Influence of Age and Sex on left ventricular remodeling in chronic aortic regurgitation.

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Conflict of interest: Bernhard L. Gerber is Editor in Chief of European Heart Journal Cardiovascular Imaging.

Grant support: Crédit de recherche FRSM-CDR-35275164 by the Fondation de la Recherche Scientifique of the Belgian Government

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Structured abstract

Aims

Aortic regurgitant volumes (RVol) and left ventricular (LV) dimensions and volumes are essential parameters for assessing the severity and guiding surgical timing in aortic regurgitation (AR). However, normal LV volumes vary with age and sex, potentially affecting the interpretation of dilation. This study investigated the impact of sex and age on LV remodeling in chronic AR using cardiac magnetic resonance (CMR).

Methods and results

This monocentric prospective cross-sectional study enrolled 290 consecutive adult patients (mean age 51±16 years, 19% women) with chronic at least moderate AR by echocardiography between 2003 and 2022 to undergo a comprehensive CMR examination for evaluation of AR severity and LV remodeling.

The correlation between RF and RVol was age and sex dependent, as both absolute but also body-surface indexed RVol represented a higher RF in women and older patients. Also, women had less dilated ventricles and LV-EDVi and LV-ESVi increased less with increasing AR severity in females and with advancing age. Therefore, LV volumes and RegVol, underestimated AR severity by RF in such patients. However, women had larger LV diameters and more spherical ventricles. Therefore, LV diameters failed to accurately identify severe AR among females as opposed to males. Comparatively, age- and sex-specific LV volume thresholds could equally assess AR severity across sexes.

Conclusion

Conventional parameters used to grade AR severity and LV remodeling are significantly influenced by age and sex. This encourages the use of age- and sex-specific volumetric thresholds for LV dilation monitoring and surgical referral in AR patients.

Keywords

Aortic Regurgitation, cardiac MRI, LV remodelling, Sex, Age

Non-standard abbreviations and acronyms

AR: Aortic Regurgitation
RVol: Regurgitant Volume
RF: Regurgitant Fraction
BSA: Body Surface Area
CMR: Cardiac Magnetic Resonance Imaging
DBP: Diastolic blood pressure
ECV: Extracellular Volume
IQR: Interquartile Range
LGE: Late Gadolinium Enhancement
LV: Left Ventricle
EF: Ejection Fraction
EDV: End-diastolic volume
ESV: End-systolic volume
EDD: End-diastolic diameter
ESD: Left ventricular end-systolic diameter
NYHA: New York Heart Association functional class
PISA: Proximal Iso-velocity Surface Area
ROC: Receiver Operating Characteristic curve

Introduction

Chronic aortic regurgitation (AR) results in combined left ventricular (LV) volume and pressure overload, which is accommodated by eccentric hypertrophy to preserve forward cardiac output. However, LV remodelling and afterload mismatch eventually progress to a stage in which wall stress can no longer be maintained leading to heart failure. Severe AR is currently defined as >60 ml regurgitant volume (RVol) or >50% regurgitant fraction (RF) conventionally derived from echocardiography guidelines due to the paucity of data regarding CMR. However, several studies suggested a lower RF of 33% (1, 2) could predict the need for surgery, the enhanced accuracy of CMR quantification techniques suggesting the potential for a future downward revision of quantitative thresholds defining severe AR (3). LV dilation, a direct consequence of volume overload, serves as a corroborating sign for the severity of AR (4, 5). Also, guidelines from the American College and European Society of Cardiology recommend surgery in asymptomatic patients with severe AR, in the presence of impaired LV function or excessive LV dilation based on thresholds of unidimensional measurements of chamber diameters by transthoracic echocardiography (6, 7).

It is now widely recognized that normal LV dimensions, stroke volumes and ejection fraction (EF) vary significantly across sexes and depend on age (8-10). Also, unidimensional evaluation of LV chamber diameters might not accurately reflect LV dilation, as they do not consider complex modification of geometry and sphericity of the LV in long-standing remodeling processes such as in AR (11). Additionally, reaching systolic dimensional surgical threshold has been suggested as a late marker of irreversible myocardial damage (12). Furthermore, a number of recent studies have shown that sex affects LV remodeling (13) in valve disease (14, 15) and particularly in AR (16-18). Age was also recently identified having a significant impact on ventricular adaptations in chronic AR (19). However, the effects of age and sex on grading AR severity and on surgical triggers are not yet fully understood. Cardiac magnetic resonance imaging (CMR) is the most accurate and reproducible (20) modality to assess LV volumes and remodeling (5) with additional benefits of allowing direct assessment of AR severity by phase contrast imaging and adverse interstitial remodeling through T1 mapping and extracellular volume computation (21). In this study, we sought to evaluate the impact of sex and age on LV remodeling in a large cohort of patients with chronic AR using CMR. Specifically, we aimed to evaluate whether LV diameters used to define current guidelines surgical triggers could indicate different degrees of AR severity and LV remodeling in female versus male patients.

