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# Aging reduces left atrial performance during adrenergic stress in middle aged and older patients

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## Abstract

**Background:** *During adrenergic stress, the influence of age on left atrial (LA) function is unknown. We hypothesized that aging decreases LA total emptying fraction (LAEF) during maximal adrenergic stress. The aim of the study was to determine the influence of aging on LA function during adrenergic stress in middle aged and older patients.*

**Methods:** *We enrolled 167 middle aged and elderly participants, and measured LA and left ventricular (LV) volumes using a multi-slice three-dimensional cine white blood cardiovascular magnetic resonance (CMR) technique before and during intravenous dobutamine infused to achieve 80% of the maximum heart rate response for age. Paired sample t-test was used to detect differences in LA and LV volumes between baseline and peak dose stage of dobutamine stress CMR, and multivariable linear regression was used to identify predictors of LA function.*

**Results:** *Participants averaged 68 ± 8 years in age, 53% were men, 25% exhibited coronary artery disease, 35% had diabetes, 9% had a remote history of atrial fibrillation, 90% had hypertension, and 11% had inducible LV wall motion abnormalities indicative of ischemia during dobutamine CMR. Increasing age correlated with LA volumes (maximal and minimal) and inversely correlated with LAEF at rest and after peak adrenergic stress. Age was an independent predictor of LAEF during adrenergic stress, even after accounting for gender, LV volumes, and other co-morbidities including inducible ischemia.*

**Conclusions:** *Age is associated with a decrease in LA function during adrenergic stress even after adjusting for co-morbidities associated with cardiovascular disease and LV function.* (Cardiol J 2012; 19, 1: 45–52)

**Key words: aging, left atrial function, adrenergic stress, cardiac MRI**

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## Introduction

Aging is associated with cardiovascular remodeling [1]. Left atrial (LA) size and volumes increase with age, leading to an increase in the ratio of LA/ /left ventricular (LV) volume [2–4]. Relative to younger individuals, older individuals often depend more on active LA contraction rather than passive LA conduit function to fill the LV during diastole at rest [5].

To date, however, the effect of aging on LA performance during adrenergic stress has not been described. Studies that have measured LA size and volumes at rest have shown that abnormalities of resting LA volume and size forecast adverse cardiovascular outcomes including heart failure (HF) and poor exercise capacity [6–10].

We hypothesized that aging decreases LA performance in response to adrenergic stress in middle aged and older patients. Adrenergic stimulation is a major mediator of the cardiovascular response to exercise. Accordingly, the aim of this study was to determine the influence of aging on LA performance during adrenergic stress. To address this aim, we measured LA volumes during dobutamine stress in elderly individuals using three-dimensional cardiac magnetic resonance imaging (DCMR). We sought to determine the association of age and adrenergic change in LA performance after accounting for other co-morbidities known to influence LA function including LV performance and the presence of inducible ischemia [11].

## Methods

### Study population

Our study was approved by the Institutional Review Board at the Wake Forest University School of Medicine, and all participants provided informed consent. Participants were enrolled for DCMR as part of the National Institutes of Health R01HL076438 entitled 'Pulmonary Edema and Stiffness of the Vascular System (PREDICT)'. PREDICT is a 550 person longitudinal cohort study designed to identify abnormalities of the cardiovascular system that forecast HF in middle aged and elderly individuals who have yet to experience HF. The study is in the early recruitment phase, and longitudinal follow-up has yet to occur.

The inclusion criteria for PREDICT are: age between 55 and 85 years; left ventricular ejection fraction (LVEF) > 45%; diabetes with a fasting glucose ≥ 126 mg/dL or treatment > 5 years; and/or hypertension defined as a systolic blood pressure (SBP) > 140 mm Hg, a diastolic blood pressure (DBP) > 85 mm Hg or receipt of antihypertensive therapy > 5 years; and/or the presence of coronary artery disease (CAD). Participants in PREDICT are identified from the community through the recruitment core of the Claude Pepper Center on Aging at the Wake Forest University School of Medicine. Eligible candidates are identified through established lines of communication that include paid advertising, mass mailing and community group presentations to a population from seven states within parts of rural Virginia, West Virginia, Tennessee, Kentucky, South Carolina, Georgia, and western North Carolina.

