The International Journal of Cardiovascular Imaging (2019) 35:41–48
https://doi.org/10.1007/s10554-018-1427-9

ORIGINAL PAPER

Reference values of left atrial size and function according to age: should we redefine the normal upper limits?

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Received: 17 June 2018 / Accepted: 26 July 2018 / Published online: 3 August 2018

Abstract

Different cut-offs have been proposed for left atrial (LA) size. Furthermore, conflicting results have been reported about the influence of age on LA size and data on the impact of age on LA myocardial function are scanty. The aim of this study was to derive references values for LA size and function in healthy subjects and to evaluate the impact of age. We conducted a systematic literature search of MEDLINE database. We included only studies evaluating healthy subjects, with age ranged between 18 and 80 years. Parameters were compared among four age groups, < 30, 30–45, > 45–60, > 60 years. Three hundred twenty-six studies met the inclusion criteria and the final population consisted of 62,821 subjects. LA volume index (LAVi) did not differ among different age groups ($p=0.21$). The normal upper limit of LAVi was 24 mL/m^2. LA reservoir function, measured by strain, did not differ among age groups (38 ± 3%, 32–43%; $p=0.74$). Left ventricular (LV) size and function were not different among groups, except LV mass index. A decrease in E/A ratio and an increase in E/e′ ratio were found with advancing age ($p<0.0001$ and $p=0.001$, respectively). In healthy subjects the normal upper limit of LAVi was lower than that recommended and is not influenced by advancing age. Furthermore, also LA function measured by strain was not affected by age. The current reference values of LAVi should be used with caution when applied to healthy subjects.

Keywords Echocardiography · Advanced cardiac imaging · Meta-analysis · Strain · Systematic review

Introduction

Strong evidence exists supporting the robust role of left atrial (LA) size in predicting cardiovascular clinical outcome, with the increased size associated with higher incidence of atrial fibrillation, stroke, congestive heart failure, hospitalization, and even death [1–5]. Therefore, providing normative data for LA size is crucial. Reference values for echocardiographic chamber quantification were jointly published by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) in 2006 [6] and revised recommendations have recently been released [7]. While normal limits of linear LA dimension and LA absolute volumes were reported in the previous document published in 2006, in the revised recommendations a new upper normal limit for LA volume indexed to body surface area (BSA) (LAVi) was reported, changing from 28 to 34 mL/m^2. However, discrepancies exist among the studies reporting the normal cut-offs for LA size [3, 8–12] and partition values for LA volume were established in the 2015 revised recommendations on an experience-based consensus rather than on published data alone [7]. Furthermore, although the cardiovascular system is affected by normal aging [13] and LA enlargement is expected to follow the same pattern [14, 15], conflicting results from observational studies cloud the potential relationship between LA dimensions and age, with some supporting [8, 14, 15] and others refuting [9, 16]. Furthermore, data based on the newly developed markers of LA myocardial function, particularly

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10554-018-1427-9) contains supplementary material, which is available to authorized users.

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those derived from speckle tracking echocardiography, is scanty enough to propose robust conclusions. The aim of this study, therefore, was to derive in a meta-analysis adult normative reference values for LA size and function and to establish the impact of age on LA size and function in healthy subjects.

Methods

Data source and searches

We conducted a systematic literature search of MEDLINE database. All searches were limited to humans and studies published between January 1st, 1990 and April 30th, 2016. The primary search used the following keywords: LA size, LA dimension, LA morphology, LA volume, LA phasic volumes, LA function, LA strain, LA ejection fraction (EF), and LA deformation. Studies not in English, review articles, editorials, case reports, and letters were all excluded.