Methods

Study design and population

This single center was approved by our institutional Review Board (2016-29FEV076 and 2020-01AVR192). Consecutive adult patients with at least moderate AR by transthoracic echocardiography were included in a prospective registry of valve disease in the Cliniques Universitaires Saint-Luc (Brussels, Belgium), and underwent a comprehensive CMR examination after providing written informed consent between July 2003 and May 2022. Inclusion criteria were patients with chronic at least moderate AR by echocardiography. Exclusion criteria were acute AR, concomitant more than moderate mitral regurgitation (22 patients), aortic stenosis, congenital complex heart disease, patients with any other known cardiomyopathy (including hypertrophic cardiomyopathy, 6 patients), known coronary disease or myocardial scar (as identified by late gadolinium enhancement during CMR, 5 patients) or intra-cardiac devices.

Prior to inclusion all patients underwent a comprehensive transthoracic echocardiographic examination using commercial ultrasound devices (Philips Medical System, The Netherlands). AR severity was evaluated according to guidelines (4, 5) using a multiparameter algorithm, including quantitative (PISA methods), as well as semi-quantitative measurements and remodeling parameters.

Cardiac magnetic resonance

CMR was performed on a 3-T system (either Ingenia, Philips Medical System, Best, Netherlands or Signa, General Electrics, USA) as previously described (22). Images were analyzed by one single reviewer using free-of-charge software Segment version 3.1 (23). Aortic RVol was determined by reversal flow during diastole and regurgitant fraction was computed as RVol / forward stroke volume using phase contrast imaging. LV EDD and ESD were measured on basal short axis view. The LV end-diastolic long-axis length (LVL) was determined as the longest measurement from the 4- and 2-chamber views. Sphericity index (SI) was computed as effective volume divided by the theoretical volume of a sphere with a diameter of LVL (volumetric method)(24) or as the ratio of LV short-to-long axis dimension from four-chamber view (dimensional method)(25). LV mass was manually drawn excluding papillary muscles and computed as 0.85g/cm³ cubic volume of myocardial. The extravascular volume fraction (ECV) was computed from the MOLLI T1 maps before and after contrast injection and computed with biological haematocrit. LV remodeling parameters were compared to normal values of EDVi and ESVi as reported in a multi-ethnic cohort from Luu (26).

Statistical method

$p<0.05$ was considered indicative of a statistically significant difference. Continuous values were expressed as the mean ± one standard deviation (SD) or the median with interquartile range (IQR) depending on their distribution. Categorical variables were expressed as counts and percentages. To compare groups, Student's t-test or chi-square tests were used when appropriate and analysis of variance was used to normalize for confounding variables. Multivariable linear regression models were used to compare AR severity and LV remodeling parameters and two-way interactions with age and sex were sequentially included. ROC models and Logistic regression models were used to compare several thresholds with continuous variables.

Results

Study Population

The characteristics of the study population are shown in **Table 1** encompassing a total of 290 patients with at least moderate AR by echocardiography. Mean age was 51±16 years and 55 (19%) were females. Age, heart rate, systolic blood pressure and cardiovascular risk factors were similar in males and females. The prevalence of bicuspid valves was significantly higher (44% vs 27%, p=0.04) in men. Three patients had unicuspid and 2 had quadricuspid valves. By echocardiography, 102 patients had moderate and 188 had severe AR according to guideline criteria. While men had more often severe AR (69% vs 47%; p<0.01), women were more often symptomatic (76% vs 42%, p<0.01) than men.

AR Severity according to age and sex

According to CMR (**Table 2**) the average RVol was significantly higher in males than in females (49±34 vs 22±16 ml, p<0.01), and this difference remained significant even after adjusting for BSA

(25±17 vs 13±9 ml/m², $p<0.01$). Similarly, the mean RF was higher in males than in females (35±18 vs 24±15%, $p<0.01$). RVol was significantly correlated to RF ($r=0.89$, $p<0.01$) in the whole population, but the relationship between absolute RVol and RF exhibited sex-related differences. Specifically in women there was a significantly gentler correlation slope ($p<0.01$ for interaction), indicating greater increase of RF for a given increase in absolute RVol (**Figure 1a**). Although this observation could be partially attributed to the smaller absolute cardiac output (4.5 vs 5.5 l/min in females and males respectively, $p<0.01$) and stroke volume (66 vs 82 ml in females and males respectively, $p<0.01$) associated with smaller body size, it is noteworthy that the difference between both sexes persisted also when RVol was indexed to BSA (**Supplementary Figure 1**, $p<0.01$ for interaction). ROC analysis revealed that the optimal RVol threshold for predicting 50% RF was lower in female (39 ml with 89% specificity and 100% sensitivity) compared to male (59 ml with 84% specificity and 93% sensitivity) patients. The relation between RF and RVol was also significantly influenced by age as illustrated in **Figure 1b**. More precisely, as age increased, the incremental rise in RVol was observed to be less pronounced for a given increase in RF. Consequently, the 50% regurgitant fraction (RF) threshold, typically indicating severe AR, may be attained before reaching the 60 ml regurgitant volume (RVol) threshold in female patients, particularly with advancing age.

LV Dimensions and Volumes and their relation to AR severity

Male patients had significantly larger diastolic and systolic LV volumes and dimensions than women, likely indicative of their greater severity of AR (**Table 2**). Interestingly, the differences in LV volumes remained significantly smaller among female patients, even when adjusting for BSA, and accounting for AR severity and age. LV volume indexes were highly correlated to RF ($r=0.61$ for iEDV and 0.56 for iESV, both $p<0.01$, **Figure 2a and b**). However, this relation was also influenced by sex as both EDVi and ESVi were lower (p for sex difference <0.01) and had a lower rate of increase per unit increase of RF (p for difference in slope=0.01 and 0.03 respectively) among women. Furthermore, both EDVi and ESVi were also found to be age dependent (adjusted $r=0.64$, $p<0.01$ and 0.57, $p=0.03$) and the extent of volume increase with rising RF was less pronounced as age increased in the overall population (p for interaction<0.01 and 0.04 respectively) (**Figure 2c and d, Supplementary Table 1**).