Participants with contraindications to DCMR, atrial fibrillation (AF) at the time of image acquisition, mitral regurgitation or mitral stenosis of greater than mild severity are excluded from participation. The present study utilizes data from the first 167 individuals consecutively enrolled into the PREDICT study, with images collected at rest and peak dose of dobutamine stress. The study is registered with clinicaltrials.gov (NCT00542503).

### Study design

Upon recruitment, baseline clinical factors such as diabetes mellitus, hypertension, CAD, AF, age, and gender were collected according to previously published techniques [12]. Each person underwent DCMR on a 1.5T Avanto scanner (Siemens Medical Solutions, Erlangen, Germany). Using steady-state free precession cine imaging, a multi-slice, multiphase stack of short axis images of both LA and LV volumes were obtained in a single breath-hold. Imaging parameters for both LA and LV volumes included a 40 × 24 cm field of view, a 6 mm thick slice thickness, a 55 ms repetition time (TR), a 2.3 ms echo-time (TE), a 192 × 109 matrix, k-space segmentation with 24 views per segment, 1,500 Hz/pixel bandwidth, and parallel imaging with an acceleration factor of 3. Typically, 16 cine frames were obtained with a 40–55 ms temporal resolution, depending on the heart rate [13, 14].

As shown in Figure 1, the maximal LA area (bottom left panel) and minimal LA area (bottom right panel) in $mm^2$ were manually traced in each slice position. The LA volumes (in $mm^3$) were calculated by summing the areas for all of the slices within the LA and then multiplying this value by the slice thickness (mm). This process was performed at rest and peak stress using CAAS-MRV software (Pie Medical Imaging, Netherlands). LA maximal volume (LAV max) and LA minimal volume (LAV min) were calculated in each slice from the LA base to the mitral annulus using CAAS-MRV software

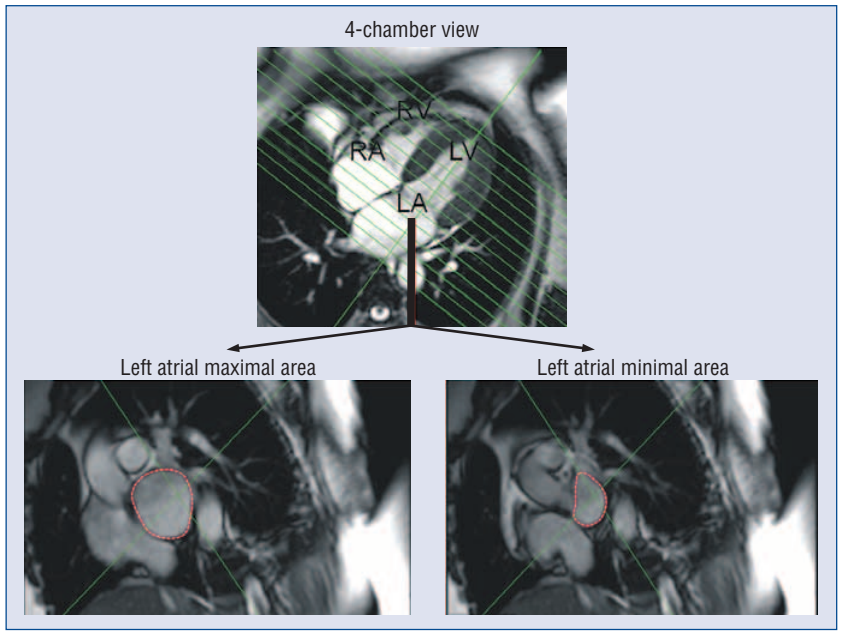


**Figure 1.** Multipanel depiction of slice positions and analysis technique used to derive left atrial (LA) volumes at baseline and peak dose of dobutamine stress. Four-chamber view of the heart (top panel) for planning the multi-slice short-axis series of images (green lines) used to calculate both LA and ventricular volumes. The right atrium, LA, right ventricle (RV), and left ventricle (LV) are denoted. As shown, the maximal LA area (bottom left panel) and minimal LA area (bottom right panel) in $mm^2$ were manually traced in each slice position and the LA volumes in $mm^3$ were calculated by summing the areas for all of the slices within the LA and then multiplying this value by the slice thickness (mm).

(Pie Medical Imaging, Netherlands). Slices near the mitral annulus were excluded from calculations if the LA wall contained more than 50% of the circumference of the LV wall within the slice.

