

# Association of Longitudinal Changes in NT-proBNP With Changes in Left Atrial Volume and Function: MESA

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## BACKGROUND

The mechanism of left atrial (LA) remodeling is poorly understood. The aim of this longitudinal study was to investigate whether changes in NT-proBNP levels relate to alterations of LA structure and function over time in a multiethnic population.

## METHODS

From the prospective cohort study, the Multi-Ethnic Study of Atherosclerosis, our analysis included 1,838 participants who underwent cardiac magnetic resonance imaging at the baseline and 10-year examinations, had NT-proBNP levels available at both time points, and did not develop heart failure, myocardial infarction, and/or atrial fibrillation. Multivariable linear regression was used to analyze the association between NT-proBNP level (log-transformed) at the 2 time points and change in LA volumes, LA emptying fractions (total, active, and passive), and LA longitudinal strain. Log NT-proBNP was categorized into Low-Low ( $N = 681$ ), Low-High ( $N = 238$ ), High-Low ( $N = 237$ ), and High-High ( $N = 682$ ) based on the median value at both time points.

## RESULTS

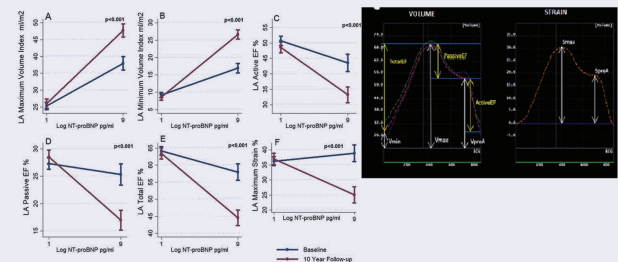
With the Low-Low group as the reference group, the High-High group experienced a greater increase in LA maximum and minimum indexed volumes: 3.1 ml/m<sup>2</sup> (95% confidence interval 1.98, 4.20) and 2.7 ml/m<sup>2</sup> (1.89, 3.51), respectively. The High-High group also experienced a greater decrease in LA total, passive, active emptying fraction, and

longitudinal strain:  $-3.3\%$  ( $-4.46, -2.11$ ),  $-0.9\%$  ( $-1.80, -0.02$ ),  $-4.2\%$  ( $-5.55, -2.76$ ), and  $-2.3\%$  ( $-3.80, -0.72$ ), respectively. The Low-High group had similar associations, but the effect sizes were not as high.

## CONCLUSIONS

Adverse LA remodeling over 10 years of follow-up strongly correlates with prolonged elevated levels of intracardiac stress, as assessed by NT-proBNP levels.

## GRAPHICAL ABSTRACT



**Keywords:** blood pressure; cardiac magnetic resonance imaging; hypertension; left atrium; multimodality tissue tracking; NT-proBNP

doi:10.1093/ajh/hpab018

Left atrium (LA) modulates left ventricular (LV) filling as it acts as a reservoir, a conduit to LV during early diastole, as well as a contractile booster pump in late diastole.<sup>1,2</sup> Recent studies suggest that changes in LA structure and function have been associated with cardiovascular disease (CVD) and clinical outcomes including atrial fibrillation (AF), stroke, and all-cause mortality.<sup>2-5</sup> LA structure and function have been identified as potentially useful prognostic markers in heart failure (HF) with both reduced (HFrEF) and preserved ejection fraction (HFpEF).<sup>4,6,7</sup> LA also functions as

a neurohumoral organ contributing to cardiovascular homeostasis by storing ANP and small amounts of BNP in the granules of atrial myocytes. The natriuretic peptide response is closely associated with myocardial wall stress and is known to be one of the criteria for the diagnosis of HF.<sup>8</sup> LA volume may reflect chronicity and severity of elevated left-sided filling pressure, and has been associated with natriuretic peptides and outcomes in different HF states.<sup>9</sup> Recently, the concept of atrial cardiomyopathy as a progressive fibrotic atrial

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Initially submitted November 16, 2020; date of first revision December 28, 2020; accepted for publication January 20, 2021; online publication January 25, 2021.

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disease has been evolved in risk for AF with stroke.<sup>10</sup> Given the relatively thin atrial wall and its complex motion, accurate quantification of LA size and function by cardiac magnetic resonance (CMR) may be challenging. Feature tracking CMR (FT-CMR) was specifically developed to measure myocardial deformation in order to overcome those shortcomings, therefore providing a complete assessment of LA phasic volumes and function with excellent accuracy and reproducibility.<sup>2,11</sup>

Indeed, in the Multi-Ethnic Study on Atherosclerosis (MESA) NT-proBNP is the single most important predictor of both AF and incident HF among all phenotypic variables measured in the baseline MESA examination.<sup>12,13</sup> Due to physiologic and pathologic alterations, levels of NT-proBNP change over time.<sup>14</sup> However, it is still unclear whether changes in NT-proBNP levels are associated with LA remodeling and what role they play, in the pathogenesis of adverse LA remodeling. Hence, the aim of this study is to establish both cross-sectional and longitudinal relationships between NT-proBNP and LA structure and function in a multiethnic population free of clinical CVD at baseline.

## METHODS

### Study participants

Between July 2000 and August 2002, 6,814 men and women aged 45–84 years who were recruited from 6 US field centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and St Paul, MN) and were enrolled in a prospective observational cohort study, MESA. MESA included participants who identified their race/ethnicity as White, African American, Chinese American, or Hispanic and with subclinical CVD at baseline. Details of the MESA study design have been previously described.<sup>15</sup> Ten-year follow-up examinations for the participants were done in 2010. All study protocols were reviewed and approved by institutional review boards of each field center and all participants signed written consent.<sup>15</sup>

At baseline, 5,004 participants had CMR, of these 4,223 had quantifiable LA imaging data available. Similarly, at 10 years, out of 3,045 participants who underwent a CMR, only 2,879 had quantifiable LA imaging data. After excluding participants without NT-proBNP there were 1,985 participants who had baseline and follow-up NT-proBNP and LA data from CMR. Of those, 147 participants developed HF, AF, and/or myocardial infarction during follow-up and were excluded from this analysis. A total of 1,838 participants were included for analysis. Only 1,633 participants have LA passive and active function available.

