Age-Related Changes in Echocardiographic Measurements 
Association With Variation in the Estrogen Receptor-α Gene


Abstract—Left ventricular (LV) mass and other LV measures have been shown to be heritable. In this study we hypothesized that functional variation in the gene coding for estrogen receptor-α (ESR1), known for mediating the effect of estrogens on myocardium, is associated with age-related changes in LV structure. Four genetic markers (ESR1 TA repeat; rs2077647, or +30T>C; rs2234693, or PvuII; and rs9340799, or XbaI) were genotyped in 847 unrelated individuals (488 women) from the Framingham Offspring Study, who attended 2 examination cycles 16 years apart (mean ages at first examination: 43 ± 9 years; at follow-up: 59 ± 9 years). ANCOVA was used to assess the association of polymorphisms and their haplotypes with cross-sectional measurements and longitudinal changes in LV mass, wall thickness, end-diastolic and end-systolic internal diameter, and fractional shortening after adjustment for factors known to influence these variables. Changes over time were detected for all of the LV measurements (P ranging from <0.0001 to 0.02), except for fractional shortening in men. The SS genotype of the ESR1 TA repeat polymorphism in the promoter region was associated with longitudinal changes in LV mass and LV wall thickness (P ranging from 0.0006 to 0.01). Moreover, the TA[L]+30[C]+PvuII[T]+XbaI[A] haplotype (frequency: 47.5%) was associated with greater LV changes as compared with the TA[L]+30[C]+PvuII[C]+XbaI[G] haplotype (frequency: 31.8%). Our results are consistent with the hypothesis that common ESR1 polymorphisms are significantly associated with age-related changes in LV structure. Understanding the mechanisms predisposing to unfavorable LV remodeling of the heart with advancing age may aid in the discovery of new therapeutic targets for the prevention of heart failure. (Hypertension. 2007;49:1000-1006.)

Key Words: echocardiography ▪ left ventricular remodeling ▪ estrogen receptor-α ▪ restriction fragment length ▪ single nucleotide polymorphism

By the year 2035, ≈1 in 4 individuals in the United States will be ≥65 years of age.1 Increasing age is associated with an exponential rise in cardiovascular morbidity and mortality, with heart failure (HF) being the most common cause of hospitalization in elderly individuals.² Over the past 2 decades, significant progress has been made in characterizing the effects of healthy aging on multiple aspects of cardiovascular structure and function (reviewed in References 1 and 3). Cardiac morphological changes during aging include increasing left ventricular (LV) wall thickening, which can impair cardiac relaxation. In the absence of cardiac events, systolic function remains largely preserved. Although these aging changes are adaptive and interpreted as a “normal” response to a stiffer and less compliant arterial tree, the role of intrinsic factors in remodeling are unclear. The superimposition of additional age-related risk factors, such as hypertension or atherosclerosis, may render the heart more susceptible to overt failure.

Although extensive evidence supports the existence of environmental factors affecting longitudinal changes in cardiac structure, genetic contributions to myocardial aging remain largely unknown. Indication that genetic factors influence cardiac structure and function comes mainly from cross-sectional studies. The proportion of total variability in LV mass (LVM) explained by genetic factors, or heritability, has been estimated to be ≈17% to 69% in humans.⁴,⁵ Recent data on other echocardiographic measurements have shown heritability estimates ranging between 9% and 33%.⁶ However, the role of genetics in age-related changes in myocardial LV wall thickness (LVWT) and dimensions has not been defined. Several studies have estimated the contribution of genetic effects to intraindividual variation over time in other cardiovascular risk factors, including changes in adiposity, cholesterol levels,⁷ cholesterol levels,⁸ and blood pressure,⁹ whereas, to our knowledge, no data on myocardial aging are available.

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Cardiac remodeling after myocardial infarction,\textsuperscript{10} HF progression,\textsuperscript{11,12} and LV hypertrophy\textsuperscript{13} are significantly different between men and women. In particular, age-associated increases in LVM and LVWT are seen more commonly in women than in men.\textsuperscript{14} Moreover, LV hypertrophy and HF with preserved LV function are more common in women after menopause. Estrogen regulates gene expression by binding to estrogen receptors\textsuperscript{15} (gene designation \textit{ESR1}) and \textit{ESR2}; reviewed in Reference 15). Estrogen receptors are expressed in cardiomyocytes and fibroblasts.\textsuperscript{16} Genetic variation in \textit{ESR1} has been shown to be associated with phenotypic variation in LVM cross-sectionally.\textsuperscript{17} Given previous studies that have analyzed the association of genetic differences with LVM at a single time point, or within a short follow-up, and considering the important role of estrogen receptor-\textalpha{} in mediating the effect of estrogens on the heart, we hypothesized that age-related LV remodeling in healthy men and women is associated with variation in \textit{ESR1}.

