Association between arterial stiffness and variations in estrogen-related genes

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Association between Arterial Stiffness and Variations in Estrogen-Related Genes

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Abstract

Increased arterial stiffness and wave reflection have been identified as cardiovascular disease risk factors. In light of significant sex differences and the moderate heritability of vascular function measures, we hypothesized that variation in the genes coding for estrogen receptors alpha (*ESR1*) and beta (*ESR2*) and aromatase (*CYP19A1*) is associated with aortic stiffness and pressure wave reflection as measured by noninvasive arterial tonometry. 1261 unrelated Framingham Offspring Study participants who attended the 7th examination cycle (mean age 62±10 years, 52% women) and had arterial tonometry and genotyping data were included in the study. ANCOVA was used to assess the association of polymorphisms with forward wave amplitude, augmented pressure, augmentation index, carotid-femoral pulse wave velocity, and mean arterial pressure with adjustment for potential confounders. In the sex-pooled analysis, those homozygous for the minor allele at any of four *ESR1* variants that were in strong linkage disequilibrium ($(TA)_n$, rs2077647, rs2234693 and rs9340799) had on average 18% higher augmented pressure and 16% greater augmentation index compared to carriers of one or two major alleles (p=0.0002–0.01). A similar magnitude of association was detected in those homozygous for the common allele at two *ESR2* SNPs (p=0.007–0.02). Our results are consistent with the hypothesis that variation in *ESR1* and *ESR2*, but not *CYP19A1*, is associated with increased wave reflection, which may contribute to previously demonstrated associations between these variants and adverse clinical events. Our findings will need to be replicated in additional cohorts.

Keywords

arterial stiffness; tonometry; estrogen receptor; polymorphism

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Introduction

Increased arterial stiffness and wave reflection play important roles in cardiovascular physiology. Aortic stiffness, estimated by measurement of carotid-femoral pulse wave velocity (CFPWV), has been identified as a cardiovascular disease (CVD) risk factor in 3 large, independent, community-based cohorts.[1–3] Some studies show that CFPWV and pulse pressure are lower in women than men prior to 60 years of age, but increase rapidly in women thereafter, resulting in comparable CFPWV and higher pulse pressure in older women. Similarly, the incidence of CVD is low in premenopausal women as compared to their male peers, but increases sharply after menopause.[4] In light of the associations between aortic stiffness and events, the disproportionate increase in aortic stiffness in older women may contribute to the higher incidence of CVD in women after the menopause. In contrast, measures of wave reflection, such as augmented pressure or augmentation index, are increased in women as compared to men at all ages, with a maximal difference just prior to menopause and a trend for values in women and men to converge after 60 years of age. Increased wave reflection in women has been attributed to shorter stature, but differences persist after adjusting for height[5] and when women and men are matched for height,[6] suggesting intrinsic sex differences in structure or function of the arterial system.

Estrogen is known to play an important role in endothelial function in both men and women. Premature ovarian failure has been shown to be associated with significant endothelial dysfunction.[7, 8] In postmenopausal women, estrogen therapy has been shown to enhance endothelium-dependent vasodilation and reduce arterial stiffness in some studies.[9, 10]

Estrogen is known to have short and long-term effects on the vasculature (reviewed in [11]). The rapid vasodilatory effects of estrogen are produced by estrogen-stimulated increases in endothelial cell nitric oxide (NO) synthase activity which regulates vascular tone,[12] suppresses smooth muscle proliferation[13] and inhibits platelet adhesion and aggregation[14]. Longer-term effects are mediated through estrogen-activated transcription factors, estrogen receptor (ER) α, (encoded by the *ESR1* gene) and ERβ (encoded by the *ESR2* gene), which are found in vascular endothelial and smooth muscle cells in both men and women.[15, 16]

Recently, genetic variations of the major proteins involved in steroid hormone conversion and receptor function have been shown to be associated with the increased risk of myocardial infarction[17] and coronary artery disease,[18–20] elevated blood pressure,[21] altered lipoprotein particles concentrations,[22, 23] adiposity, [24] and left ventricular mass,[25–27] attracting increased attention to genes implicated in estrogen metabolism. Also, variation in the gene (*CYP19A1*) encoding the enzyme aromatase, which catalyzes the conversions of testosterone to estradiol and defines the estradiol/testosterone ratio, has been found to be associated with blood pressure[21] and abdominal obesity.[28] However, despite these and other studies, potential molecular mechanisms linking estrogen-related genes with CVD risk remain incompletely understood.