Study selection

The included studies were assessed using the following previously defined criteria: (1) the study evaluated healthy subjects or healthy controls, with no history of cardiovascular disease; (2) subjects with hypertension, diabetes mellitus and/or supraventricular arrhythmias were excluded; (3) athletes and pregnant women were excluded; (4) the study reported at least one parameter of LA dimensions and/or function, measured by one dimensional, two-dimensional echocardiography, and/or speckle-tracking echocardiography (STE) according to current clinical standards [7, 17]; (5) the study cohort age ranged between 18 and 80 years; and (6) a measure of statistical variance was reported. Study arms that reported individuals which potentially overlapped with other studies as well as those included < 30 subjects were excluded. A flowchart showing derivation of the reference cohort is reported in Fig. 1.

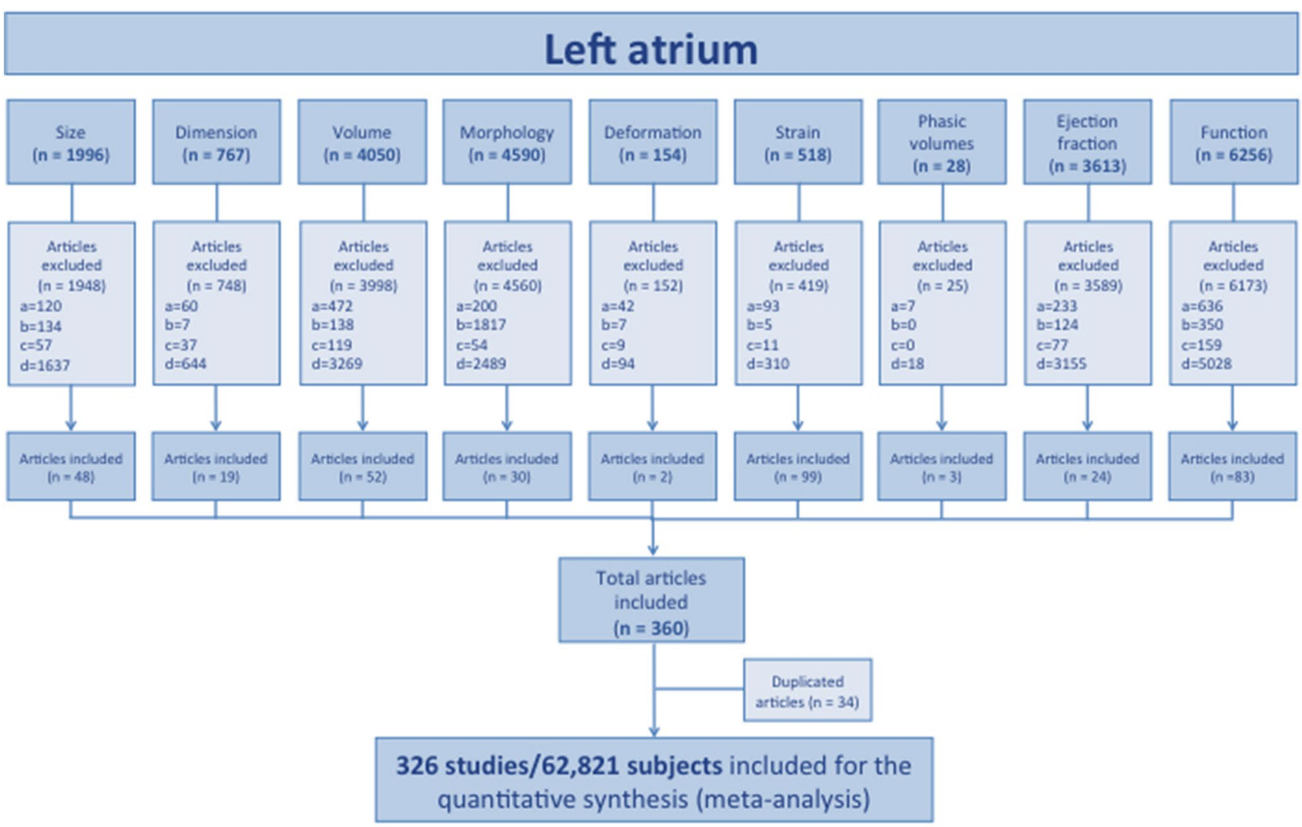

Fig. 1 Results of the literature search according to the different keywords used. (*a*) inadequate sample size; (*b*) publication type (e.g. reviews, meta-analysis, case reports, editorials…); (*c*) insufficient data available; (*d*) inadequate echocardiographic techniques and/or subjects not fulfilling the inclusion criteria (e.g. athletes, pregnant women…)