Like volumes, LV dimensions indexes were also correlated to RF, although this correlation were comparatively weaker (respectively r=0.37 and 0.40, both p<0.01 for LV-EDDi and LV-ESDi, **Supplementary Figure 2**). Likewise, LV-ESDi and EDDi and RF tended to diminish with increasing age (adjusted r=0.40, p<0.01 and 0.41, p=0.06). However, in contrast to LV volumes, both ESDi and EDDi were significantly greater in women than in men (respectively p<0. 01 and 0.04).

LV Geometry vs AR severity and Sex

Indexed LV diameters exhibited a strong correlation with indexed LV-volumes with respective correlations of r=0.72 for end-diastolic measures and r=0.80 for end-systolic measures (both p<0.01) across all patients. However, these correlations varied by sex as evidenced in **supplementary Figure 3 a and b.** Notably for a given LV volume index, both the diastolic and systolic diameter indexes were significantly higher in females than in males (p<0.01 for sex difference) and there were significant sex interaction effects (respectively p=0.04 and <0.01 for diastolic and systolic measurements). Thus, female patients with AR had more pronounced basal circumferential dilation leading to a greater increase in sphericity when either LV end-diastolic (**Supplementary Figure 4a,** p<0.01 for sex difference p<0.01 for sex interaction) or end-systolic (**Supplementary Figure 4b** p<0.01 for sex difference p=0.02 for sex interaction) volumes increased.

Interstitial fibrosis vs AR severity and sex

Data for T1 mapping was available in 120 (41%) patients and 109 (38%) had ECV assessment. Notably, both native T1 relaxation time (1270±61ms vs 1197+/-84ms, p<0.01) and ECV (31±6% vs 27±5%, p=0.03) were significantly higher in women than in men. Moreover, both parameters were significantly correlated with age (respectively adjusted r=0.45, p<0.01 and 0.34, p<0.01) with differences remaining significant in multivariable analysis. However, there was no significant correlation between either native T1 time or ECV and AR severity (respectively r=0.09, p=0.34 and r=0.13, p=0.20).

Implications of sex on guideline triggers according to AR severity

Figure 3 a and b show RVol and RF in female and male patients with or without dimensional triggers for guidelines (either ESD>50 mm or ESDi>25 mm/m2). Men meet surgical dilation triggers at significantly higher volumes than women. Also, RVol and RF were significantly higher in men with or without dilatation triggers ($p<0.001$) but not different in women with or without such triggers ($p=0.20$). **Figure 3c** shows ROC curves for RF predicting reaching guideline triggers while **Figure 3d** shows the ROC curve for predicting abnormal LVESVi. Using logistic regressions, abnormal LVESDi was only predicted by RF in males ($p<0.01$) but not in women ($p=0.63$), whereas LV dilation assessed by abnormal age and sex specific LVESVi was equally predicted by RF in both sexes (respectively $p<0.01$ and $p=0.03$).

Discussion

Our study highlights the intricate influence of age and sex on the relationship between RF and both RVol and LV dilation in AR. Women and elderly individuals exhibited a steeper increase in RF for any given rise in RVol, a phenomenon driven by their comparatively smaller stroke volumes. In line with this, we observed that the linear relationship between RF and LV volumes was also age- and sex-dependent, as a direct consequence of the influence of RVol on LV volumes. Women and elderly individuals demonstrated less LV dilation in response to increasing RF, underscoring the importance of age and sex-specific LV volume monitoring in AR. Additionally, LV geometry differed significantly between sexes. Women generally exhibited a more spherical LV shape, and their LV diameter indexes were consistently higher than those of men for a given LV volume index. However, these diameter measures appeared to be less reflective of AR severity in women than volumes, raising concerns about their indiscriminate use in surgical decision-making across sexes. Finally, our findings challenge the assumption that indexing RVol or LV volumes to BSA sufficiently accounts for differences across age and sex groups. Despite normalization to BSA, significant disparities in RVol and LV dilation remained with RF, suggesting that current indexing methods cannot equally account for age and sex differences as RF does. These insights further underscore the need for tailored volumetric monitoring to better reflect AR severity as quantified by RF.