### Multimodality tissue tracking image analysis

Details of the CMR protocol have been described previously.<sup>2</sup> LA parameters were obtained using semi-automated MTT software version 5.0 (Toshiba, Tokyo, Japan) by a trained radiologist from baseline 4- and 2-chamber cine CMR images. LA endocardial and epicardial borders were drawn manually by using marked points by a single experienced operator at a reference frame, the ventricular end-systolic frame just before the mitral valve opening (Figure 1). The software

then searches for pixel pattern that most closely matches the epicardial and endocardial contours in the subsequent frames using the marked points. For quality control, the user retraced the borders through all the subsequent frames if necessary. LA volume was calculated by using the biplane area-length modified Simpson method from apical 4- and 2-chamber views by generating a volume/time curve. Longitudinal strain curves for each atrial wall segment were generated.

Using the volume/time curve, measurements for LA volumes were extracted. All measured LA volumes were subsequently indexed according to body surface area. The parameters of LA function and volume derived from the curves:

- Maximum LA volume ( $LAV_{max}$ ): LA volume at end-systole before mitral valve opening.
- Minimum LA volume ( $LAV_{min}$ ): LA volume at end diastole after mitral valve closure.
- Pre-atrial contraction ( $LAV_{preA}$ ): LA volume before atrial contraction.
- LA passive emptying fraction (LAPEF):  $100 \times (LAV_{max} - LAV_{preA}) / LAV_{max}$ .
- LA active emptying fraction (LAAEF):  $100 \times (LAV_{preA} - LAV_{min}) / LAV_{preA}$ .
- LA total emptying fraction (LATEF):  $100 \times (LAV_{max} - LAV_{min}) / LAV_{max}$ .

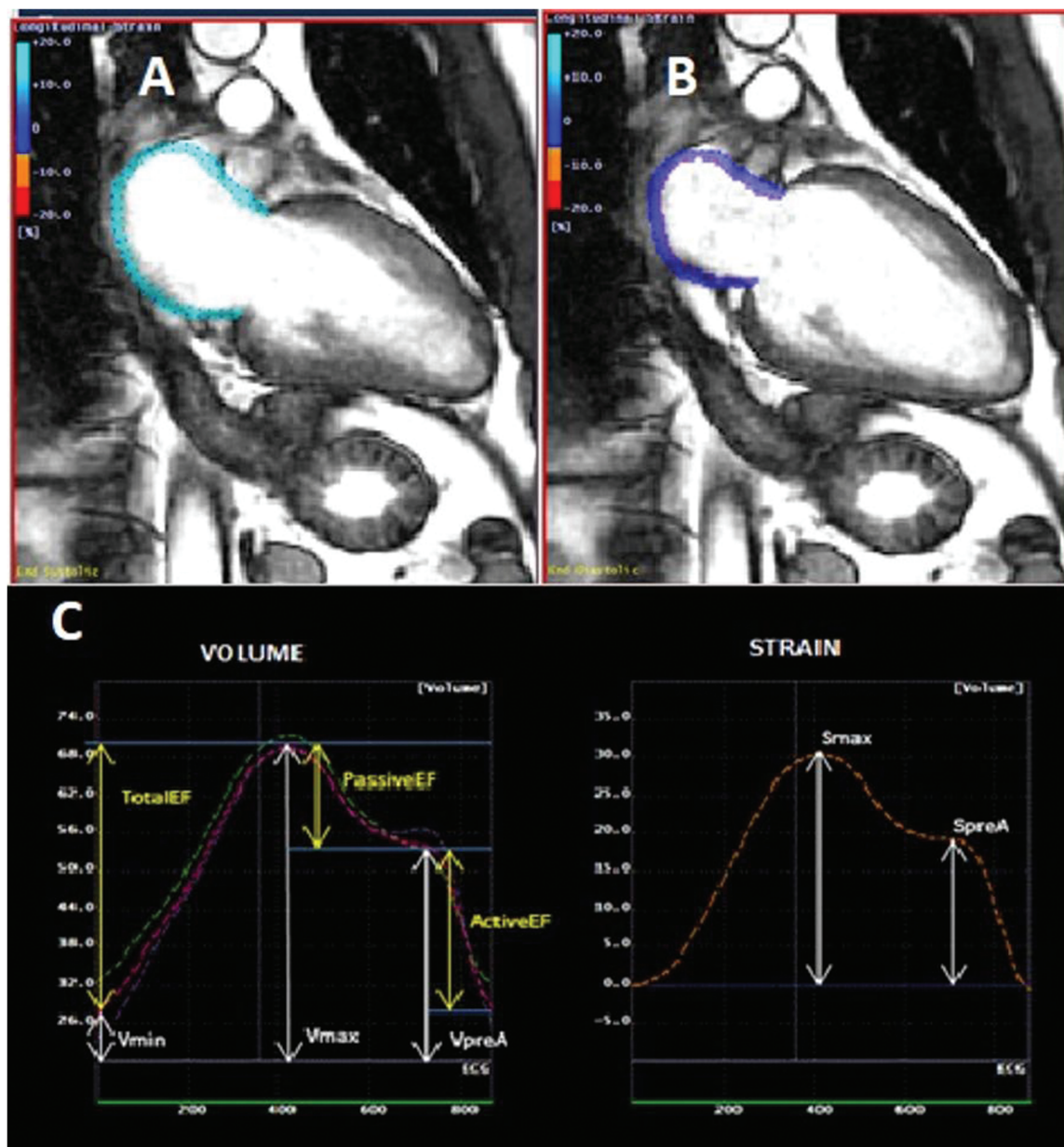
LA strain was calculated from the average of global values in the longitudinal direction at each time frame, determined by the software's automatic division of the LA wall into equal segments. From the longitudinal strain curve, peak longitudinal LA strain ( $LAS_{max}$ ) is calculated. Excellent inter- and intraobserver reliability have been demonstrated.<sup>4</sup>