Data collection

Two investigators (C.S. and V.C.) collected study characteristics, demographic values, echocardiographic and strain data from individual studies. Discrepancies were resolved by consensus among all authors. Each data set was reviewed for units and methods of measurement, range checks were performed to identify and exclude biologically inconsistent values, and summary statistics were cross-checked against published results, where available. Among the dimensional parameters, the following echocardiographic indexes evaluated in the current meta-analysis were: LA diameter, indexed diameter to BSA, LA absolute and indexed area, LA volume and indexed volume, left ventricular (LV) absolute and indexed end-diastolic and end-systolic diameter and volumes and LV EF, peak early (E) and late (A) mitral flow velocity ratio (E/A) and E/e′. Two-dimensional echocardiography and the derived phasic volumes, three-dimensional echocardiography, and STE were also performed to assess LA myocardial function, from which we obtained the following parameters: LA strain, defined as peak atrial longitudinal strain (PALS), with the R wave (R-R gating) or P wave (P–P gating) as the onset of the strain calculation, LA phasic volumes obtained by two-dimensional echocardiography and LA EF obtained by 3-dimensional echocardiography.

Data synthesis, statistical analysis, and development of reference values

To provide reference values and to explore the impact of age on LA size and function, a meta-analysis was conducted to integrate the results of a set of studies about LA parameters measured by echocardiography in healthy subjects. Specifically, meta-regressions were used [18–20] which allowed for potential residual heterogeneity. LA dimensional data and LA function were analysed in the overall population without distinguishing between men and women because of the lack of gender-related studies in the available literature. The outcome variable in each meta-regression was the raw mean of the LA parameters and the explanatory variable was expressed by the sample average age reported by the included studies. To allow for the residual heterogeneity among intervention effects not to be modelled by age, random-effects models were considered for the meta-regressions. The Knapp-Hartung adjustment [21] to the standard errors of the estimated coefficients was applied in order to adjust the statistics and the confidence intervals of the estimates whose properties are closer to the nominal. Therefore, the tests on individual coefficients as well as the confidence intervals relied on the distributions with k-1 degrees of freedom, where k is the number of studies. The coefficients from the fitted model estimated the direction and magnitude of the relationship between the average 'true' outcome in the population of studies and the moderator variable included in the model. Upper reference values were defined at the 95th percentile and lower reference values at the 5th percentile. These values defined 90% of the population as normal, but they allowed for abnormal distributions. The 99th confidence interval was also reported for dimensional parameters.

Homogeneity statistics were computed to quantify the amount of the residual unexplained variance in true effects across studies (between-study variance). We calculated both the Q and the I^2 statistics, which measure the proportion of overall variation that is attributable to between-study heterogeneity rather than chance. I^2 statistic > 50% and p values < 0.05 for the Q statistic suggested significant heterogeneity among the studies [22]. Reference values were derived for LA size (LA diameter, LA area, LA volume, and their indexed values) and for LA function (LA PALS, LA reservoir volume, and LA EF). In order to report a comprehensive analysis of the left heart from the selected studies, reference values for LV end-diastolic and end-systolic volume, LV mass, LV EF, E/A ratio, and E/e′ ratio were derived. All statistical analyses were carried out with the comprehensive software meta-analysis package for R: metafor 1.9-8 (2015-09-28) [23].