Given significant sex differences in vascular stiffness and moderate heritability of key arterial pressure waveform phenotypes,[29, 30] we hypothesized that variation in *ESR1*, *ESR2*, and *CYP19A1* are associated with aortic stiffness, pressure wave reflection and vasodilator function as measured by noninvasive tonometry and brachial ultrasound in the Framingham Offspring Study.

Material and Methods

Study cohort

The study sample was derived from unrelated participants in the longitudinal community-based Framingham Offspring cohort of European descent and is described in detail elsewhere.[31] Eligible participants consented to genetic analysis and attended the 7th examination cycle (1998–2001), during which they underwent routine medical history, physical examination, tonometry measures and brachial ultrasound. Unrelated participants (N=3539) were selected based on family structure alone without regard to any phenotypic traits and were excluded from the present analysis if they did not have tonometry measures or brachial ultrasound data (N=1508) or had missing genotype data (N=770). The final sample included 1261 individuals: 604 men and 657 women.

All participants gave written informed consent including consent for DNA analyses. The FHS protocol was approved by the Boston University Medical Center Institutional Review Board.

Noninvasive Tonometry Measures

Participants were studied in the supine position after several minutes of rest as described previously.[5] Arterial tonometry, with simultaneous ECG, was obtained from the brachial, radial, femoral, and carotid arteries. Transit distances were assessed by body surface measurements from the suprasternal notch to each pulse recording site. Tonometry waveforms were analyzed as described previously.[5]. CFPWV was calculated from tonometry waveforms and body surface measurements. The CFPWV distance was measured with a fiberglass tape measure. The central forward wave amplitude was defined as the difference between pressure at the waveform foot and pressure at the first systolic inflection point or peak of the carotid pressure waveform. Augmented pressure was defined as the difference between central systolic pressure and pressure at the forward wave peak. Augmentation index (AI) was calculated as previously described.[32] Systolic ejection period was defined as the time interval from the carotid pressure waveform foot to the dicrotic notch.

Brachial Artery Measures

Brachial artery diameter and mean flow velocity at baseline and 1-minute after reactive hyperemia, induced by 5-mintue forearm cuff occlusion, were assessed as previously described,[33, 34] by using a Toshiba SSH-140A ultrasound system and commercially available software (Brachial Tools, version 3.2.3). Mean Doppler flow velocity was analyzed using a semi-automated signal averaging approach (Cardiovascular Engineering, Inc.).

Single Nucleotide Polymorphism (SNP) Selection and Genotyping

To investigate pathophysiologic connection between arterial stiffness and cardiovascular disease, we selected *a priori* SNPs in *ESR1*, *ESR2*, and *CYP19A1* found to be associated with cardiovascular risk phenotypes in the Framingham Offspring cohort by our previous studies.[17, 21–24, 26, 27] Genomic DNA was extracted from peripheral blood leukocytes using standard methods. Genotyping for the individual SNPs in *ESR1* (*rs2077647*, *rs2234693*, *rs9340799*, and *rs1801132*), *ESR2* (*rs944460*, *rs1256059*, *rs1256034*, and *rs1256031*), and *CYP19A1* (*rs700518*, *rs726547*), was performed as described previously.[21, 35] *ESR1* $(TA)_n$, *ESR1* $(CA)_n$, *ESR2* $(CA)_n$, and *CYP19A1* $(TTTA)_n$ repeat polymorphisms were genotyped using restriction fragment length analyses.[36]