### NT-proBNP

NT-proBNP levels were measured from frozen serum samples drawn at baseline and 10-year follow-up and stored at a temperature range of  $-70^{\circ}\text{C}$  to  $-80^{\circ}\text{C}$ . All measurements were performed on the Elecsys electrochemiluminescence immunoassay based on the double-antibody sandwich method (Roche Diagnostic, Indianapolis, IN, USA). A 250  $\mu\text{l}$  serum sample previously unfrozen or only thawed once was used for analysis. The measuring range was 5–35,000 pg/ml (defined by the lower detection limit and the maximum of the standard curve). The intraassay and interassay coefficients of variation for baseline examination: at 175 pg/ml, 2.7% and 3.2%; at 355 pg/ml, 2.4% and 2.9%; at 1,068 pg/ml, 1.9% and 2.6%; and at 4,962 pg/ml, 1.8% and 2.3%. The interassay CVs on 3 controls run with 10-year follow-up sample: 4.03%, 3.05%, and 3.18%.<sup>12,16</sup>

### Statistical analysis

Continuous variables were expressed as mean  $\pm$  SD or as median (interquartile range) based on the distribution of the variable, and categorical variables were expressed as percentages. NT-proBNP was log-transformed to approximate a normal distribution. The change in log NT-proBNP was divided into 4 categories based on the median values and median value was chosen for this analysis as an



**Figure 1.** The figure illustrates phasic LA volumes, function (left), and longitudinal strain (right) corresponding to 1 cardiac cycle. (a and b) Feature tracking CMR imaging of LA in a 2- and 4-chamber view. (c)  $V_{max}$ —maximum LA volume,  $V_{min}$ —minimum LA volume, and  $V_{preA}$ —LA volume before atrial contraction, respectively. On the longitudinal strain curve (right),  $S_{max}$ —maximum LA longitudinal strain and  $S_{preA}$ —LA longitudinal strain before atrial contraction. Abbreviations: CMR, cardiac magnetic resonance; LA, left atrium.

approximation to the point at which most slopes changed. Based on log NT-proBNP value relative to median at baseline and 10 years it was categorized into Low-Low, Low-High, High-Low, and High-High. Differences in baseline clinical characteristics, risk factors, LA, and LV MRI parameters by log NT-proBNP categories were tested using analysis of variance (continuous variables) or  $\chi^2$  tests (categorical variables) and Kruskal–Wallis test for skewed distribution.

For cross-sectional association, with LA parameters as the dependent variable and log NT-proBNP as the independent variable, we used linear regression at 10 years. Next, to assess for nonlinear association, the log NT-proBNP value at which

the dependent variables had a substantial change in slope, i.e., the inflection point was determined using linear splines. Linear splines were performed by fitting the data to the regression equation and knots for the linear splines were chosen at log NT-proBNP value of 4.2 pg/ml. The log NT-proBNP value at which linear spline offered the best fit was chosen as the inflection point for the dependent variables. The line segments were constrained to be continuous between the 2 categories.

For longitudinal analysis, a delta variable was created for LA outcome variables. We performed several analyses with categorizing NT-proBNP values based on specific thresholds at baseline and 10-year follow-up such as different cutoffs

which produced qualitatively similar trends. For both cross-sectional and longitudinal models, multivariable linear models were adjusted for age, gender, race, body mass index, systolic blood pressure, diastolic blood pressure, antihypertensive medication use, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, lipid lowering medications, smoking status, LV mass, LV ejection fraction, and LV mass–volume ratio (measure of LV diastolic dysfunction). The variables included in the multivariable regression models were chosen *a priori*. For testing interactions of log NT-proBNP with gender and race/ethnicity on LA function, volume, and strain, the likelihood ratio test was used. All analyses were performed using STATA v15.0 (StataCorp), and significance was declared for  $P \leq 0.05$ .

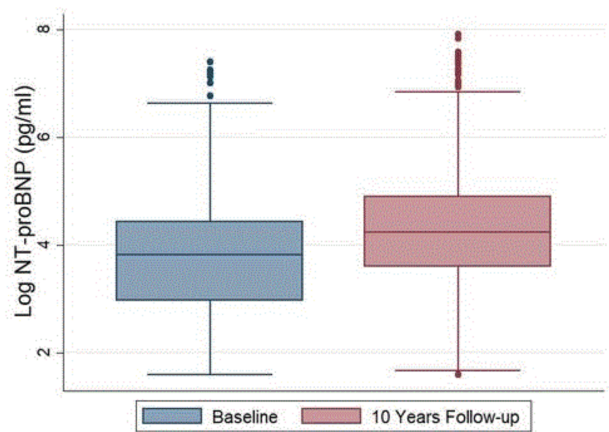
## RESULTS

At baseline, the mean (SD) age was 59 (9.2) years and 52% were men. Of 1,838 participants, 43.9% were Caucasian, 21.6% were African American, 21.6% were Hispanic, and 13.3% were Chinese. The median log NT-proBNP at baseline was 3.81 pg/ml and at 10 years was 4.21 pg/ml (Figure 2). Over 10 years, NT-proBNP levels increased from a median (IQR) of 45.2 (19–85) to 69.5 (36.1–135.4). Based on clinical cutoffs of NT-proBNP for acute HF,<sup>17</sup> only 7 (0.4%) participants and 14 (0.8%) participants had abnormal NT-proBNP levels at baseline and 10-year follow-up, respectively. Out of this, only 4 (0.2%) participants had persistent high NT-proBNP level over 10 years.