Results

The literature search (Fig. 1) for LA size and function identified 1996 articles with the keyword LA size, 767 with LA dimension, 4050 with LA volume, 4590 with LA morphology, 154 with LA deformation, 518 with LA strain, 28 with LA phasic volumes, 3613 with LA EF, and 6256 with LA function. Among the selected studies, 1948 articles with the keyword LA size, 748 with LA dimension, 3998 with LA volume, 4560 with LA morphology, 152 with LA deformation, 419 with LA strain, 25 with LA phasic volumes, 3589 with LA EF, 6173 with LA function, were excluded for various reasons, mainly because populations were not free of cardiovascular disorders or risk factors or because LA was not accurately evaluated. Thus, after excluding 34 duplicates, 326 studies met the inclusion criteria and a final population of 62,821 subjects were included into the analysis. The Supplemental Table 1 summarizes the demographic characteristics of the articles evaluating LA size and function and which are included in this analysis. Parameters were compared among four age groups, < 30, 30–45, > 45–60, > 60 years.

In the overall population neither BSA nor body mass index differed ($p=0.19$ and $p=0.48$, respectively) between groups but systolic and diastolic blood pressure (BP) increased with increasing age (systolic BP: 115.9 ± 0.8 vs. 119.6 ± 0.5 vs. 123.2 ± 0.5 vs. 126.8 ± 0.9 mmHg, $p < 0.0001$ and diastolic BP: 74.1 ± 0.5 vs. 75.3 ± 0.3 vs. 76.5 ± 0.3

vs. 77.6 ± 0.6 mmHg, p = 0.005 for the four age groups, respectively).

Normative reference values of LA size and impact of age on LA and LV structure

Table 1 shows LA and LV parameters in the overall population divided in four age groups. LAVi did not differ between age groups. The upper limit of LAVi was 24 and 25 mL/m^2 when the 95th and the 99th confidence interval were taken into account, respectively. LV dimensions were not different among groups neither were LV end-diastolic volume or LV end-systolic volume. While LV mass did not differ, LV mass index increased with age ($p < 0.0001$). LV EF did not change with age, but LV diastolic function was significantly influenced by age with a decrease in E/A ratio and an increase in E/e′ ratio with advancing age ($p < 0.0001$ and $p = 0.001$, respectively).

Impact of age on LA and LV function

Table 2 shows reference values of LA functional parameters. We selected 25 studies, of a total of 1842 subject, which estimated LA strain, i.e. reservoir function, by STE. The impact of age was not significant among the groups ($p = 0.74$). This lack of effect was further confirmed when only studies using the GE software were included in the analysis (22 studies, 1648 subjects). Additional parameters of LA size and function are reported in Supplemental Table 2.

The number of studies and subjects used to derive each parameter are reported in Table 3.

Discussion

The present meta-analysis derived reference values for LA size on the basis of the previously published echocardiographic studies and is the largest database currently available. We confirm the reference values of LA antero-posterior diameter recommended by the ASE and EACVI in 2006. However, assessment of LA size using only the antero-posterior diameter assumes that when the cavity enlarges, all its dimensions equally change, which is not often the case during LA remodelling. Therefore, although this measurement has been used extensively in clinical practice and research, it has become clear that frequently it may not represent an accurate picture of LA size contrary to LAVi [24, 25]. In our study we derive the normal limit for LAVi: contrary to LA antero-posterior diameter, the upper normal limit for LAVi differs from that recommended by the revised scientific consensus published in 2015, being lower and similar to the previous cutoff proposed in 2006. Indeed, while the revised document suggested an upper limit of 34 mL/m^2, the previous recommendations for echocardiographic chamber quantification reported a cutoff of 28 mL/m^2 for distinguishing between a normal vs. a mild dilated atrium. The current study, including for LAVi 117 studies and 31,201 healthy subjects, demonstrated an upper limit of 24 or 25 mL/m^2 according to the 95th or 99th CI, respectively. Discrepancies have been reported among the studies investigating LA size in the general population. Indeed, while some authors reported upper limits similar to those recommended by the 2015 chamber quantification [8, 10, 11], others reported values similar to those found in the current study [3, 9, 12]. Discrepancies among the studies could be explained by the different populations enrolled in the studies: in the current meta-analysis we included only studies investigating LA size in healthy subjects, excluding not only patients affected by cardiovascular disorders but also individuals with factors potentially influencing LA volume such as arrhythmias or hypertension. Indeed, other authors found that, when these factors were excluded, the normal upper limit of LAVi was lower than that currently recommended [3].