Statistical Analysis

Observed genotype frequencies were compared with those expected under Hardy–Weinberg equilibrium (HWE) using a χ^2 test. Given multiple alleles observed for the repeat

polymorphisms and their bimodal distribution, the genotype carrier status for each variant was coded using the median number of repeat sequence base pairs as a cutoff. Specifically, genotype *LL* was assigned if both alleles contained at least the median number of base pairs (≥176 for *ESR1 (TA)*$_n$; ≥277 for *ESR1 (CA)*$_n$; ≥162 for *ESR2 (CA)*$_n$, and ≥298 for *CYP19A1 (TTTA)*$_n$); *SS* was assigned if both alleles were 'short' (<176 for *ESR1 (TA)*$_n$; <277 for *ESR1 (CA)*$_n$; <162 for *ESR2 (CA)*$_n$, and <298 for *CYP19A1 (TTTA)*$_n$), and *LS* if one allele was 'long' and another one was 'short'.

We used a general model of inheritance and sex-pooled analyses to assess relations between estrogen pathway genotypes and vascular phenotypes. Multivariable linear regression analyses were carried out to assess genetic associations with forward wave amplitude, augmented pressure, AI, and CFPWV. All analyses were adjusted for age, sex, heart rate, body mass index (or weight and height for augmented pressure and AI), mean arterial pressure (for CFPWV), total/high-density lipoprotein cholesterol ratio, triglycerides, fasting glucose, diabetes, smoking within past 6 hours, prevalent cardiovascular disease, hormone replacement therapy (in women), hypertension medication, and lipid-lowering medication. To account for sex-specific differences previously reported in relations between estrogen pathway genotypes and cardiovascular phenotypes in the Framingham sample,[17, 22, 23, 27] interactions between sex and genotype were assessed by the addition of a multiplicative term to the fully adjusted model. Forearm vascular resistance was skewed and was natural log transformed to normalize the variance.

Pairwise linkage disequilibrium (LD) was evaluated by Lewontin's D′.[37] Haplotypes were inferred by using the expectation maximization algorithm.[38] To account for allelic interaction, haplotypes were used as predictors in the regression models along with the above covariates.

The nominal threshold for statistical significance of all analyses was set at 0.05 and was not adjusted for multiple testing. All analyses were performed using SAS/STAT and SAS/Genetics software version 9.1 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

The clinical characteristics of the unrelated Framingham Offspring Study participants included in this analysis are shown in Table 1. Vascular phenotypes are summarized in Table 2 and characteristics of the genotyped polymorphisms are summarized in Table 3.

ESR1 association analysis

In the sex-pooled analysis, those homozygous for the minor alleles for *ESR1 (TA)*$_n$, *rs2077647*, *rs2234693*, and *rs9340799* had higher augmented pressure and AI (Table 4) as compared to carriers of one or two major alleles (recessive model, p range 0.0001–0.04). Associations were more pronounced in individuals not receiving antihypertensive treatment and in women, who had particularly higher augmented pressure and AI (data not shown). No significant sex-genotype and treatment-genotype interaction was detected. Also, we observed a modest association of several of the *ESR1* variants on heart rate, which was lower in the groups with higher AI (Online Supplement Table I). In our sample, lower heart rate significantly correlated with higher augmented pressure and AI (r=−0.25 and −0.28, respectively; p<0.0001).

Strong LD detected between four of the six *ESR1* markers (pairwise D′ ranges between 0.82 and 0.99, Online Supplement Figure) resulted in three common haplotypes, H5: *(TA)*$_n$ *[L]-rs2077647[C] - rs2234693[C] rs9340799[G]* with the frequency of 32.7%, H6: *(TA)*$_n$ *[L]-rs2077647[C] - rs2234693[C] rs9340799[A]* with the frequency of 6.9% and H12: *(TA)*$_n$ *[S]-rs2077647[T] - rs2234693[T] rs9340799[A]* with the frequency of 45.8%. However, the data

indicate that haplotypes did not explain larger proportions of variation in augmented pressure and AI than individual SNPs.