The mean LA volume indices where the mean maximum volume (LAVIMAX) showed an increase of 5.2 ml/m<sup>2</sup>, mean minimum volume (LAVIMIN) showed an increase of 4.1 ml/m<sup>2</sup>. On the contrary, the LA function showed a decline with the mean active emptying fraction (LAAEF) decreasing from 48.2% to 42.4%, passive emptying fraction (LAPEF) decreasing from 26.6% to 23.8%, and total emptying fraction (LATEF) from 62.1% to 55.7%. The maximum longitudinal strain had a similar trend of decline from a mean of 37.1% to 32.1% (Figure 3). Table 1 shows the characteristics of our study participants by log NT-proBNP categories. The relationship of LA volume, function, and strain with log NT-proBNP at baseline and at 10 years can be seen in Figure 4.

Table 2 shows the cross-sectional relationship between LA parameters with log NT-proBNP at 10-year follow-up by performing a linear spline regression. The inflection point for LA volume, function, and strain was at log NT-proBNP value of 4.2 pg/ml. LA volumes showed a positive association, and LA function and strain showed an inverse association with log NT-proBNP within log NT-proBNP >4.2 pg/ml, which plateaus for log NT-proBNP ≤4.2 pg/ml. The coefficients decrease when adjusted for demographics, cardiovascular risk factors. Similar trend was seen with additional adjustment for LV ejection fraction, mass, and mass–volume ratio.

Table 3 shows the coefficients and 95% confidence intervals of change in LA parameters with log NT-proBNP from baseline to 10 years with LA parameters as dependent variables and log NT-proBNP as independent variables.



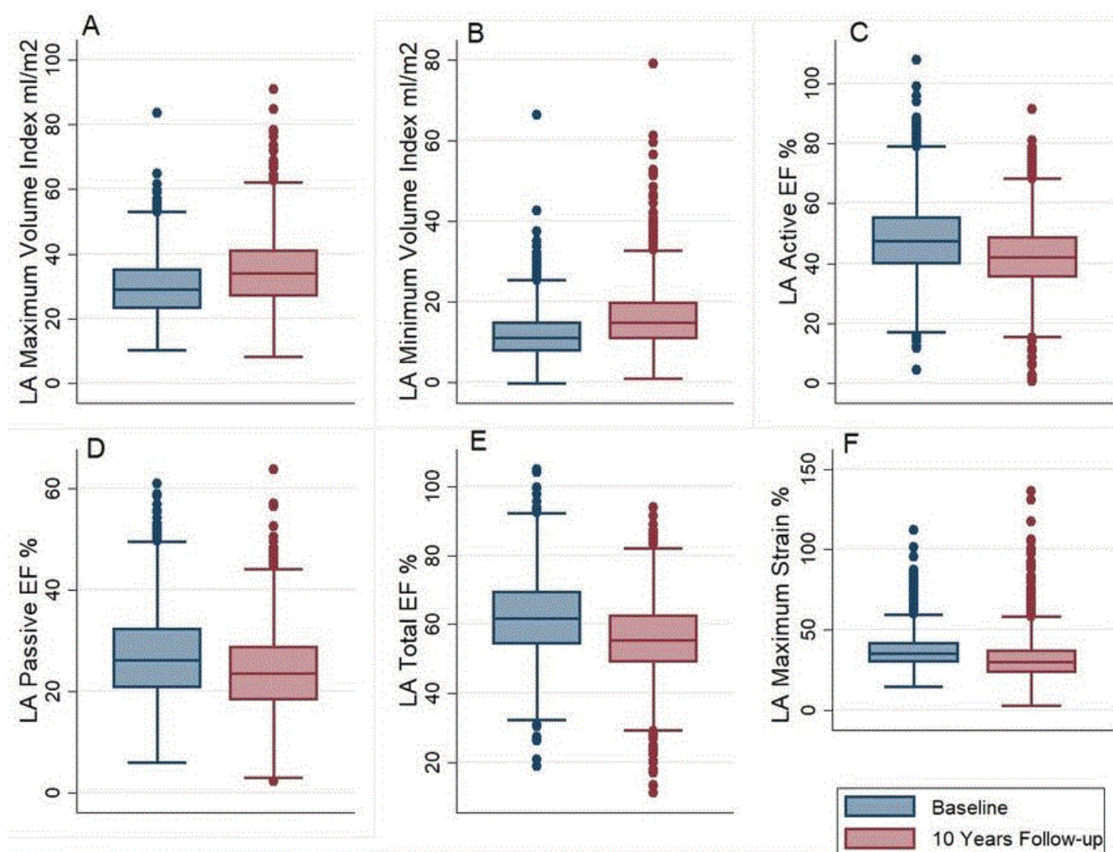
**Figure 2.** Boxplot showing distribution of log NT-proBNP shown at baseline (blue) and at 10 years (red). Wilcoxon signed rank test showed statistically significant difference in the values of log NT-proBNP at baseline and at 10-year follow-up.