LAVi with a cut-off of 34 mL/m^2 has demonstrated its ability in providing relevant prognostic information [11, 26]. However, also LAVi with a cut-off of 28 mL/m^2 has demonstrated to be sensitive in predicting cardiovascular outcomes and providing uniform and accurate risk stratification [27, 28]. Furthermore, as suggested by our findings, when applied to low-risk populations, the cutoff of 34 mL/m^2 could lose its sensitivity in distinguishing normal from abnormal, with the possibility to have a relevant percentage of subjects with early LA abnormalities being classified as normal. Therefore, further studies are needed to evaluate the best performance in predicting cardiovascular outcomes between these two different cut-offs and to contemporary identify the best cut-offs for the general population.

The current study evaluated also the impact of age on LA size. The available literature reports conflicting data on the influence of age on LA size. Using LA volume measurements, Pearlman et al. found that LAVi is independent of age from childhood [16]. Thomas et al. confirmed these results in a population of varying age from 17 to 86 years [9]. Also, in a cohort of 966 patients with no known cardiovascular disease or risk factors, no difference in LAVi or relationship was found across age decades, which suggested any increase of LA dimensions to be pathological. On the other hand, using LA antero-posterior diameter, the calculated LA size was found to significantly increase with age [14, 15]. More recently, Nistri et al. in a population of 418 healthy subjects (age range 16–84 years) found that age is a predictor of LAVi, both in the athletes and non-athletes, independent of changes in LV diastolic properties [8]. In order to reconcile the two means of measuring LA size, we designed the current meta-analysis which included the largest ever analysed cohort of 65,052 subject.

Table 1 Left atrial size according to age obtained from the overall population

	Mean ± SE	95% CR	99% CR	p value for age
LA area (cm^2)	14.9 ± 0.9	11–18	10–20	0.35
Age ≤ 30 years				
Age > 30 and age ≤ 45				
Age > 45 and age ≤ 60				
Age > 60				
LA volume index (mL/m^2)	22.2 ± 0.6	21–24	20–25	0.19
Age ≤ 30 years				
Age > 30 and age ≤ 45				
Age > 45 and age ≤ 60				
Age > 60				
LV end-diastolic diameter (mm)	47.4 ± 0.4	45–50	44–50	0.20
Age ≤ 30 years				
Age > 30 and age ≤ 45				
Age > 45 and age ≤ 60				
Age > 60				
LV end-systolic diameter (mm)	28.8 ± 0.8	23–34	21–36	0.10
Age ≤ 30 years				
Age > 30 and age ≤ 45				
Age > 45 and age ≤ 60				
Age > 60				
LV EDV (mL)	97.5 ± 4.0	79–116	72–123	0.46
Age ≤ 30 years				
Age > 30 and age ≤ 45				
Age > 45 and age ≤ 60				
Age > 60				
LV ESV (mL)	31.6 ± 1.9	25–38	23–40	0.30
Age ≤ 30 years				
Age > 30 and age ≤ 45				
Age > 45 and age ≤ 60				
Age > 60				
LV EDV index (mL/m^2)	54.9 ± 1.8	51–59	50–60	0.06
Age ≤ 30 years				
Age > 30 and age ≤ 45				
Age > 45 and age ≤ 60				
Age > 60				
LV ESV index (mL/m^2)	20.1 ± 0.7	19–22	18–22	0.14
Age ≤ 30 years				
Age > 30 and age ≤ 45				
Age > 45 and age ≤ 60				
Age > 60				
LV mass (g)	128.6 ± 8.6	66–192	45–213	0.15
Age ≤ 30 years				
Age > 30 and age ≤ 45				
Age > 45 and age ≤ 60				
Age > 60				
LV mass index (g/m^2)				< 0.0001
Age ≤ 30 years	66.4 ± 3.2	40–93	31–102	
Age > 30 and age ≤ 45	74.6 ± 1.8	48–101	40–110	
Age > 45 and age ≤ 60	82.9 ± 1.8	57–109	48–118	
Age > 60	91.2 ± 3.1	64–118	56–127	