No association was detected between *ESR1* polymorphisms and forward pressure wave amplitude or CFPWV. Both of these measures showed weak to moderate correlations with augmented pressure (r=0.18, p<0.0001 and r=−0.08, p=0.009, respectively), AI (r=−0.14, p<0.0001 and r=−0.08, p=0.005, respectively) and the heart rate (r=0.04, p=0.13 and r=0.20, p<0.0001, respectively). In addition, no associations were detected between *ESR1* polymorphisms and any of the brachial flow measures (p>0.05).

ESR2 association analysis

Similar to the *ESR1* analysis, in the sex-pooled sample, *ESR2 rs944460* and *rs1256034* genotypes were related to augmented pressure and AI (Table 5). Those homozygous for the major allele of *ESR2 rs944460* and *rs1256034*, had higher augmented pressure and AI than carriers of the minor allele.

Strong LD was detected between the two pairs of *ESR2* SNPs (Table 5). However, the correlation between them, or r^2, was small due to low minor allele frequency for *rs944460* and *rs1256034* (Online Supplement Figure), which resulted in a large number of rare haplotypes.

No association was detected between *ESR2* polymorphisms and forward pressure wave or CFPWV. In addition, no associations were detected between *ESR2* polymorphisms and any of the brachial flow measures (p>0.05).

CYP19A1 association analysis

No association was detected between the *CYP19A1* SNPs (Online Supplement Figure) and studied vascular measures (Online Supplement Table II) (p>0.05).

Interaction effects

On the basis of significant interactive effects of *ESR1 rs2234693* and smoking status on lipoprotein profile detected in a previous study,[22] we tested the hypothesis that *ESR1 rs2234693* interacts with smoking status. Regardless of genotype, in the multivariable-adjusted model smokers had higher augmented pressure and greater AI than non-smokers (10.4±5.0 vs. 8.6±4.8 mm Hg; p=0.01 and 20.0±7.1 vs. 15.8±6.4%; p<0.0001, respectively). Furthermore, homozygosity for the *ESR1 rs2234693 C allele* had an enhanced association with augmented pressure and AI in smokers (p=0.04 and p=0.02, respectively, for the genotype-smoking interaction term) (Figure).

Discussion

We evaluated relations between genetic variants in the *ESR1*, *ESR2* and *CYP19A1* genes and key arterial function phenotypes assessed by tonometry and brachial reactivity in unrelated individuals from the Framingham Heart Study Offspring cohort. In models that adjusted for a number of potential confounders, rare alleles of the closely related *ESR1* polymorphisms and common alleles of the linked *ESR2* polymorphisms were associated with higher augmented pressure and greater AI. In sex-pooled analyses, those homozygous for the minor allele at any one of the four *ESR1* SNPs, which were all in strong LD, had on average 17% higher augmented pressure and 15% greater AI compared to carriers of one or two major alleles. A similar direction and magnitude of association was detected in those homozygous for the common allele at two strongly linked *ESR2* SNPs. No association was found between the *CYP19A1* SNPs and vascular measures. These analyses were prompted by significant associations detected between *ESR1* and *ESR2* gene polymorphisms and a number of cardiovascular

phenotypes in the Framingham Heart Study, including myocardial infarction,[17] elevated blood pressure,[21] altered lipoprotein profile,[22, 23] adiposity,[24] and changes in left ventricular structure.[26, 27] The present findings of an association between common variants in estrogen pathway genes and measures of wave reflection suggest that abnormal pulsatile load may be involved in the pathogenesis of the foregoing adverse clinical phenotypes.

Reported associations were seen in four closely linked *ESR1* SNPs, two of which may have direct relevance to vascular function. Specifically, the *ESR1 TA* polymorphism is located in the regulatory region of the gene ~1174 base pairs upstream of the first exon[39] between promoters B and C.[40] The *long* allele has been associated with worse cardiovascular risk profile in previous reports. Namely, compared with *short* allele carriers, the *TA L* polymorphism has been linked with more severely diseased coronary arteries,[19, 41] and a higher risk of myocardial infarction.[41] In the present study, *ESR1* $(TA)_n$ *LL* homozygotes had significantly lower heart rate and higher augmented pressure amplitude and AI compared to carriers of one or two *S* alleles. Although the exact mechanism whereby the *ESR1 TA* repeat polymorphism may affect the vasculature is unclear, it is possible that this variant alters *ESR1* transcript length or RNA splicing causing significant heterogeneity in ERα mRNA transcripts. It has been shown previously that alternative splicing may result in variants with deletions of exons encoding regions of the hormone-binding domain with truncated forms of ERα discovered in many tissues including vascular endothelium and showing altered ligand-activation properties (reviewed in [42]).