To test this hypothesis, we selected the single nucleotide polymorphisms (SNPs) that were of most relevance to cardiovascular disease based on previous literature, in particular, those that were part of a haplotype block studied intensively.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Location of \textit{ESR1} polymorphisms relative to exons 1 and 2 and their quantitative characteristics. Numbered boxes indicate exons; solid black lines indicate introns; vertical arrows indicate SNPs; (TA)\textsubscript{n} indicates promoter region polymorphism; rs2077647, or 30T>C, is a coding synonymous SNP; and rs2234693, or \textit{PvuII}, and rs9340799, or \textit{XbaI}, are intronic SNPs.}
\end{figure}

\begin{table}
\centering
\begin{tabular}{lcccc}
\hline
\textbf{Genetic marker} & \textbf{TA repeat} & \textbf{+30T>C} & \textbf{PvuII} & \textbf{XbaI} & \textbf{Frequency} \\
\hline
\textbf{D' for LD} & & & & & \\
+30T>C & 0.87 & & & & \\
\textit{PvuII} & 0.84 & 0.81 & & & \\
\textit{XbaI} & 0.88 & 0.88 & 0.98 & - & \\
\textbf{Common haplotypes} & & & & & \\
Haplotype 1 & \textit{L} & \textit{C} & \textit{C} & \textit{A} & 6.8\% \\
Haplotype 2 & \textit{L} & \textit{C} & \textit{C} & \textit{G} & 31.8\% \\
Haplotype 15 & \textit{S} & \textit{T} & \textit{T} & \textit{A} & 47.5\% \\
\hline
\end{tabular}
\caption{Location of \textit{ESR1} polymorphisms relative to exons 1 and 2 and their quantitative characteristics. Numbered boxes indicate exons; solid black lines indicate introns; vertical arrows indicate SNPs; (TA)\textsubscript{n} indicates promoter region polymorphism; rs2077647, or 30T>C, is a coding synonymous SNP; and rs2234693, or \textit{PvuII}, and rs9340799, or \textit{XbaI}, are intronic SNPs.}
\end{table}

\begin{table}
\centering
\begin{tabular}{lcccc}
\hline
\textbf{Study Characteristics} & \textbf{Examination Cycle 2*} & \textbf{Examination Cycle 6*} & \textbf{P of Change Between Cycles†} \\
& \textbf{Men (N=359)} & \textbf{Women (N=488)} & \textbf{Men (N=359)} & \textbf{Women (N=488)} & \textbf{Men} & \textbf{Women} \\
\hline
\textbf{Age, y} & 42±9 & 43±9 & 58±9 & 59±9 & \ldots & \ldots \\
\textbf{BMI, kg/m²} & 26.1±3.2 & 24.1±4.2 & 28.0±4.1 & 26.9±5.1 & \textless 0.0001 & \textless 0.0001 \\
\textbf{Diabetes mellitus, %} & 6 & 2 & 13 & 8 & 0.004 & 0.0001 \\
\textbf{Hypertension, %} & 22 & 15 & 43 & 41 & \textless 0.0001 & \textless 0.0001 \\
\textbf{Hypertension treatment, %} & 9 & 7 & 26 & 26 & \textless 0.0001 & 0.004 \\
\textbf{Current smokers, %} & 30 & 31 & 16 & 16 & \textless 0.0001 & \textless 0.0001 \\
\textbf{Postmenopausal women, %} & \ldots & 33 & \ldots & 76 & \textless 0.0001 & \textless 0.0001 \\
\textbf{Systolic blood pressure, mm Hg} & 123±14 & 118±17 & 129.2±17.8 & 128.8±19.7 & \textless 0.0001 & \textless 0.0001 \\
\textbf{Diastolic blood pressure, mm Hg} & 80±9 & 75±10 & 77.0±9.0 & 74.4±9.1 & \textless 0.0001 & 0.09 \\
\textbf{LVM, g‡} & 185.0±2.1 & 125.3±4.8 & 192.4±1.2 & 142.3±6.3 & 0.0002 & \textless 0.0001 \\
\textbf{LVM/ht²‡} & 40.4±1.5 & 34.6±2.8 & 42.0±1.2 & 39.4±3.4 & 0.0002 & \textless 0.0001 \\
\textbf{LVWT, cm‡} & 1.91±0.05 & 1.62±0.07 & 2.02±0.03 & 1.83±0.07 & \textless 0.0001 & \textless 0.0001 \\
\textbf{RWT, ratio‡} & 0.37±0.01 & 0.35±0.02 & 0.41±0.01 & 0.40±0.02 & \textless 0.0001 & \textless 0.0001 \\
\textbf{LVDD, cm‡} & 5.12±0.05 & 4.62±0.05 & 5.02±0.03 & 4.55±0.01 & \textless 0.0001 & \textless 0.0001 \\
\textbf{LVDS, cm‡} & 3.30±0.05 & 2.88±0.05 & 3.24±0.05 & 2.81±0.02 & 0.02 & \textless 0.0001 \\
\textbf{FS, ratio‡} & 0.357±0.003 & 0.377±0.005 & 0.356±0.007 & 0.382±0.004 & 0.70 & 0.02 \\
\hline
\end{tabular}
\caption{Participant Characteristics at Examination Cycles 2 and 6 (16 Years Apart)}
\begin{footnotesize}
\textsuperscript{a}Study characteristics are mean±SD for continuous measures, % for categorical variables.