LV volumes, cardiac output and stroke volumes are well recognized to be influenced by sex and age in the general population (8, 26) and are in part these differences can be explained by difference in body size. Consistent with previous research (16, 18) our study in patients AR demonstrated significant influence of age and sex on RVol and various parameters of LV remodeling. Importantly, it highlighted that indexing to BSA fails short in addressing sex related differences in these variables. Indeed, despite female patients in our cohort having lower AR severity, they were more symptomatic. Additionally, our study revealed that the relation between RF and RVol remained influenced by age and sex influenced even when normalizing to BSA. Therefore, a given RVol even indexed to BSA corresponded to a higher RF in females. For these reasons we believe that RF is likely a more homogeneous parameter of AR severity among different categories of patients than RVol. We also observed that females were less prone to dilate their ventricles compared to males for a given AR severity, and that they dilate differently, with more spherical remodeling than male patients. Therefore, LV diameters even when indexed to BSA do not correlate with LV volumes as well in females and are therefore an imperfect refection of AR severity. Although LV volumes as measured by CMR, were a better reflection of AR severity and are theoretically more relevant to monitor LV remodeling, the relation between RF and LV volumes remained sex and age dependent, beyond simple normalization to BSA. Additionally, we highlighted the importance of age as it does interact with LV remodeling as well but without having implications on LV geometry. Interestingly in our study, age was similar between males and females, in contrast to other studies (16, 18). Our results appear to be consistent with those of Akintoye et al (19), who showed that although ventricular volumes remained lower among women and older patients on serial echocardiographic evaluation, they had lower volume thresholds for a significant increase in adverse events. This suggests outcome may be better predicted by AR severity and therefore RF rather than an absolute LV volume. The findings of higher native T1 relaxation time and ECV (27) and age dependency (28) have well been described previously. However, neither had an obvious link with AR severity nor LV dilation in accordance with the literature (29).

Clinical implications

Our study yields two major clinical implications. The first pertains to the assessment of AR severity, a process currently reliant both on absolute RVol and RF, alongside LV dilatation as ancillary criteria. Our study demonstrated that absolute RVol is less suited for grading AR severity than RF in females. Female patients can achieve a RF of >50% before reaching the threshold of >60 ml RVol for categorizing AR as severe, and this phenomenon becomes even more pronounced with increasing age. These findings advocate for the routine utilization of RF as a preferred metric for quantifying AR rather than relying solely on RVol. We also highlight the limitations of LV dimension indexes and volumes as corroborating sign for AR severity, especially in female patients. LV dimension indexes were higher and overestimated volumes in females and were less correlated with AR severity than volumes. Considering LV volumes rather than LV dimensions as the basis for surgical referral could offer a potential avenue for mitigating referral bias, as LV volume dilation exhibited a strong correlation with AR severity. Nevertheless, it's imperative to underscore the necessity for age- and sex-specific LV volume criteria since women and elderly patients tend to have lower LV volumes for a given level of AR severity. The implication is that AR severity might be underestimated in such patients when LV volumes are not normalized to age and sex (8). This could result in late indications and rescue surgery. Lower rates of AR surgery and higher mortality have been described in female patients in previous work (30). Our study provides some explanations for this difference in outcomes between sexes in the management of AR.

Another critical clinical concern in AR pertains to the timing of surgical intervention. Present guidelines rely on LV end-systolic and end-diastolic diameters. These criteria are essential for avoiding the associated survival decrement linked to late surgical triggers, which encompass heart failure symptoms or reduced EF (12). Our study demonstrated significant discrepancies between LV remodeling assessment based on absolute diameters and volumes – directly linked to RVol - and AR severity assessment, according to RF. While ventricular remodeling is the main trigger for referral to surgery, making decisions solely on diameters is imprecise since these diameters (or LV volumes) may be low in the presence of a high regurgitant fraction. Also, the more spherical geometry and dilation of women indicates that guideline thresholds of ESDi are reached at lower AR than in men. Therefore, using LV volumes or volume indexes may require sex and age-specific thresholds as for given LV volume, females and elderly seem to be at a higher stage of adverse remodeling.

Limitations

Our study was monocentric, conducted in a tertiary center for aortic valve surgery, and although patients were prospectively recruited to undergo CMR for AR evaluation, we cannot exclude a potential referential bias. We evaluated basal LV diameter using CMR rather than echocardiography. Differences in measurements between these two techniques have been reported.

among the 265 patients with accessible transthoracic echocardiography (TTE) images, our analysis revealed strong correlations between CMR and TTE measurements (r=0.69 for diastolic and 0.71 for systolic measurements). In addition, the three-dimensional (3D) capabilities of CMR enable a more precise delineation of LV diameters compared to TTE, enhancing the accuracy and reliability of our measurements. Tissue characterization was not available for every patient because T1 mappings were not yet available at the onset of the study. Lastly, the study did not encompass an exploration of the outcome implications of our findings, as this was outside the purview of our research objectives.

Conclusion

Current dimension-based LV cutoffs for surgical referral in AR display limitations by exhibiting bias and a weak correlation with AR severity, particularly in females. This discrepancy is partly due to distinct female LV geometry. Additionally, LV dilation, traditionally linked to regurgitant volume (RVol), doesn't consistently reflect regurgitant fraction (RF), especially in settings with reduced stroke volume. This leads to underestimation of AR severity when relying solely on RVol or LV absolute volumes, particularly impacting women and elderly patients.

We advocate for the development and implementation of age- and sex-specific volumetric CMR thresholds for RVol and LV dilation to improve alignment with regurgitant fraction and prevent delayed surgical intervention in asymptomatic patients with severe AR. Further research based on these criteria is crucial to refine surgical intervention guidelines, ensuring optimal care for diverse patient populations.

Clinical perspectives

What is new?

- Our analysis revealed significant age and sex interactions between age, sex, and LV and aortic regurgitant volumes resulting in underestimation of AR severity in women and elderly individuals when using conventional threshold values.

- Women having a more spherical ventricular remodeling, LV diameters and their guideline triggers failed to equally discriminate AR severity across sexes, demonstrating limitations in their universal application.
- Implementing age- and sex-specific volumetric thresholds may offer improved, sex-neutral assessment of AR severity.