Higher augmented pressure and AI were also detected with the *C* allele of another variant, *ESR1 rs2234693,* which is known to produce a functional *myb* binding site that might amplify ERα transcription or produce ERα isoforms with properties that differ from those of the full-length gene product.[43]

ERϐ is required for normal vasodilatation and blood pressure in both male and female mice, with loss of ERϐ causing substantial hypertension, particularly in males.[44] We found associations of higher augmented pressure and AI with common variants in the two linked intronic SNPs that have no known functional effect on the receptor. These variants may regulate RNA splicing or transcription causing differences in expression levels, relative abundance of multiple *ESR2* splice forms, or ligand binding affinity. However, given an unusually large distance between the *ESR2* SNPs that are in LD (>30,000 base-pairs), it is possible that the observed associations may be due to the existence of as yet undetected coding variants located between and in LD with the genotyped SNPs.

We also observed a modest effect of several of the *ESR1* variants on heart rate. In our sample, lower heart rate significantly correlated with higher augmented pressure and AI and could contribute to the increase in AI. Noteworthy, it has been shown that AI shares 4.6% common genetic component with heart rate.[29] However, it is important to emphasize that our models included an adjustment for systolic ejection period or heart rate.

In the present study, we found no association of ER genotype carrier status with forward pressure wave amplitude or CFPWV. Both of these measures showed weak to moderate correlations with augmented pressure and heart rate. However, in an earlier study, Japanese women who were carriers of *ESR1 rs2234693 CC* were shown to have lower brachial-ankle pulse wave velocity, which is a measure of the spatially averaged properties of the aorta and peripheral arteries.[46] Interestingly, female carriers of the common *ESR1 rs2234693 C* allele from the Framingham Offspring cohort had a larger average low-density lipoprotein (LDL) particle size and a lower concentration of small LDL particles, which is a protective lipid profile.[23] Taken together, these data suggest that brachial-ankle pulse wave velocity may be modified through favorable estrogen-induced changes in lipoprotein properties in carriers of

the minor allele. In contrast, the same genotypes may increase arterial wave reflection because of direct effects of estrogen on vascular tone in the periphery.

In the present study we detected effect modification by smoking status. That is, among smokers, those who were homozygous for the *ESR1 rs2234693 C* allele had a 40% higher augmented pressure and 33% greater AI than carriers of one or two major alleles (Figure). Importantly, significant *ESR1 rs2234693* - smoking status interaction in this cohort has been found with lipoprotein fraction concentrations.[22] Among smokers, female carriers of *ESR1 rs2234693 TT* genotype had higher small LDL particle concentrations and lower LDL particle sizes than non-carriers, while no such association was detected in non-smokers. It has been shown that acute tobacco use provokes endothelial dysfunction and abolishes the protection of circulating estrogen.[47] It will require further studies to determine how variation in *ESR1* interacts with cigarette smoking.