\textsuperscript{b}Calculated using Mantel–Haenszel \textit{\chi}² test for change for categorical variables, \textit{t}-test otherwise.

\textsuperscript{c}Age adjusted.
\end{footnotesize}
\end{table}
in relation to blood pressure.\textsuperscript{18,19} Here, we present the association of LV changes over a 16-year period with 4 members of \textit{ESR1} that include a thymine–adenine (TA) dinucleotide repeat polymorphism in the promoter region, a synonymous coding region SNP in exon 1 (\textit{ESR1} 30T\textr/H11022 C), and 2 SNPs in the first intron (\textit{ESR1} Pvu\textr and \textit{Xba}I).

### Methods

#### Study Cohort

The sample was derived from the longitudinal community-based Framingham Heart Study offspring cohort of unrelated individuals of European descent and is described elsewhere.\textsuperscript{20} Participants included in the present investigation attended examination cycles 2 and 6 (1979–1982 and 1995–1998) and underwent routine medical history, physical examination, and echocardiography. Participants were excluded if they had a history of myocardial infarction, HF, or significant valvular disease; had no \textit{ESR1} TA repeat data; or had unavailable echocardiograms at either examination. The total sample contained 847 individuals.

All of the subjects gave written informed consent. The Framingham Heart Study protocol is approved by the Boston University Medical Center Institutional Review Board.

#### Echocardiography

Measurements were performed using 2D-guided M-mode echocardiography in accordance with American Society of Echocardiography recommendations.\textsuperscript{21} For examination 2, M-mode measurements were made with hand-held calipers off printed strip charts.\textsuperscript{22} For examination 6, echocardiographic measurements were made with commercially available software (Tomtec) averaging 3 digitized beats. The measurements obtained at examinations 2 and 6 included LVWT [posterior wall thickness + ventricular septal thickness], LV internal diameter end diastole (LVIDD), LV internal diameter end systole (LVIDS), LVMI indexed to height (LVMI/ht\textsuperscript{2.7}),\textsuperscript{23,24} and fractional shortening (FS; relative wall thickness). Changes in LVM, LVMI/ht\textsuperscript{2.7}, LVWT, relative wall thickness, LVIDD, LVIDS, and FS were presented as subtracted values between the examination cycles 6 and 2, as well as by percent changes.