There were 681 (37.1%) participants in the Low-Low, 238 (13.0%) in the Low-High, 237 (12.9%) in the High-Low, and 682 (37.1%) in the High-High groups. The Low-Low category was used as the reference. The High-High group experienced a greater increase in LAVIMAX and LAVIMIN: 3.1 ml/m<sup>2</sup> (95% confidence interval 1.98, 4.20) and 2.7 ml/m<sup>2</sup> (1.89, 3.51), respectively. The High-High group also experienced a greater decrease in LATEF, LAPEF, and LAAEF fractions: −3.3% (−4.46, −2.11), −0.9% (−1.80, −0.02), and −4.2% (−5.55, −2.76), respectively. Similarly, the High-High group experienced a decrease in LA longitudinal strain −2.3% (−3.80, −0.72). Similar significant associations were observed for the Low-High group compared with the Low-Low group, but little difference was observed for the High-Low group compared with the Low-Low group.

There was no statistically significant interaction between NT-proBNP group and gender for any of the CMR outcomes studied (all  $P > 0.05$ ). There was no interaction between NT-proBNP group and race on LA volumes (LAVIMAX  $P$  value = 0.12, LAVIMIN  $P$  value = 0.08) but there was an NT-proBNP-race/ethnic interaction for LA function (LATEF  $P$  value = 0.001, LAPEF  $P$  value = 0.03, LAAEF  $P$  value = 0.05) and strain ( $P$  value = ≤0.001). White and Hispanics demonstrated similar trends and patterns as whole cohort in the associations between change in LA function and strain and log NT-proBNP, but these associations were not statistically significant for individuals of Chinese and Black Americans. The association of LA parameters and NT-proBNP was not statistically significant among participants with interim HF which could be due to small sample size.

## DISCUSSION

Our study demonstrates that in a multiethnic population increasing levels of NT-proBNP over 10 years as well as high levels at both baseline and 10-year follow-up examination, were associated with greater increase in LA volume, and greater decrease in LA function and LA strain when compared with those with stable low levels over the 10-year



**Figure 3.** Bar graph showing mean LA structural and functional parameters at baseline (blue) and 10-year follow-up (red). (a) LA Maximum Volume Index; (b) LA Minimum Volume Index; (c) LA Active EF; (d) LA Passive EF; (e) LA Total EF; (f) LA Maximum Strain. There is a statistically significant difference in the mean values of LA parameters at baseline and at 10-year follow-up using paired *t*-tests. Abbreviations: EF, emptying fraction; LA, left atrium.

follow-up period. Moreover, a drop in log NT-proBNP over 10 years was not associated with differences in LA parameters during that time. Additionally, Low-High and High-High groups showed statistically significant relationships with LA parameters inferring that the elevated levels of log NT-proBNP at the most recent examination was strongly correlated with increase in LA volume, as well as decrease in LA global function and strain. Importantly also LA parameters correlated with elevated log NT-proBNP independently of LV mass and volume.

In most previous studies, 2-dimensional echocardiography has been used for volume measurements of LA. Given the location of LA and its thin asymmetric wall, the assessment of the function is challenging and CMR has been shown to have excellent reproducibility and accuracy in the measurement of cardiac volumes, making it a gold standard modality.<sup>18</sup> One study comparing LA volume measured using CMR and echocardiography showed that echocardiography consistently underestimated volumes compared with CMR.<sup>19,20</sup> To our knowledge, there are no other studies assessing the association between NT-proBNP and phasic LA function using CMR. Ability to identify high cardiovascular risk is essential for prevention strategies and asymptomatic subjects may benefit from early risk stratification. However, traditional risk assessment tools have not been rigorously evaluated in asymptomatic older adult population.

Additionally, the direct contribution of intracardiac stress in the initiation, progression, and acceleration of age-related remodeling is undisputed although the natural history at the population level remains largely unknown due to the absence of longitudinal studies. Hence, the results of our study add to the knowledge of the mechanisms behind NT-proBNP as a marker of adverse cardiac remodeling, in particular LA, which would aid in risk stratification of asymptomatic adults particularly those with high-risk burden.

LA remodeling is associated with incident hypertension and has emerged as a strong predictor of CVDs.<sup>21–23</sup> Assessment of LA function is valuable in the evaluation of LV diastolic performance and LA volume index is now included as parameter to diagnose HF.<sup>4,24,25</sup> Early phases of LA remodeling are adaptive and reversible while over time it becomes adverse, maladaptive, and permanent.<sup>20,26</sup> Understanding the mechanism of LA remodeling and markers associated with it is crucial to the development of novel strategies for screening and management of hypertensive heart disease and CVDs. Studies have suggested that inflammation and oxidative stress may contribute to the process of adverse LA remodeling.<sup>20,21,27</sup> In this regard, NT-proBNP has been associated with atrial dilatation, fibrosis, and dysfunction in AF and hypertensive heart disease, cross-sectionally.<sup>28–30</sup> In MESA, studies have shown the association of elevated NT-proBNP with incident