Table 1 (continued)

	Mean ± SE	95% CR	99% CR	p value for age
EF (%)	65.0 ± 0.6	60–70	59–71	0.75
Age ≤ 30 years				
Age > 30 and age ≤ 45				
Age > 45 and age ≤ 60				
Age > 60				
E/A ratio				< 0.0001
Age ≤ 30 years	1.65 ± 0.03	1.50–1.80	1.45–1.84	
Age > 30 and age ≤ 45	1.41 ± 0.02	1.27–1.56	1.23–1.60	
Age > 45 and age ≤ 60	1.18 ± 0.01	1.04–1.32	1.00–1.37	
Age > 60	0.95 ± 0.02	0.81–1.10	0.76–1.14	
E/e′ ratio				0.001
Age ≤ 30 years	6.8 ± 0.3	5–9	4–10	
Age > 30 and age ≤ 45	7.3 ± 0.2	5–9	5–10	
Age > 45 and age ≤ 60	7.8 ± 0.2	6–10	5–11	
Age > 60	8.3 ± 0.3	6–10	6–11	

Also left ventricular dimensional and functional parameters are reported in the table

Data are presented for all the age groups only if p value is < 0.05

LA left atrial, *AP* antero-posterior, *LV* left ventricular, *EDV* end-diastolic volume, *ESV* end-systolic volume, *EF* ejection fraction

Table 2 Left atrial function in overall population estimated by 2-dimensional phasic volumes, speckle tracking, and three-dimensional echocardiography

	Mean ± SE	95% CR	p value for age
PALS (%)	37.5 ± 2.8	32–43	0.74
Age ≤ 30 years			
Age > 30 and age ≤ 45			
Age > 45 and age ≤ 60			
Age > 60			

Data are presented for all the age groups only if p value is < 0.05

PALS peak atrial longitudinal strain

The present findings demonstrate an impact of age on LA absolute volumes, but, when LAVi was considered, no differences were found among age groups. This finding is of significant importance due to the ability of LAVi, the recommended method for measuring LA size [7], to provide relevant prognostic information [29]. The results of the effects of advanced age on LAVi should be taken into account more relevantly according also to the demonstration of heterogeneity of studies reporting LA volumes, contrary to studies analysing LAVi (see Table 3). Our findings support the current guidelines in justifying the accurate role of LAVi in reflecting cavity size, with any increase due to an underlying structure or function disturbances as pathological.

Despite not planning this meta-analysis to study the effect of age on LV structure and function, it was inevitable not to ignore the available data in different studies, in an attempt to interpret the overall findings. The present meta-analysis shows that the only structural LV change with age is the increase in indexed cavity mass while LV diastolic function was the most sensitive cardiac measure affected by age with E/A ratio reducing and E/e′ ratio increasing. Conversely, LV systolic function, measured by LV ejection fraction, was not influenced by age. These findings are consistent with what we previously reported using myocardial tissue Doppler velocity analysis, having demonstrated that not only EF but even segmental systolic velocities are not affected by age but it is the early diastolic velocities that drop and the late diastolic ones that increase with age. In the same report we also highlighted the close relationship, we found, between myocardial velocities and spectral cavity diastolic velocities. These results are supported by the recently published differences in phasic LA volumes. The latter explains the significant relationship our meta-analysis showed between LV E/A and E/e′ ratios and age [8, 9, 12, 14, 30–33].