#### SNP Genotyping

Participants’ genomic DNA was extracted from peripheral blood leukocytes using standard methods. Four polymorphic markers at the \textit{ESR1} gene were genotyped for this study (Figure 1). The dinucleotide TA repeat in the 5' promoter region at 1174 bp upstream of exon 1 was amplified by PCR, as described previously.\textsuperscript{20} The 3 SNPs: c.30T\textr>C (rs2077647; a synonymous substitution, Ser\textarrow{}Ser); intron 1 c.454 to 397C > T (also known as PvuII, rs2234693), and intron

![Figure 2. Cross-sectional echocardiographic measurements at the examination cycles 2 and 6. Means and SEs are presented after adjustment for age, BMI, systolic and diastolic blood pressure, antihypertension treatment, and diabetes status. A and B, LVM in men and women, respectively (overall P for difference in men and women combined between SS and LS and LL at examination 2=0.11, at examination 6=0.03). C and D, LVWT (P=0.17 and 0.07). E and F, LVIDD (P=0.09 and 0.32). G and H, LVIDS (P=0.001 and 0.99).](http://hyper.ahajournals.org/cover-image)
c.454 to 351A (also known as XbaI, rs9340799) were genotyped as described previously.26

Statistical Analysis
Observed genotype frequencies were compared with those expected under Hardy–Weinberg equilibrium using a χ² test. Given multiple alleles observed for the ESR1 microsatellite (number of the TA repeats ranged between 9 and 31; median: 18), and their bimodal distribution, the genotype for this polymorphism was coded as LL if both alleles contained at least the median number of repeats (≥18 repeats), SS if both alleles were “short” (<18), and LS if 1 allele had ≥18 and the other allele had <18 repeats.

Multivariable ANCOVA was performed to detect associations of the cross-sectional values and changes in quantitative echocardiography measures over time with ESR1 TA genotypes. Repeated-measures ANCOVA was used to examine the rate of change in LV sizes associated with ESR1 TA genotypes exploring effects on change as interaction term. Lewontin’s D27 was calculated to assess the linkage disequilibrium between the ESR1 TA repeat and the 3 SNPs of interest. Haplotype analysis including all 4 of the genotyped markers was carried out.

All of the analyses were performed using SAS/STAT and SAS/Genetics (including the proc haplotype procedure; SAS 9.1, SAS Institute, Inc). A 2-sided P<0.05 was considered statistically significant. An expanded Methods section is available online at http://hyper.ahajournals.org.

Results
The characteristics of the 359 male and 488 female unrelated Framingham Heart Study Offspring participants from 2 examination cycles 16 years apart are shown in Table 1. Both men and women had significantly higher body mass index (BMI), systolic blood pressure, and more treatment for hypertension and diabetes at examination cycle 6; however, diastolic blood pressure was lower in men, and fewer men and women smoked. For both sexes, the LVM and LVWT were significantly greater at the later examination. Significant changes in echocardiographic measures over time were detected in both men and women in all of the tested features, except for FS in men (Table 1).

Significant sex-specific differences in longitudinal changes for all of the studied variables were detected (Table 1). Women had a greater increase in BMI and systolic blood pressure than men (12.0% versus 7.3%, P<0.0001; 9.2% versus 4.7%, P=0.01, respectively, for sex difference). Women showed a greater increase compared with their male counterparts in LVM (13.8% increase versus 4.4%; P<0.0001) and LVWT (12.3% increase versus 5.8%; P=0.0008). LV diameters were smaller for both sexes at examination cycle 6.

The genotype frequencies for the 4 polymorphisms under study (Figure 1) conformed to those expected under the Hardy–Weinberg equilibrium. All 4 of the genetic markers were in strong linkage disequilibrium. Given a potential functional importance of the ESR1 TA repeat because of its location in the promoter region of the gene, and its previous
association with LVM, we chose to study the association between this variant and changes in cardiac structure with aging first.

No significant differences were observed between the 3 ESR1 TA genotype groups (SS, LS, and LL) in age, sex, hypertension, and incidence of diabetes (data not shown). In multivariable-adjusted cross-sectional analysis, ESR1 TA SS carriers, compared with individuals with LL and LS, had lower LVM, LVIDD, and LVIDS at examination 2 but higher LVM and LVWT 16 years later (Figure 2; Table S1, available online at http://hyper.ahajournals.org). Also, carriers of both short alleles (SS) were shown to have a greater increase in LVM and LVWT than carriers of other genotypes (general and recessive models) in both males and females in adjusted (Table 2) and unadjusted analyses (Table S2). Similar trend was observed for another SNP under study, rs2234693, or PvuII (data not shown).