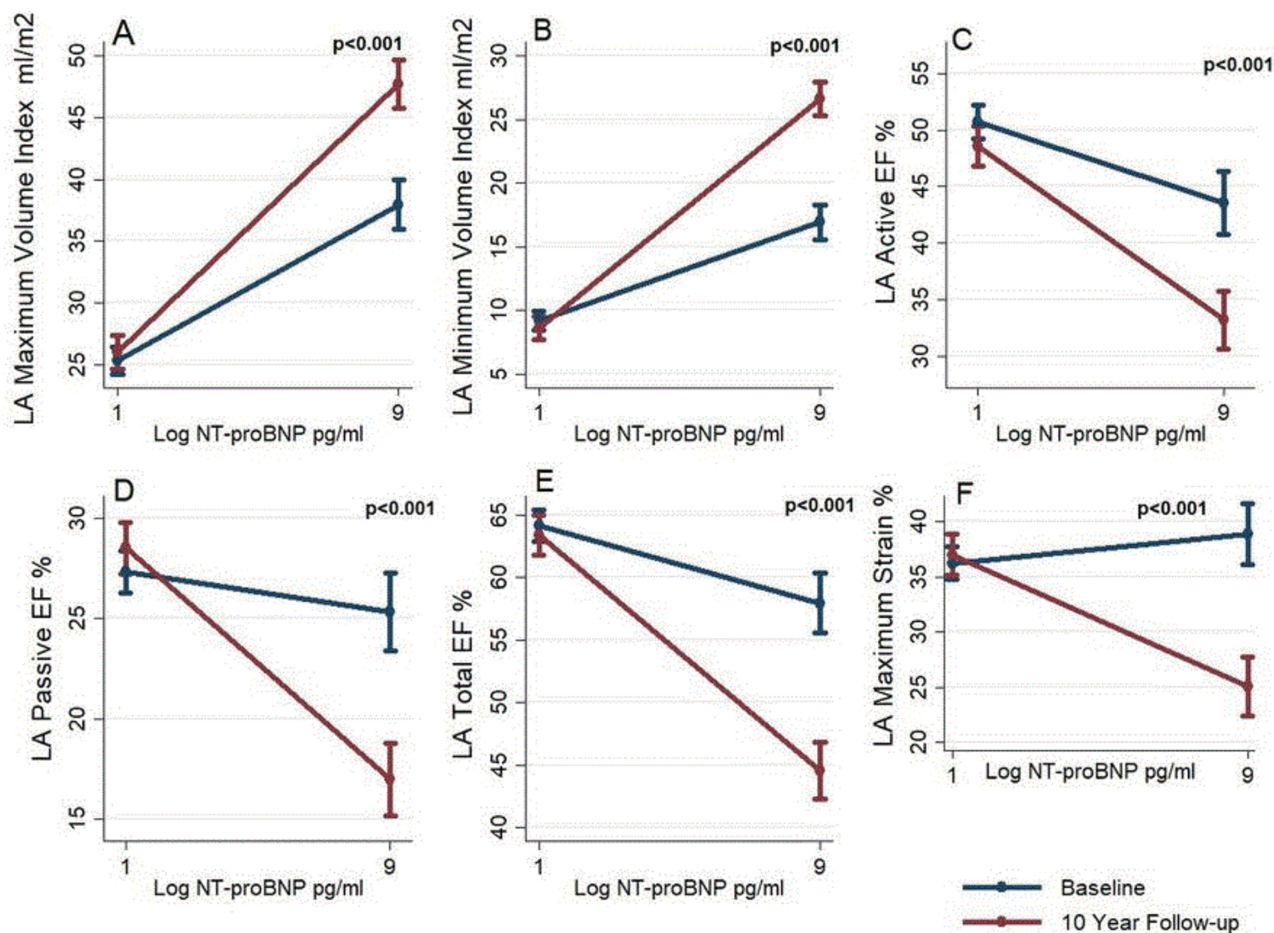
**Table 1.** Baseline characteristics of log NT-proBNP categories

	Low-Low	Low-High	High-Low	High-High	P value
Participants, n (%)	681 (37.1)	238 (13.0)	239 (13.0)	680 (37.0)	
Age in years, mean (SD)	55.0 (7.6)	59.8 (8.8)	56.7 (7.8)	63.5 (9.2)	<0.001
Males, n (%)	446 (65.5)	134 (56.3)	88 (36.8)	211 (31.0)	<0.001
Race					
Caucasian American	233 (34.2)	91 (38.2)	124 (51.9)	360 (52.9)	
Black American	166 (24.4)	70 (29.4)	42 (17.6)	120 (17.7)	<0.001
Hispanic American	153 (22.5)	53 (22.3)	45 (18.8)	136 (20.0)	
Chinese American	129 (18.9)	24 (10.1)	28 (11.7)	64 (9.4)	
BMI, kg/m <sup>2</sup> , mean (SD)	27.65 (4.5)	28.61 (5.2)	27.75 (5.0)	27.48 (5.3)	0.02
SBP, mm Hg, mean (SD)	117.55 (15.4)	124.66 (16.6)	120.87 (22.6)	126.98 (22.8)	<0.001
DBP, mm Hg, mean (SD)	72.80 (9.3)	73.58 (9.1)	71.27 (11.7)	69.84 (10.55)	<0.001
HDL cholesterol, mg/dl, mean (SD)	47.68 (12.8)	49.00 (14.2)	53.45 (16.2)	55.07 (15.6)	<0.001
LDL cholesterol, mg/dl, mean (SD)	119.76 (29.6)	120.14 (35.3)	110.97 (26.8)	117.0 (31.9)	0.001
Total cholesterol, mg/dl, mean (SD)	194.41 (34.6)	195.84 (39.2)	189.90 (35.6)	196.47 (34.5)	0.09
Lipid lowering medication, n (%)	87 (12.8)	45 (18.9)	35 (14.6)	91 (13.4)	0.12
Diabetes mellitus, n (%)	58 (8.5)	42 (17.6)	13 (5.5)	59 (8.7)	<0.001
Hypertension, n (%)	169 (24.8)	93 (39.1)	86 (36.0)	305 (44.9)	<0.001
Antihypertensive medication use, n (%)	141 (20.7)	82 (34.5)	75 (31.4)	245 (36.0)	<0.001
Current smoker, n (%)	82 (12.0)	29 (12.2)	30 (12.6)	62 (9.1)	0.25
NT-proBNP, pg/ml, median (IQR)	15.34 (6.8–27.9)	28.6 (18.3–37.8)	66.9 (53.0–85.9)	99.16 (67.0–149.7)	<0.001
LA maximum volume index, ml/m <sup>2</sup> , mean (SD)	28.07 (7.9)	28.39 (8.7)	30.23 (8.6)	31.25 (9.4)	<0.001
LA minimum volume index, ml/m <sup>2</sup> , mean (SD)	10.88 (5.0)	11.37 (5.6)	11.83 (5.7)	12.80 (6.5)	<0.001
LA total emptying fraction, %, mean (SD)	62.93 (11.4)	61.87 (12.0)	62.75 (12.1)	61.06 (11.1)	0.02
LA passive emptying fraction, %, mean (SD)	26.67 (9.4)	26.71 (9.5)	27.69 (9.4)	26.16 (8.3)	0.21
LA active emptying fraction, %, mean (SD)	49.38 (12.4)	47.93 (14.0)	48.24 (14.4)	47.21 (16.7)	0.04
LA maximum strain, %, mean (SD)	36.73 (10.2)	36.70 (11.6)	38.74 (12.1)	37.13 (11.4)	0.10
LV ejection fraction, %, mean (SD)	62.09 (5.6)	62.42 (5.3)	62.93 (5.6)	63.25 (5.6)	0.001
LV mass, g, mean (SD)	125.36 (27.7)	125.44 (25.9)	116.63 (28.7)	115.32 (29.5)	<0.001
LV end-diastolic volume index, ml/m <sup>2</sup> , mean (SD)	71.19 (11.8)	69.08 (12.6)	71.18 (10.9)	69.49 (12.2)	<0.001
LV end-systolic volume index, ml/m <sup>2</sup> , mean (SD)	26.93 (5.8)	25.98 (6.2)	26.34 (5.5)	25.60 (6.8)	0.001