According to previously published techniques, [2] LAV max was defined as the largest LA volume during the entire cardiac cycle; similarly, LAV min was defined as the smallest LA volume during the cardiac cycle. LA total emptying volume was defined as (LAV max – LAV min) and LA total emptying fraction (LAEF) was defined as (LAV max – LAV min)/LAV max. To account for the influence of LV function on LA performance during adrenergic stress, we simultaneously measured LV volumes in all the participants. According to previously published techniques [15], LV end-diastolic volume (LVEDV), LV end-systolic volume (LV ESV), and LVEF were calculated using a modified Simpson's Rule determination.

All volumes were indexed to body surface area, and tracings of LA and LV volumes were performed by individuals blinded to participant identifiers as well as assessments performed on the other heart chamber (i.e. those performing LA calculations were blinded to LV calculations, and *vice versa*).

## Statistical analysis

To estimate the impact of age on LA performance during dobutamine stress, we calculated differences in baseline and peak dose (delta) LAEF. Similarly, differences between baseline and peak dose (delta) LVEF were calculated. To assess the inter-observer variability for the measure of LA volumes, a random sample of 20 participants was drawn by another study team member (HC) in a blinded fashion. Statistical analyses were performed using the Statistical Program for Social Sciences (version 13.0 SPSS Inc., Chicago, IL, USA). Continuous variables are represented as mean ± ± standard deviation. Chi-square tests were used to test association between categorical variables. Pearson's correlation analysis was used to find the correlation between age, LA volumes and function for baseline and peak dose stage of DCMR. Paired sample t test was used to detect the differences in LA and LV volumes, LAEF, and LVEF between baseline and peak dose stage of DCMR. To estimate the impact of age on LA performance during adrenergic stress, we performed two linear regression models with peak dose LAEF and delta LAEF as dependent variables. Age, gender, diabetes melli-

**Table 1.** Demographics of the study population (n = 167).

| Variable | Percentage |
|---|---|
| Age [years] | 68 ± 8 |
| Men | 53% |
| Coronary artery disease | 25% |
| Diabetes | 35% |
| Hypertension | 90% |
| History of atrial fibrillation | 9% |
| Inducible wall motion abnormalities | 11% |
| Mean baseline SBP [mm Hg] | 142 ± 18 |
| Mean baseline DBP [mm Hg] | 81 ± 12 |
| Mean baseline heart rate [bpm] | 65 ± 12 |
| Mean peak dose SBP [mm Hg] | 126 ± 22 |
| Mean peak dose DBP [mm Hg] | 72 ± 16 |
| Mean peak dose heart rate [bpm] | 123 ± 18 |

SBP — systolic blood pressure; DBP — diastolic blood pressure

tus, hypertension, CAD, history of AF and peak dose LVEF or delta LVEF as appropriate, were the variables included in the regression models. Linear regression results are given by presenting the standardized regression co-efficient (B). A two-sided p-value of $< 0.05$ was considered to be statistically significant.

## Results

The demographics of the study population are shown in Table 1. The study group was not homogenous. The majority of patients exhibited hypertension (90%) and 35% had diabetes (Table 1) with an average duration of diabetes of 9.5 ± 6.8 years. The baseline and peak dose SBP, DBP and heart rate are shown in Table 1. The differences in mean LA and LV volumes and function between baseline and peak dose stage of DCMR are shown in Table 2. LA volumes decreased and the LAEF increased with peak dose dobutamine stress (Table 2). Similarly LV volumes decreased with increasing stress, and LVEF increased with stress (Table 2).

### Correlations between age and left atrium volumes and function

Increasing age correlated with LAV max at baseline and peak dose stage of DCMR (baseline: $r = 0.26$, $p = 0.001$, and peak dose: $r = 0.23$, $p = 0.003$). Similarly, age correlated with LAV min (baseline: $r = 0.303$, $p < 0.001$, and peak dose: $r = 0.275$, $p < 0.001$). Increasing age was inversely correlated with LAEF at baseline and peak dose stage of DCMR (baseline: $r = -0.18$, $p = = 0.02$, and peak dose: $r = -0.29$, $p < 0.001$; Fig. 2).