Finally, our results also show that age has not a significant impact on LA myocardial intrinsic function as shown by deformation analysis, despite a slight decrease in strain with advanced age. These findings were received not with any surprise since various LA volumes were not affected either. Therefore, changes in pattern of LV diastolic filling with age should always be seen as a reflection of LV myocardium function rather than LA function.

Table 3 Number of studies and subjects used to derive each parameter

	Studies (n)	Subjects (n)	I^2	Q	P value Q
Overall					
LA antero-posterior diameter	187	21,589	24.65	308.1	< 0.0001
LA area	28	4120	25.7	32.5	0.17
LA volume index	117	31,201	0.51	54.4	1.0
LV end-diastolic diameter	167	36,002	16.5	0.7	0.20
LV end-systolic diameter	109	13,373	53.4	243.4	< 0.0001
LV end-diastolic volume	40	5289	35.3	77.3	0.0002
LV end-systolic volume	33	3511	12.8	24.7	0.78
LV end-diastolic volume index	33	2452	0	13.4	1.0
LV end-systolic volume index	29	1830	0	8.5	1.0
LV mass	50	24,058	80.5	417.4	< 0.0001
LV mass index	128	37,739	68.0	889.7	< 0.0001
LV ejection fraction	222	39,133	31.8	312.0	< 0.0001
E/A ratio	171	14,757	7.8	95.6	1.0
E/e′	88	8481	49.5	177.6	< 0.0001
PALS	32	2087	0	29.3	0.50
3D ejection fraction	6	516	0	1.8	0.78
Ejection fraction by phasic volumes	5	304	0	2.3	0.50

I^2 and Q factor for each parameter are also shown

LA left atrial, *LV* left ventricular, *PALS* peak atrial longitudinal strain, *3D* three-dimensional

Limitations

Our results should be interpreted in the context of the following limitations. First, as all meta-analyses, our study is limited by variations in the studies included, which themselves may be limited by biases in the recruitment process. Although most of the studies were performed according to the international recommendations, some variations may have occurred in image capturing or measurement.

LA volume measured from 2D echocardiography in the studies we included may underestimate the exact value measured by cardiac computed tomography (about 19% for LAVi) [34]. However, in those studies the LA volume was compared with the normal values determined by the same imaging technique using the same methodology. For the characterization of LA function, we included data obtained using the most recent echocardiographic techniques, including STE, which is known for its limitations, and requires expertise and highly trained operators. Furthermore, while for LA size the sample size is adequate to derive conclusions, further studies investigating LA function in large cohorts of subjects are needed to confirm the current findings.

Meta-analyses have inherent limitations, not the least of which is that all studies are assumed to have equal value. The heterogeneity of studies in meta-analyses is considered by some to be a limitation, although it is through this that the performance (and variability) of a test can be appreciated in different patient groups and sources of variation identified. Indeed, heterogeneity among studies represented the real world in clinical and academic centers. In order to provide most possible information, in Table 3 we reported the results of the heterogeneity tests for each parameter. Finally, any comparison of reference values obtained by different measurement modes or echocardiographic views was limited because very few subjects had measurements repeated from more than one mode or view.

Conclusions

In subjects free of cardiovascular disease or risk factors the normal upper limit of LAVi is lower than that currently recommended. LAVi and LA reservoir function, estimated by atrial strain, are not significantly influenced by advancing age. These findings suggest that the reference values of LAVi should be likely redefined when assessing LA size in healthy subjects in order not to loose the sensitivity of this parameter.

Conflict of interest The authors declare that they have no conflict of interest.

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