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LA, left atrium; LDL, low-density lipoprotein; LV, left ventricle; SBP, systolic blood pressure.

CVDs.<sup>12,31</sup> In recent years, prognostic implications of serial measurements of NT-proBNP in different clinical settings such as HF and myocardial infarction.<sup>32,33</sup> Furthermore, reduction in NT-proBNP level over time have been associated with better outcomes in both HF<sub>rEF</sub> and HF<sub>pEF</sub>.<sup>34,35</sup> While most previous studies focused on ischemic LV function, our study, we demonstrated the associations between changes in NT-proBNP and changes in LA remodeling independent of LV structural and functional parameters including LV mass, volumes, and ejection fraction after excluding congestive heart failure (CHF), myocardial infarction, and AF. *In lieu*, a

recent study showed that LA reservoir and conduit function were associated with higher BNP levels and are early markers of age-related remodeling, independent of LV morphology and function using echocardiography.<sup>36</sup> Additionally, previous studies have suggested that LA myocardium could be more easily susceptible to remodeling compared with LV myocardium and thus could be an early marker of age-related remodeling independent of LV remodeling.<sup>36,37</sup> Our findings, hence, suggest that disrupting the pathological process leading to continuous rise in NT-proBNP may help prevent adverse LA remodeling in older adults.



**Figure 4.** The figure shows the longitudinal changes of LA volume, function, and strain with log NT-proBNP at baseline and 10 years. x axis: log NT-proBNP; y axis: LA parameters. (a) LA Maximum Volume Index; (b) LA Minimum Volume Index; (c) LA Active EF; (d) LA Passive EF; (e) LA Total EF; (f) LA Maximum Strain. The values represent the adjusted mean and standard errors. Each line represents the starting point at lowest value of log NT-proBNP and ending with highest value of log NT-proBNP for baseline and 10-year follow-up. Lines are shown for average change in LA CMR parameters with log NT-proBNP at baseline (blue) and at 10-year follow-up (red). Marginal means obtained after adjusting for demographics and traditional cardiovascular risk factors. Abbreviations: CMR, cardiac magnetic resonance; EF, emptying fraction; LA, left atrium.

There are several hypotheses to explain the link between NT-proBNP and its change with LA parameters. The first and more intuitive possibility is that individuals with elevated NT-proBNP levels are more likely to have both clinical and subclinical CVDs. Second, we propose that the longitudinal increase in NT-proBNP, an index of enhanced myocardial stress, could lead to progressive subclinical LA dysfunction that encompasses an adverse response to neuroendocrine hormonal overstimulation, and hypoxia mechanisms leading to myocardial dysfunction and progressive cardiomyocyte death.<sup>31,38,39</sup> The fact that increasing NT-proBNP levels remained significantly associated with LA remodeling despite adjustment for CVD risk factors such as diabetes, BMI, hypertension, and smoking indicate that LA remodeling accompanied by high NT-proBNP begin early in the course of progressive cardiac dysfunction. This suggests that early and aggressive control of risk factors associated with increase NT-proBNP levels documented in this and other studies could significantly alter progressive LA remodeling and dysfunction in older adults.

### Limitations

First, the threshold adopted (median log NT-proBNP) is specific for this population. Second, the NT-proBNP included analysis was only measured at 2 time points—at baseline and 10-year follow-up. The measure of NT-proBNP at these 2 time points can be confounded by endocrine disorders or renal function which could not be accounted for in this study. Third, based on 2 cross-sectional examinations performed 10 years apart, our study was not designed to account for physiologic intraindividual variability in NT-proBNP levels. Fourth, we used linear methods to measure LA volumes which may have underestimated the true volumes even though this method has been widely validated.<sup>40</sup> LA CMR-FT faces several challenges as opposed to ventricular deformation tracking that may limit the performance of the LA tracking. The LA myocardial wall is thinner than the ventricular myocardial wall and LA anatomy is more variable than ventricular anatomy. LA physiology is quite complex (reservoir function, conduit function, booster