Secondary Analyses

The reported association between ESR1 TA genotypes and changes in LVM persisted if the study sample was stratified by the change in health status with regard to diabetes and menopause in women. Individuals with diabetes at both examination cycles (N=34) had a more marked mean increase in LVM, LVIDS, and LVIDD (0.08 cm; 0.08 cm; and 0.04 cm; P<0.05) change across previously published studies. LVM, an important indicator of ventricular remodeling, in cross-sectional studies has been associated with advancing age in some28,29 but not all studies.30–32 Given considerable heritability estimates reported for LVM and other measures of LV structure and function, it is reasonable to suggest that the discrepancies between studies may be because of genetic factors, in addition to study design.

The ESR1 TA polymorphism is located in the regulatory region of the ESR1 gene, ≈1174 bp upstream of the first proposed transcribed site in exon 1,33 between promoters B and C,34 and is more likely to drive this effect than other ESR1 SNPs under study. The long allele has been associated with increased cardiovascular risk factor profile in previous reports. Namely, compared with short allele carriers, the TA L polymorphism has been linked with more severely diseased coronary arteries35,36 and a higher risk of myocardial infarction.35 At baseline (examination cycle 2), our results are consistent with a previous report that ≈1 long TA allele is associated with higher LVM.17 However, in our study, TA SS carriers demonstrated substantial LV remodeling consistent with a pattern of age-associated concentric hypertrophy. Intriguingly, this association maintained after the adjustment for longitudinal changes in other risk factors, such as BMI, systolic and diastolic blood pressure, occurrence of diabetes, hypertension, or menopause in women. For example, in individuals with diabetes mellitus at both exams, there was, on average, a 27.3% difference in the change in LVM

### Table 2. Mean 16-Year Changes in the Echocardiographic Measurements by ESR1 TA Repeat

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Men Mean Change±SE (N)</th>
<th>Women Mean Change±SE (N)</th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVM, g</td>
<td>15.4±2.0</td>
<td>5.4±1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM/hF²</td>
<td>3.6±0.1</td>
<td>1.1±0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVWT, cm</td>
<td>0.15±0.02</td>
<td>0.09±0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RWT, ratio</td>
<td>0.04±0.001</td>
<td>0.03±0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVDD, cm</td>
<td>-0.05±0.02</td>
<td>-0.09±0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVDS, cm</td>
<td>-0.01±0.01</td>
<td>-0.08±0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FS, ratio</td>
<td>-0.006±0.002</td>
<td>0.004±0.001</td>
<td></td>
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</tr>
</tbody>
</table>

RWT indicates relative wall thickness.

*predicted means after adjustment for sex, age, echocardiographic measurement at examination cycle 2; BMI at examination cycle 2 (weight for LVM/hF²); changes in systolic and diastolic blood pressure, BMI (weight for LVM/hF²), and diabetes status between the examination cycles; and current antihypertensive treatment.

†Comparison between ESR1 TA SS carriers and LL and LS carriers. Recessive model is not shown if p for the genotype effect in general model was >0.05. For trait definition see Methods section.

### Discussion

In this study we report significant longitudinal changes in LV structure measured by M-mode echocardiography in ambulatory community-based individuals from the Framingham Heart Study over a period of 16 years. The changes include an increase in LVM and LVWT and a reduction in LV diameter at end systole and end diastole. However, the nature and magnitude of changes in LV structure has not been consistent across previously published studies. LVM, an important indicator of ventricular remodeling, in cross-sectional studies has been associated with advancing age in some28,29 but not all studies.30–32 Given considerable heritability estimates reported for LVM and other measures of LV structure and function, it is reasonable to suggest that the discrepancies between studies may be because of genetic factors, in addition to study design.
between carriers of 2 short alleles (SS) versus no short alleles (LL), suggesting a significant disadvantage in developing LV hypertrophy. A similar trend was observed in women regardless of the change in their menopausal status and/or hormone replacement therapy over a period of 16 years. The fact that TA S allele carriers had greater LVM 16 years later, whereas the L carriers showed the least change, suggests that ESR1 TA SS genotype is associated with greater age-dependent LV remodeling.