There are several potential limitations of our study. The design of this study, like any other genetic association studies, does not allow drawing definitive conclusion about the exact mechanisms that may lead to increased wave reflection. Moreover, the study cohort was middle-aged to elderly and white of European descent, which may limit the generalizability of our findings to younger individuals and other ethnic backgrounds. Also, we analyzed SNPs that have been previously implicated in cardiovascular phenotypes; thus, we may have missed associations attributable to other polymorphisms not sufficiently linked to the SNPs that we evaluated. In addition, no adjustment for multiple testing was carried out. A standard correction for multiple hypothesis testing relies on the assumption that all statistical comparisons are independent. In the case of *ESR1*, *ESR2* and *CYP19A1*, most of the polymorphisms were in strong LD with one another, and tonometry measures were correlated. Moreover, we tested *a priori* hypotheses based on reported findings with regard to these gene variants; therefore rigorous adherence to the correction for multiple testing may have increased Type II error. The consistency and biological relevance of these associations should motivate further research to verify and extend these findings. We acknowledge that our findings will need to be replicated in other cohorts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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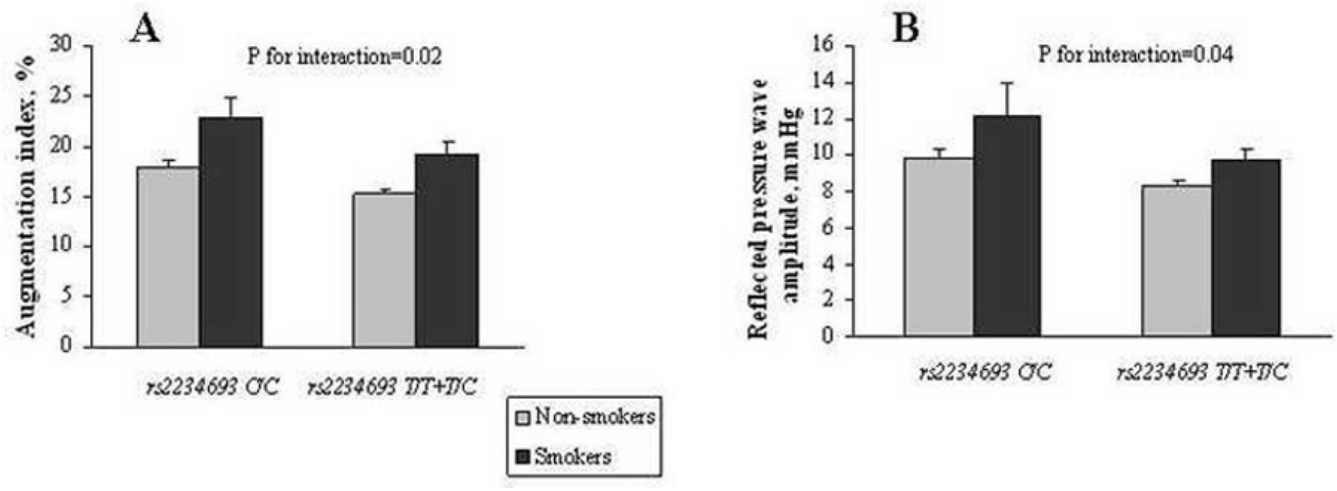

Figure. Tonometry phenotypes by smoking status and the *ESR1 rs2234693* genotype in the sex-pooled sample

Gene*smoking interaction adjusted

Table 1

Sample characteristics.

Variable	Men (N=604)	Women (N=657)
Age, years	62±10	62±9
Systolic blood pressure, mmHg	129±18	127±20
Diastolic blood pressure, mmHg	76±10	72±10
Heart rate, bpm	62±11	64±10
Body mass index, kg/m^2	28.6±4.5	27.3±5.5
Total/high-density cholesterol, ratio	4.4±1.3	3.6±1.1
Triglycerides, mg/dL	141±104	128±74
Fasting glucose, mg/dL	109±28	101±25
Diabetes, %	15	9
Smoking within past 12 month, %	12	14
Smoking within past 6 hours, %	8	9
Prevalent cardiovascular disease, %	19	10
Postmenopausal women, %	-	86
Hormone replacement therapy, %	-	37
Hypertension, %	51	46
Hypertension medication, %	39	33
Lipid-lowering medication, %	25	18

Table 2

Vascular phenotypes.

Variable	Men (N=604)	Women (N=657)
Tonometry variables (mean±SD)		
Forward pressure wave amplitude, mmHg	41±14	42±13
Augmented pressure amplitude, mmHg	7±6	11±9
Carotid-femoral pulse wave velocity, m/s	11±4	10±3
Augmentation index, %	13±10	20±12
Systolic ejection period, ms	308±29	319±27
Brachial reactivity variables (median (Q1–Q3))		
Baseline Diameter (mm)	4.90 (4.51–5.33)	3.65 (3.31–4.01)
Flow-Mediated Dilation (%)	1.8 (0.5–3.6)	2.8 (1.1–5.1)
Baseline Volume Flow (ml/s)	1.4 (0.9–2.0)	0.7 (0.5–1.0)
Hyperemic Flow Velocity (cm/s)	45 (30–61)	52 (36–70)

Q1, indicates first quartile; Q3 indicates third quartile.