**Table 2.** Cross-sectional association between log NT-proBNP and LA parameters at 10 years

	Univariate		Multivariable		R <sup>2</sup>
	Log NT-proBNP	Log NT-proBNP	Log NT-proBNP	Log NT-proBNP	
	≤4.2 pg/ml	>4.2 pg/ml	≤4.2 pg/ml	>4.2 pg/ml	
LA maximum volume index, ml/m <sup>2</sup>	1.23* (0.18, 2.28)	3.61* (2.86, 4.36)	0.56 (-0.42, 1.53)	3.36* (2.64, 4.09)	0.33
LA minimum volume index, ml/m <sup>2</sup>	-0.04 (-0.76, 0.68)	3.76* (3.24, 4.27)	0.06 (-0.64, 0.77)	3.30* (2.78, 3.82)	0.30
LA total emptying fraction, %	1.10* (0.05, 2.15)	-4.75* (-5.51, -4.00)	-0.12 (-1.12, 0.87)	-3.94* (-4.68, -3.20)	0.30
LA passive emptying fraction, %	0.04 (-0.76, 0.84)	-2.50* (-3.07, -1.92)	-0.21 (-0.92, 0.50)	-1.08* (-1.61, -0.55)	0.36
LA active emptying fraction, %	1.30* (0.18, 2.43)	-4.07* (-4.89, -3.26)	-0.07 (-1.19, 1.06)	-4.22* (-5.06, -3.39)	0.20
LA maximum strain, %	1.90* (0.53, 3.27)	-3.72* (-4.70, -2.74)	-0.06 (-1.36, 1.24)	-3.02* (-3.99, -2.06)	0.27

Coefficients and 95% confidence intervals (in brackets) for multivariable linear spline regression models to assess the cross-sectional associations at 10-year follow-up. The inflection point was chosen at log NT-proBNP value of 4.2 pg/ml. Multivariable model is adjusted for age, gender and race/ethnicity, systolic blood pressure, diastolic blood pressure, hypertension, antihypertensive medications, HDL cholesterol, LDL cholesterol, total cholesterol, lipid lowering medications, BMI, diabetes mellitus, smoking status, LV ejection fraction, LV mass, and mass-volume ratio. Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LA, left atrium; LDL, low-density lipoprotein; LV, left ventricle. \*If P value <0.05.

**Table 3.** Longitudinal association of log NT-proBNP with LA parameters over 10 years

		Univariate				Multivariable			R <sup>2</sup>
		Low-Low	Low-High	High-Low	High-High	Low-High	High-Low	High-High	
Δ LA maximum volume index, ml/m <sup>2</sup>	REF	3.37 (1.94, 4.79)*	-0.09 (-1.52, 1.34)	3.32 (2.28, 4.35)*	1.73 (0.38, 3.09)*	0.34 (-1.01, 1.69)	3.10 (1.98, 4.20)*	0.34	
Δ LA minimum volume index, ml/m <sup>2</sup>	REF	2.23 (1.23, 3.23)*	0.05 (-0.95, 1.06)	2.79 (2.07, 3.52)*	1.24 (0.25, 2.23)*	0.40 (-0.59, 1.39)	2.70 (1.89, 3.51)*	0.27	
Δ LA total emptying fraction, %	REF	-2.38 (-3.87, 0.89)*	-0.47 (-1.96, 1.02)	-3.07 (-4.14, -1.99)*	-1.81 (-3.25, -0.37)*	-0.97 (-2.40, 0.47)	-3.29 (-4.46, -2.11)*	0.47	
Δ LA passive emptying fraction, %	REF	-2.30 (-3.48, -1.11)*	-0.68 (-1.90, 0.54)	-2.30 (-3.16, -1.42)*	-1.20 (-2.28, -0.12)*	-0.55 (-1.65, 0.55)	-0.91 (-1.80, -0.02)*	0.60	
Δ LA active emptying fraction, %	REF	-2.13 (-3.81, -0.45)*	-0.36 (-2.08, 1.37)	-2.55 (-3.78, -1.31)*	-2.15 (-3.84, -0.46)*	-1.11 (-2.83, 0.62)	-4.15 (-5.55, -2.76)*	0.52	
Δ LA maximum strain, %	REF	-1.80 (-4.13, 0.54)	-2.91 (-5.25, -0.57)*	-1.69 (-3.37, -0.01)*	-1.78 (-3.68, 0.12)	-1.72 (-2.61, 0.17)	-2.26 (-3.80, -0.72)*	0.43	

Coefficients and 95% confidence intervals (in brackets) for multivariable regression models to assess the change in associations with log NT-proBNP with changes in LA parameters over 10 years. Multivariable model adjusted for age, sex, race, systolic blood pressure, diastolic blood pressure, hypertension, antihypertensive medications, HDL cholesterol, LDL cholesterol, total cholesterol, lipid lowering medications, BMI, diabetes mellitus, smoking status, LV ejection fraction, LV mass, and mass-volume ratio. Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LA, left atrium; LDL, low-density lipoprotein; LV, left ventricle. \*If P value <0.05.

pump function). The presence of pulmonary veins and LA appendage can compromise tracking quality. Fifth, with this study design, we may have introduced survival bias as systematically healthier participants were more likely to return for a follow-up CMR examination.

This longitudinal analysis performed in a multiethnic, middle, to older age cohort demonstrates that elevated NT-proBNP at baseline and at the 10-year follow-up examination is strongly associated with adverse anatomical remodeling and contractile dysfunction of the LA over



10 years of follow-up. Future studies should expand on our findings to better understand the pathophysiology of intracardiac stress induced LA remodeling.

## ACKNOWLEDGMENTS

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org>. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

## FUNDING

This research was supported by contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences (NCATS). Additional support was provided by grant R01 HL 127659 from NHLBI.

## DISCLOSURE

The authors declared no conflict of interest.

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