What are the clinical implications?

- Compared to regurgitant volume, regurgitant fraction may offer broader applicability for quantifying AR severity across sexes and ages, accounting for corresponding differences in stroke volume.
- Considering age and sex when establishing thresholds for RVol severity thresholds ans LV volume monitoring for surgical referral in AR could improve alignment with regurgitant fraction.

Acknowledgements

This work was supported by the Fondation Nationale de la Recherche Scientifique of the Belgian Government (FRSM CDR 35275164).

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures legends

Figure 1: Relation between AR severity metrics according to sex and age.

Panel a) Relation between regurgitant volume (RVol) and fraction (RF) according to sex in female (pink) and male (blue) patients. The slopes were significantly different in female than male patients, without accounting for age.

Panel b): Multi-interaction model showing the additional effect of age and sex on the relation between RVol and RF in female (pink) and male (blue) patients with a significant continuous decline in the regression slopes with advancing age. The dark red points illustrate the proportion of female patients reaching 50% RF with less than 60 ml RVol.

Figure 2: Ventricular volume dilation according to regurgitant fraction, sex and age.

Panel a) and panel b) show the relation between left ventricular end-diastolic (LVEDVi) and end-systolic (LVESVi) volume indexes in female (pink) and male (blue) patients against regurgitant fraction. Slopes were statistically different according to sex, without accounting for age.

Panel c) and d) show 3D plots illustrating the additional influence of age on LVEDVi (c) and LVESVi (d) on the overall population, without accounting for sex, leading to a significant decline in regression slopes with advancing age.

Figure 3: Aortic regurgitation severity according to left ventricular dilation thresholds.

Panel a and b) Difference in regurgitant volume (RVol) and fraction (RF) in female (pink) and male (blue) patients with and without end-systolic surgical dilatation triggers (either left ventricular end-systolic diameter (LVESD) >50 mm or index (LVESDi) >25 mm/m²). In male patients RVol and RF was significantly higher in patients meeting guideline triggers, but not in females. Also, RVol and RF were higher in males than in females with guideline triggers.

Panel c and d) and receiver operating characteristic curve of RF for the prediction of end-systolic surgical dilatation triggers (either LVESD >50 mm or LVESDi >25 mm/m², panel c) and for predicting significantly abnormal LVESVi volumetric (>3 SD according to normal values reported by to Luu et al) in female (pink) and male (blue) patients.

Tables

Table 1: Baseline characteristics of the study population.

Baseline characteristics	Overall population N=290	Males N=235	Females N=55	P value overall
Age (years)	51±16	50±16	55±16	0.065
BSA (m²)	1.9±0.2	2.0±0.2	1.7±0.2	<0.001
Severe AR*	188 (65%)	162 (69%)	26 (47%)	0.004
Bicuspid valve	118 (41%)	103 (44%)	15 (27%)	0.036
Heart rate (bpm)	68±13	68±13	70±12	0.305
SBP (mmHg)	134±23	134±23	136±22	0.706
DBP (mmHg)	68±14	67±14	73±13	0.036
Dyslipidemia	94 (35%)	74 (33%)	20 (43%)	0.3
Hypertension	128 (48%)	106 (48%)	22 (47%)	1
Diabetes	10 (4%)	8 (4%)	2 (4%)	1
History of smoking	80 (30%)	66 (30%)	14 (30%)	1
COPD	15 (6%)	14 (6%)	1 (2%)	0.319

*Severe AR as defined by ASE and ESC echocardiographic multiparametric approach.
AR: Aortic regurgitation, BSA: Body Surface Area, COPD: Chronic obstructive pulmonary disease. DBP: Diastolic blood pressure, SBP: Systolic blood pressure, NYHA: New York Heart Association functional class.

Table 2: CMR LV remodeling parameters according to sex and their correlation with age.

	Overall population N=290	Males N=235	Females N=55	P value[a]	Correlation with age[a] Adjusted R	P value
RVol (ml)	44±33	49±34	22±16	<0.001	0.316	0.976
RVol index (ml/m²)	23±17	25±17	13±9	<0.001	0.044	0.455
RF (%)	33±18	35±18	24±15	<0.001	0.243	0.081
LV-EDD (mm)	64±9	66±8	58±7	<0.001	0.546	<0.001
LV-EDDi (mm/m²)	34±5	34±5	35±5	0.001	0.395	0.003
LV-ESD (mm)	44±9	45±9	39±9	0.002	0.489	0.062
LV-ESDi (mm/m²)	23±5	22.9±5.30	23±5	0.038	0.405	0.057
LV-EDV (ml)	254±84	272±81	176±47	<0.001	0.623	<0.001
LV-EDVi (ml/m²)	132±42	139±42	105±25	<0.001	0.635	<0.001
LV-ESV (ml)	122±56	132±56	80±32	<0.001	0.569	0.025
LV-ESVi (ml/m²)	64±29	67±30	48±17	0.004	0.565	0.011
EF (%)	53±9	53±9	55±9	0.627	0.33	0.433
Aortic SV (ml)	122±39	131±37.4	87±24	<0.001	0.516	<0.001
Forward flow (ml)	79±24	82±24	66±19	<0.001	0.443	0.002
Forward flow index (ml/m²)	41±12	42±12	39±11	<0.001	0.497	<0.001
LVMi (g/m²)	164±54	177±50	108±30	<0.001	0.552	0.031
ASW (mm)	10±2	11±2	9±2	<0.001	0.257	0.034
LV length (mm)	103±11	106±10	91±7	<0.001	0.57	<0.001
SI (volumetric)	0.43±0.09	0.43±0.09	0.45±0.09	0.092	0.077	0.316
SI (dimensionnal)	0.61±0.06	0.60±0.06	0.62±0.06	0.106	NA	0.789
Native T1 time[b] (ms)	1213±85	1197±84	1270±61	<0.001	0.336	<0.001
ECV[b] (%)	28±6	27±5	31±6	0.019	0.271	0.004
Echo parameters					N=	
LV-EDV (ml)	236±77	252±74	164±44	<0.01	258	
LV-ESV (ml)	105±46	113±45	70±31	<0.01	258	
EF (%)	56±9	56±9	58±10	0.15	258	
RVol (ml)	64±23	67±22	51±21	<0.01	222	
ERO (cm²)	0.31±0.13	0.32±0.13	0.25±0.10	<0.01	222	