### Effect of baseline and peak dose blood pressure and heart rate on left atrium volumes and LAEF

There were significant correlations between baseline SBP and LAV max ($r = 0.24$, $p = 0.02$), LAV min ($r = 0.22$, $p = 0.03$), LA emptying volume ($r = 0.22$, $p = 0.03$) but not with LAEF ($r = 0.01$, $p = 0.9$). Baseline DBP did not correlate with LAV max ($r = -0.001$, $p = 0.9$), LAV min ($r = -0.022$, $p = 0.8$), LA emptying volume ($r = 0.03$, $p = 0.7$) or LAEF ($r = 0.07$, $p = 0.5$). Baseline heart rate did not correlate with LAV max ($r = -0.17$, $p = 0.06$), LAV min ($r = -0.17$, $p = 0.06$), LAEF ($r = -0.12$, $p = 0.17$) or LA emptying volume ($r = 0.07$, $p = 0.46$).

Peak dose SBP significantly correlated with LAV max ($r = 0.22$, $p = 0.03$), and LAV min ($r = 0.23$, $p = 0.03$), but not with LA emptying volume ($r = 0.13$, $p = 0.2$) or LAEF ($r = -0.09$, $p = 0.36$). Peak dose DBP significantly correlated with LAV max ($r = 0.32$, $p = 0.002$), LAV min ($r = 0.29$, $p = 0.006$), and LA emptying volume ($r = 0.27$, $p = 0.01$) but not with

**Table 2.** Mean left atrial (LA) volumes, left atrial total emptying fraction and left ventricular (LV) volumes and left ventricular ejection fraction at baseline and peak dose dobutamine stress.

| | Baseline | Peak dose | P |
|---|---|---|---|
| Left atrium | | | |
| LA maximal volume* | 31 ± 9 | 25 ± 7 | < 0.001 |
| LA minimal volume* | 18 ± 6 | 12 ± 5 | < 0.001 |
| LA total emptying fraction | 42 ± 7 | 51 ± 8 | < 0.001 |
| Left ventricle | | | |
| LV end-diastolic volume* | 65 ± 14 | 50 ± 13 | < 0.001 |
| LV end-systolic volume* | 29 ± 10 | 17 ± 8 | < 0.001 |
| LV ejection fraction | 56 ± 9 | 67 ± 10 | < 0.001 |

*Values indexed to body surface area

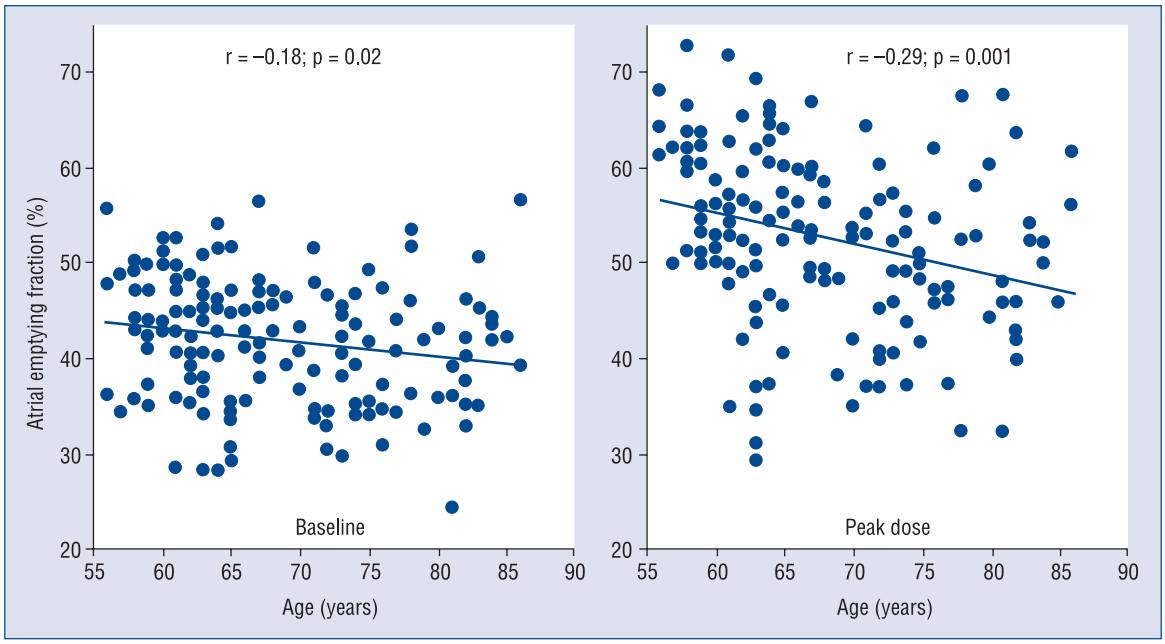


**Figure 2.** Correlation between age and left atrium total emptying fraction; r = Pearson's correlation, baseline: r = –0.18, p = 0.02, p = 0.03 and peak dose: r = –0.29, p < 0.001.

