98, median 64). The mean age of the women was 58.3 and the mean age of the men was 60.9.

Ageing and LA function

Table 3 presents the results of the logistic regression analysis of the relation between age and LA function parameters, corrected for having aortic and mitral valve disease, high blood pressure or systolic and diastolic LV dysfunction. The influence of age is represented in odds ratios per 10 years increase of age. Analysis showed a significantly increased risk of enlarged maximal LA volume, de-

Table 3. Logistic regression: odds ratios for influence of age and gender.

LA parameters	Age per decade		Gender male vs. female	
	Crude OR (95% CI)	Corrected OR† (95% CI)	Crude OR (95% CI)	Corrected OR† (95% CI)
Increased max LA volume	1.5 (1.3-1.8)*	1.6 (1.3-2.0)*	2.2 (1.5-3.3)*	2.5 (1.5-4.2)*
Decreased LA ejection fraction	1.9 (1.6-2.4)*	1.9 (1.4-2.6)*	1.4 (0.9-2.3)	1.4 (0.7-2.8)
Increased LA kinetic energy	1.6 (1.5-1.9)*	1.5 (1.3-1.7)*	0.8 (0.6-1.1)	1.0 (0.6-1.4)

* Significance $p < 0.05$, † corrected comorbidity: only aortic valve disease, only mitral valve disease, both aortic and mitral valve disease, high blood pressure, only systolic left ventricle dysfunction, only diastolic left ventricle dysfunction, both systolic and diastolic left ventricle dysfunction, OR age per decade: OR per 10 years increase, OR gender: male compared with female, Value >1 =increased parameter compared with females, Value $0-1$ =decreased parameter compared with females.

creased LA ejection fraction and increased kinetic energy (OR=1.5, 1.9 and 1.6, respectively). When correcting for comorbidity the odds ratios were almost equal to the uncorrected odds ratios and remained significant (OR=1.6, 1.9, 1.5).

Gender and LA function

Table 3 presents the results of the logistic regression analysis of the relation between gender and LA function parameters, corrected for having aortic and mitral valve disease, high blood pressure or systolic and diastolic LV dysfunction. Analysis of the influence of gender showed a significantly increased risk of enlarged maximal LA volume (OR 2.2) in males compared with females. Decreased LA ejection fraction and increased kinetic energy showed no significant difference (OR 1.4 and 0.8 respectively) and the kinetic energy parameter showed a decreasing trend in males compared with females. When correcting for comorbidity the odds ratio for enlarged maximal LA volume increased (OR 2.5) and was still significant. The odds ratios of the ejection fraction and kinetic energy stayed insignificant and the decreasing trend in kinetic energy disappeared (OR 1.4 and 1.0 respectively).

Discussion

Summary of main findings

In our study, age was correlated with LA dysfunction, as expressed by increased LA volume, decreased ejection fraction compensated by raised LA kinetic energy. Age, corrected for comorbid dysfunction conditions such as mitral and aortic valve disease, hypertension and heart failure showed an increased risk of LA dysfunction. Also gender, more specifically males, correlated with only increased LA volume as a parameter of LA dysfunction.

Ageing and gender on LA function

LA maximal volume increased with progressing age. This is in line with other studies reporting that age was significantly associated with LA vol-

ume and LA dimension.¹⁷ LA kinetic energy also increases with age, since the decreased LV compliance leads to compensatory LA contraction.^{1,18,19} Conversely, the LA ejection fraction significantly decreases with age. The decrease in ejection fraction is due to rising effort put into filling the LV, contrary to the increased overall LA volume.

LA maximal volume is larger in men compared with women. LA ejection fraction and LA kinetic energy showed no significant difference between men and women. This is in line with other studies reporting that men have a significantly larger LA volume.¹⁷ The difference in LA volume may be contributed to the difference in body size of men compared with women.

Age and gender corrected for comorbidity

To determine the association of ageing and gender with LA function parameters corrected for relevant comorbidity, i.e. valve disease, high blood pressure and systolic and diastolic LV dysfunction, a logistic regression analysis was performed. 'Aortic and mitral valve disease' was selected because of the influence they have on left atrial and ventricular function. 'High blood pressure' was included in the logistic regression, considering the high association between hypertension and systolic and diastolic dysfunction in other studies.²⁰⁻²² Our results showed an increased risk of LA dysfunction in relation to age.

A larger LA maximal volume was found in men. Women seem to be less prone to an enlarged LA maximal volume than men. Therefore women might have a decreased risk of developing the consequences of an enlarged LA volume such as atrial rhythm disorders, atrial embolisms and diastolic heart failure.

Strengths and limitations

The database reflected a population in primary health care referred for echocardiography, representing patients with suspected but undiagnosed heart failure. Because comorbidity was not an ex-

clusion criterion in our study, the average age was almost 60 years. Comparable studies show a mean age of 60 years in the oldest age category with an overall average of 45 to 50 years.²³ Finally, the application of different parameters for LA function contributes to the reliability of judgements made in the present study.¹⁶

Although useful echocardiography data were not available in only 26 patients (2.6%), in many patients it was not possible to perform all echocardiography measurements (e.g. transmitral flow velocities could be measured while LA volumes could not) due to the poor apical image quality. Another potential limitation is that 'high blood pressure' was based on a single measurement.

Clinical implications

It turned out that LA volume is an indicator of LV filling and reflects the seriousness of diastolic heart failure which shows the emerging evidence of LA volume as a prognostic factor in heart disease.¹⁰ Impaired LA function induces thrombogenesis, thereby increasing the risk of embolism.^{11,24} Besides the amount of stretching of LA and LV pressure, overload causes the myocardium to secrete cardiac peptides, which are strongly correlated with the survival after myocardial infarction.²⁶

There is little evidence for the benefit of any methods to treat patients with LA dysfunction, whether prognostic or symptomatic.²⁵ However, early diagnosis of LA dysfunction by echocardiography might result in timely treatment of the underlying pathology preventing its progression to LA dysfunction and the development of thrombotic complications or atrial fibrillation.^{26,27} This early recognition is especially of importance in elderly patients and women because of their increased risk of heart failure. Antihypertensive medication (e.g. ACE inhibitors and thiazide diuretics) could normalise LA function and regress LV hypertrophy.¹¹ ■

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