ASW: Anteroseptal wall thickness, ECV: Extracellular volume, EDD: End-diastolic diameter, EDDi: End-diastolic diameter index, EDV: End-diastolic volume, EDVi: End-diastolic volume index, ESD: End-systolic diameter, ESDi: End-systolic diameter index, ESV: End-systolic volume, ESVi: End-systolic volume index, EF: Ejection fraction, LV: Left Ventricle, LVMi: left ventricular mass index, SI: Sphericity index, SV: Stroke volume.

[a]Corrected for RF, excepted for RVol, RF, Native T1, ECV and echo parameters.

[b]Available data: Native T1 n=120; ECV n=109

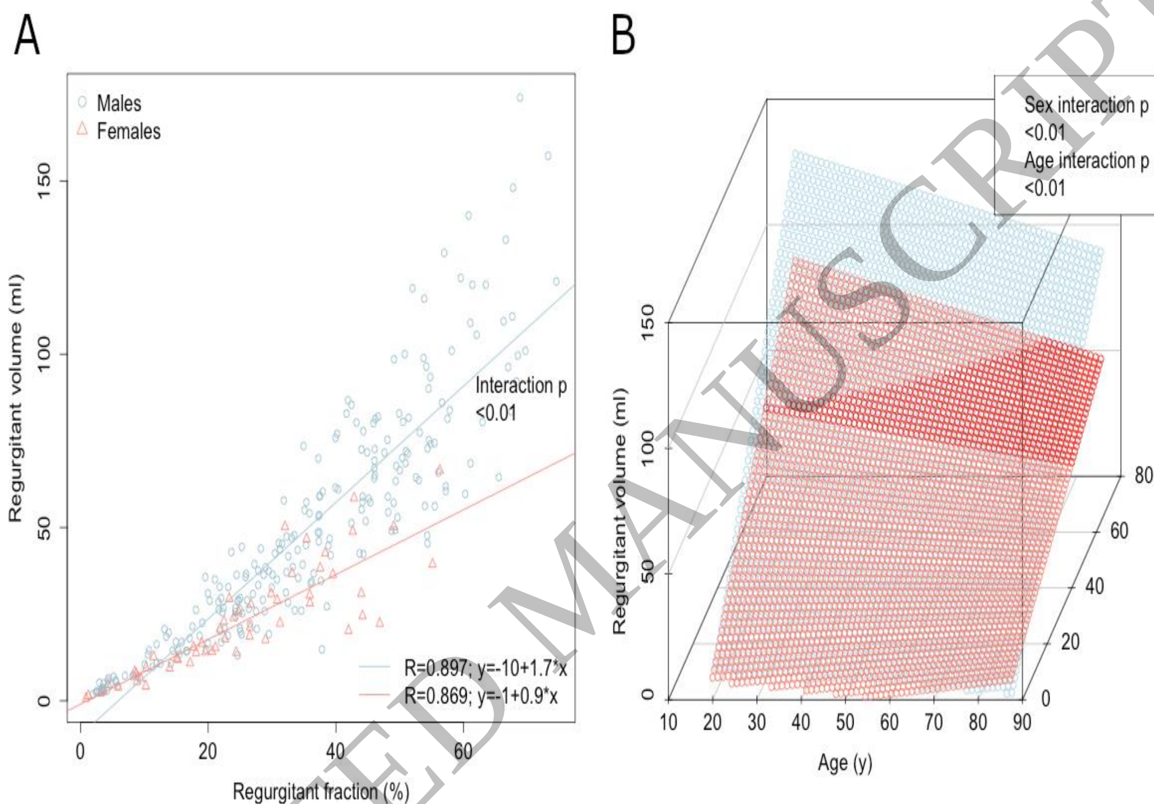


Figure 1

423x212 mm (x DPI)