LAEF (r = –0.04, p = 0.7). Peak dose heart rate significantly correlated with LAV max (r = –0.29, p = 0.001), LAV min (r = –0.334, p = 0.001), LAEF (r = 0.257, p = 0.001) and LA emptying volume (r = –0.13, p = 0.09)

The change in SBP (baseline SBP – peak dose SBP) did not correlate with delta LAV max (r = 0.07, p = 0.5), delta LAV min (r = 0.1, p = 0.3), delta LA emptying volume (r = 0.01, p = 0.9) or delta LAEF (r = –0.03, p = 0.8). Similarly, the change in DBP did not correlate with delta LAV max (r = –0.06, p = 0.55), delta LAV min (r = –0.06, p = 0.59), delta LA emptying volume (r = –0.05, p = 0.6) or delta LAEF (r = –0.05, p = 0.6). However, change in heart rate (baseline heart rate – peak dose heart rate) significantly correlated with delta LAV max (r = –0.26, p = 0.005), LAV min (r = –0.27, p = = 0.003), and LA emptying volume (r = –0.19, p = = 0.04) but not with delta LAEF (r = 0.11, p = 0.24).

## Effect of history of atrial fibrillation on left atrium volumes and LAEF

Patients with prior history of AF (not during imaging) had significantly lower baseline LAEF (38 ± 8 *vs*. 42 ± 6, p = 0.03) and peak dose LAEF (46 ± 8 *vs*. 51 ± 8, p = 0.02) when compared to those without a history of AF. However, patients with prior history of AF did not have statistically significant lower delta LAEF (7.7 ± 7 *vs*. 9 ± 1, p = 0.5) when compared to those without a history of AF.

## Regression analysis

Linear regression analysis was performed to determine the association between age and LAEF during adrenergic stress after adjusting for other possible confounding factors (Table 3). Age was an independent predictor of LAEF during peak dose DCMR, even after adjusting for the influence of LVEF and other co-morbidities (Table 3).

## Impact of exclusion of participants with positive stress test on the analyses

Nineteen (11%) participants had inducible LV wall motion abnormalities indicative of ischemia during DCMR. To exclude the possibility that inducible LV wall motion abnormalities indicative of ischemia may have confounded our results, regression analysis was conducted after exclusion of participants who had inducible LV wall motion abnormalities during DCMR. After exclusion of participants with positive DCMR, age remained an independent predictor of LAEF during peak doses of adrenergic stress.

## Inter-observer variability

A random sample of 20 participants was drawn by another study team member (HC) in a blinded

**Table 3.** Multivariate predictors of left atrial total emptying fraction during adrenergic stress.

| Outcome | Variables | Peak dose | | Delta LAEF | |
|---|---|---|---|---|---|
| | | B | P | B | P |
| LAEF | Age | –0.28 | < 0.001* | 0.2 | 0.01* |
| | Male | 0.14 | 0.06 | –0.17 | 0.02* |
| | CAD | 0.13 | 0.08 | –0.09 | 0.27 |
| | DM | 0.07 | 0.35 | –0.113 | 0.16 |
| | HTN | 0.16 | 0.04* | –0.15 | 0.06 |
| | Prior AF | 0.13 | 0.1 | –0.003 | 0.97 |
| | LVEF | 0.23 | 0.002* | 0.145 | 0.06* |

*Final independent predictors in linear regression model; LAEF — left atrial total emptying fraction; CAD — coronary artery disease; DM — diabetes mellitus; HTN — hypertension; prior AF — prior history of atrial fibrillation; LVEF — left ventricular ejection fraction; peak dose LVEF was used in the peak dose LAEF regression model and delta LVEF was used in the delta LAEF regression model; Delta LAEF — difference between baseline LAEF and peak dose LAEF; B — standardized co-efficient

fashion. The correlation between the two measures was very high (r = 0.91).

### Impact of age on left atrium function during dobutamine stress

After adjusting for co-morbidities and delta LVEF (peak dose – baseline LVEF), age remained an independent predictor of change in LA function (delta LAEF) during adrenergic stress (Table 3). These results did not change after performing stratified analyses which excluded participants with inducible wall motion abnormalities indicative of ischemia.