Pollak et al16 have reported association between the ESR1 TA S allele and narrowed coronary segments in older individuals, while showing reverse relation in younger individuals. Significant associations with numerous cardiovascular outcomes have been reported for other ESR1 SNPs that are in strong linkage disequilibrium with the ESR1 TA repeat polymorphism. The common ESR1 PvuII T allele that is linked with the ESR1 TA S allele has been shown to interact with cigarette smoking, resulting in significantly higher concentrations of small low-density lipoprotein particles among female smokers.37 We observed that the TA[S]−+30[T]–PvuII[T]–XbaII[A] haplotype, although strongly linked with LV remodeling, did not improve the explained variance over the ESR1-TA polymorphism.

To our knowledge, this is the first report of a candidate gene approach to assess genetic susceptibility to myocardial aging. Previously, we found that the association between ESR1 SNPs and longitudinal blood pressure was stronger at older compared with younger ages.19 The previous blood pressure data and the associations that we report here support the hypothesis that genetic effects have age-dependent penetrance resulting in a difference of cross-sectional relations at 2 different ages. Despite the adjustment for age, our cross-sectional data suggest that there must be an age when the ESR1 TA genotype and LV relations are flat (Figure 2).

It has been suggested that changes in cardiovascular risk factors with advancing age reflect gene–environmental interactions.38 Also, reductions in the cellular RNA concentrations, the rate of protein synthesis, and changes in gene expression have been shown to occur with aging.38 Estrogen receptor–dependent changes may occur indirectly through their effect on lipoprotein metabolism and blood vessel stiffness or directly by modulating gene expression in cardiac muscle and fibroblast cells. The TA repeat is located in the regulatory region of ESR1; therefore, modified ESR1 may alter expression of a number of genes, including endothelial NO synthase, prostacyclin synthase, inducible NO synthase, endothe-lin 1, progesterone receptor, and others.15

HF with a normal ejection fraction is more common with increasing age, particularly in women.39 Typically, persons with HF and normal LV function have thickened ventricular walls and smaller cavity dimensions. These changes render the ventricle less compliant, which, in concert with increased vascular stiffness, can contribute importantly to HF. The greater increase of LVM and LVWT found in TA[S]/PvuII[T] haplotype carriers over 16 years suggests that carriers of this haplotype may have a greater susceptibility to HF with preserved cardiac function.

**Study Limitations**

This study was strengthened by the long period of time between echocardiograms, community-based setting, and comprehensive measurement of cardiac function. However, because of the lack of persons of diverse ethnic backgrounds, the generalizability to other ethnicities is unknown. We acknowledge that, to assess the genetic contribution to LV remodeling, one must account for environmental and extra-cardiac influences. Although we adjusted for numerous risk factors, we cannot exclude residual confounding by other factors not included in the multivariable models. To limit the artifact of multiple testing, we began our study with the TA repeat polymorphism that has been linked previously with LV remodeling and then confirmed our findings using haplotype analysis. In addition, because of advances in echocardiography technology, the equipment evolved from largely M-mode examination to 2D guided M-mode at the later examination. Although no data directly comparing the 2 techniques are available, improvements in technology potentially reduced both measurement error and random misclassification of LV measurements at examination 6, which would introduce a conservative bias. Moreover, the measurements could not have been biased by genotype, which was the primary exposure examined in this study. We also acknowledge the possibility of depletion of susceptibilities if carriers of the TA LL genotype who had the highest LVM at examination 2 died because of cardiovascular disease over the 16-year period and never came back to get DNA at examination cycle 6. Because we did not account for specific classes of antihypertensive medications, such as diuretics, although unlikely, it is possible that more individuals with the TA LL genotype were nonrandomly on diuretics at the follow-up visit. However, in an observational cohort, confounding by medications is inevitable.

**Conclusions**

The findings of this study are consistent with the hypothesis that longitudinal changes in LVM, as assessed by M-mode echocardiography, differ not only by sex, age, and body size but also by a regulatory region polymorphism in ESR1. Carriers of the common ESR1 TA[SS] genotype demonstrated an increase in LVM and LVWT. These findings will need to be replicated in other cohorts.

**Perspectives**

Quantitative data on age-related changes in myocardial structure and function in the absence of major cardiovascular disease are essential to identify the specific characteristics of the aging process in the heart. Knowledge that a specific carrier status may predispose to significant disadvantage in the development of cardiovascular risk factors may lead to targeted intervention strategies to reduce age-associated risk among genetically susceptible individuals.

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Disclosures
None.

References
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