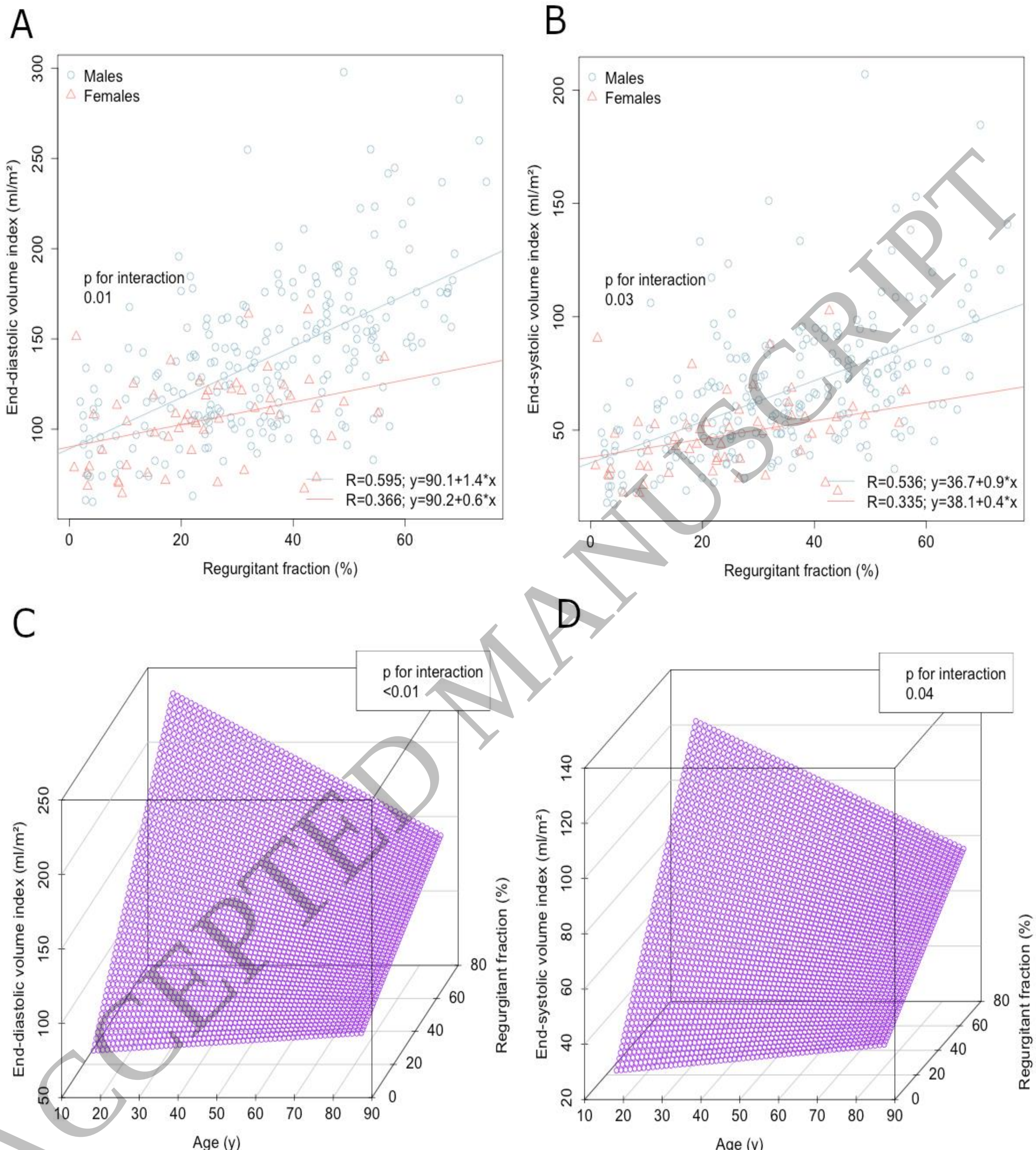
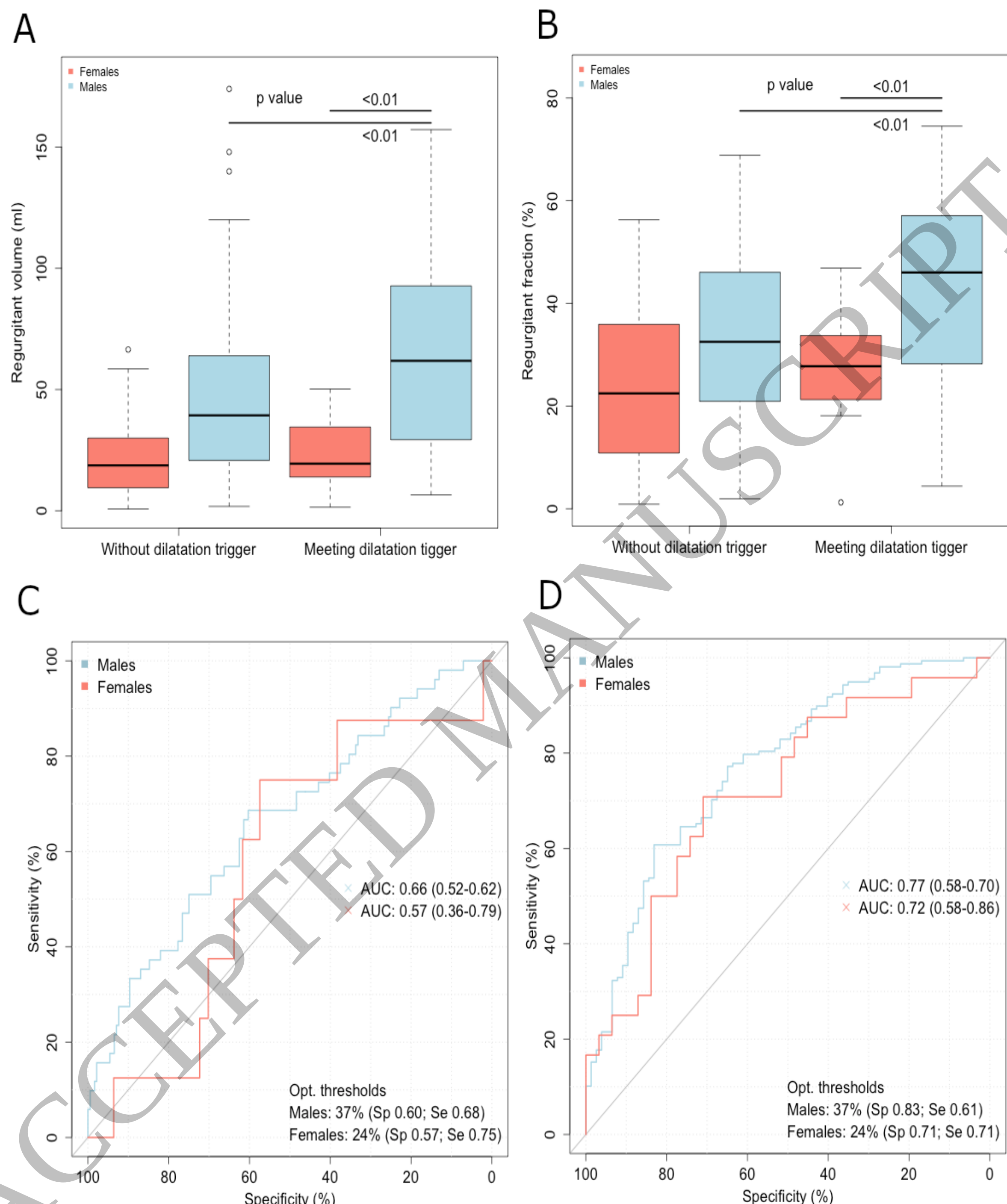