## Discussion

Our study is the first to demonstrate that age is an independent predictor of LA performance (LAEF) after catecholamine induced stress. This finding is true even after accounting for the influence of potentially confounding clinical conditions such as LV function or underlying hypertension, diabetes, or CAD. These results are also the first to describe LA function during stress using three-dimensional imaging techniques. Breathheld LV volumetric MRI image acquisitions have been shown to be both highly accurate and reproducible relative to two-dimensional techniques [16, 17]. Our results indicate that three-dimensional LA volumetric image acquisitions are feasible throughout pharmacologic stress at relatively high heart rate, and analyses of these images can be accomplished with low interobserver variability.

Prior studies evaluating LA function have been performed at rest. The findings from our baseline or resting LA measurements (Table 2 baseline values) are consistent with these previous studies [3, 18]. With peak dose of intravenous dobutamine, LAV min decreased. This observation is similar to changes in LV volumes reported in other dobutamine infusion studies [19–21]. Also, LAV max (a measure of LA preload) decreased with peak dose of intravenous dobutamine. LVEDV has also been reported to decrease with increasing doses of intravenous dobutamine [19]. The results of our study indicate that LA preload diminishes along with LVEDV, which presumably occurs due to diminished preload at peak dobutamine.

A history of AF correlated inversely with LA function in our study. Since we did not employ high temporal resolution studies to measure LA function in patients with AF, these patients were excluded from this study. However, a history of AF did not correlate with change in LAEF between baseline and peak dose. Regression analysis also showed that history of AF was not a significant predictor of peak dose LAEF and delta LAEF when adjusted for other factors (Table 3). LV function impacts LA function by increasing its reservoir capacity during LV systole through the downward displacement of the mitral annulus. The LV also influences LA conduit function by its strong suction during early LV diastole [11]. As shown in Table 3, age remained an independent predictor of LA function, even after adjusting for the influence of LV function on LA function during adrenergic stress.

In patients with CAD, both LVEDV and LVESV have been shown to exhibit an abnormal increase with high intravenous infusion rates of dobutamine in the setting of inducible ischemia [20]. To determine whether LV ischemia influenced our observed association between age and LA performance, we performed stratified analyses (excluding participants with dobutamine-induced ischemia) and found that the relationship between aging and LA perfor-

mance was maintained. These results suggest that the relationship between age and adrenergic stress induced change in LA performance is independent of the presence of inducible LV myocardial ischemia.

The results of this study could have potential clinical implications. Abnormal LA function during adrenergic stress could contribute to the age-related decreases in cardiovascular function that may be operative in syndromes such as HF with preserved ejection fraction [1, 22, 23]. Loss of LA contribution to LV filling in older persons at risk for, or with established, HF may lead to decompensation and pulmonary edema or exertional dyspnea [24, 25]. Even though our study was not specifically designed to examine this association, future studies could be performed to determine if differences exist in LA function during stress in healthy older individuals compared to those with HF. Such studies could add additional understanding of the pathophysiology of HF in individuals in whom LVEF appears preserved.

There are limitations to our study. Firstly, we used LAEF to evaluate LA function. Measures of LA performance incorporate passive conduit as well as active contractile components. We could not readily differentiate between these two components in our overall assessment of LA performance. Secondly, we did not characterize LA tissue using a late gadolinium enhancement technique [26, 27]. Future studies incorporating gadolinium contrast could identify LA fibrosis that may contribute to LA dysfunction. Thirdly, a disadvantage of our design is that we have little data on completely healthy individuals. The advantage of our design is that we enrolled patients with relatively common cardiovascular co-morbidities (e.g. hypertension or diabetes) associated with abnormal resting LA function, and therefore, our results are applicable to patients seen in clinical practice. Fourthly, the effect of dobutamine on LA preload could not be completely ruled out. As detailed in our results, peak dose SBP and DBP did not correlate with peak dose LAEF, and the changes between baseline and peak dose SBP, DBP and heart rate did not correlate with delta LAEF.

## Conclusions

Aging reduces LA performance during adrenergic stress, even after accounting for the influence of LV performance, and other co-morbid conditions. This indicates that the LA response to adrenergic stimulation is reduced with aging, a potentially novel mechanism contributing to the age-related declines in cardiovascular performance.

## Acknowledgements

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**Conflict of interest:** none declared

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