Figure 2
423x423 mm (x DPI)

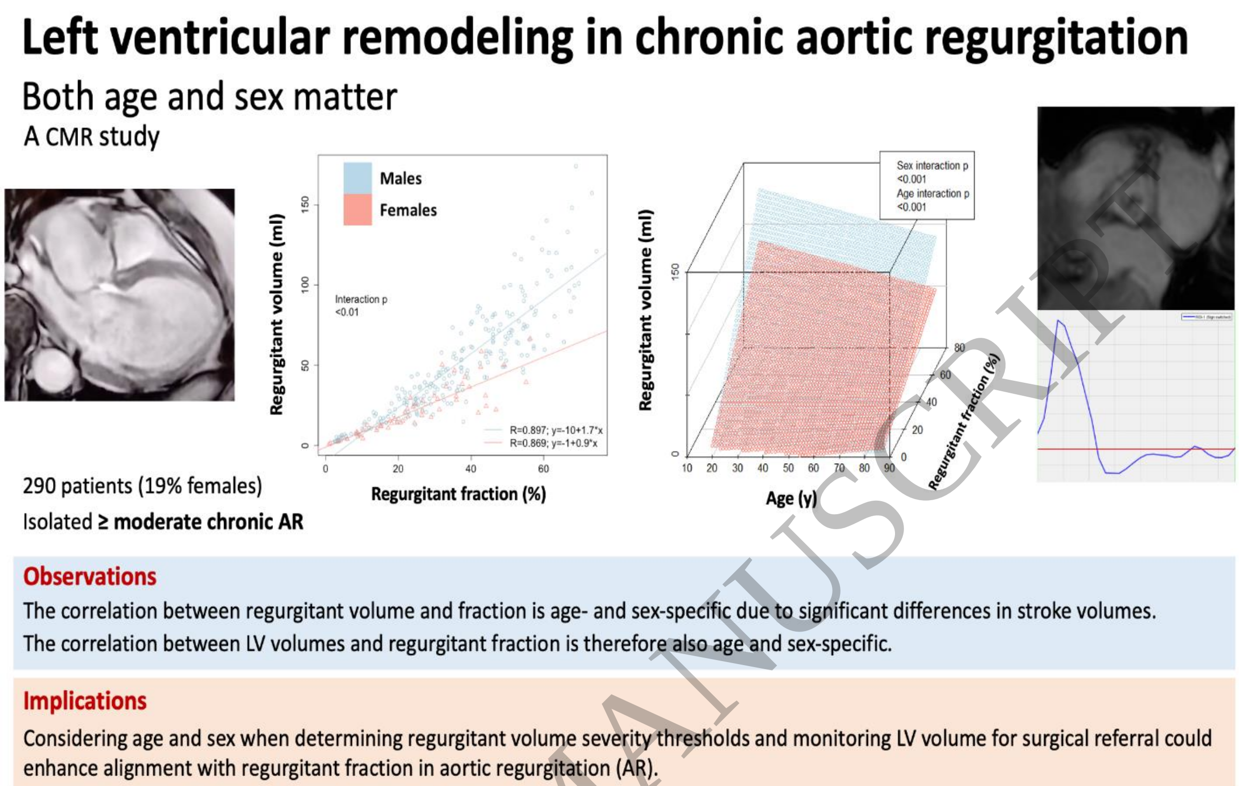


1

2 *Figure 3*

3 *423x423 mm (x DPI)*

4



Graphical abstract
339x190 mm (x DPI)