Table 3

Polymorphism characteristics.

Gene	dbSNP rs#	SNP position	Nucleotide substitution	Minor Allele Frequency	*P* for HWE
ESR1	$(TA)_n$	Promoter	$(TA)_n$	.50*	0.95
6q25.1	rs2077647	Exon 1 (Ser10Ser)	T/C	.46	0.22
	rs2234693	Intron 1	T/C	.45	0.66
	rs9340799	Intron 1	A/G	.36	0.80
	rs1801132	Exon 4 (Pro325Pro)	C/G	.23	0.15
	$(CA)_n$	Intron 5	$(CA)_n$	.36*	0.05
ESR2	rs944460	Intron 2	C/G	.03	0.29
14q23.2	rs1256059	Intron 2	C/T	.45	0.13
	$(CA)_n$	Intron 5	$(CA)_n$	.20*	0.28
	rs1256034	Intron 6	G/A	.03	0.29
	rs1256031	Intron 7	T/C	.49	0.59
CYP19A1	rs4646	5′ UTR	C/A	.25	0.18
15q21.1	rs700518	Exon 3 (Val80Val)	A/G	.48	0.01
	$(TTTA)_n$	Intron 4	$(TTTA)_n$	.49*	0.82
	rs726547	Intron 4	C/T	.05	0.41

*calculated using median number of repeats.

Table 4

Tonometry phenotypes in the pooled sample by *ESR1* genotypes.

SNP	Genotype	N	Augmented pressure, mmHg		Augmentation index, %	
			LS mean±SE	*P*	LS mean±SE	*P*
$(TA)_n$	S/S	250	8.6±0.3	**0.004**	15.7±0.4	**0.001**
	L/S	506	8.5±0.2		16.0±0.3	
	L/L	257	10.2±0.3		18.8±0.4	
rs2077647	T/T	320	8.8±0.3	**0.01**	15.9±0.4	**0.009**
	T/C	594	8.4±0.2		15.8±0.3	
	C/C	237	10.0±0.3		18.2±0.4	
rs2234693	T/T	360	9.2±0.3	**0.001**	16.4±0.4	**0.001**
	T/C	572	8.1±0.2		15.3±0.3	
	C/C	244	10.1±0.3		18.6±0.4	
rs9340799	A/A	488	8.9±0.2	**0.006**	16.2±0.3	**0.0002**
	A/G	540	8.3±0.2		15.4±0.3	
	G/G	159	10.3±0.3		19.7±0.5	
rs1801132	C/C	683	9.1±0.2	0.80	16.6±0.3	0.98
	C/G	389	8.4±0.2		15.9±0.3	
	G/G	67	7.7±0.6		15.6±0.8	
$(CA)_n$	S/S	398	9.0±0.3	0.68	16.2±0.4	0.44
	S/L	419	8.7±0.3		16.6±0.4	
	L/L	140	9.7±0.4		18.0±0.6	

LS mean, least square estimate of the mean adjusted for age, sex, weight, height, diabetes, total/HDL cholesterol ratio, triglycerides, fasting glucose, smoking within past 6 hours, prevalent cardiovascular disease, menopausal status and hormone replacement therapy (in women), lipid-lowering medication, hypertension medication and systolic ejection period.

Table 5

Tonometry phenotypes in the pooled sample by *ESR2* genotypes.

SNP	Genotype	N	Augmented pressure, mmHg		Augmentation index, %	
			LS mean±SE	*P*	LS mean±SE	*P*
rs944460	C/C	1108	8.9± 0.2	**0.009**	16.5± 0.2	**0.02**
	C/G	71	7.3± 0. 6		13.7± 0.7	
rs1256059	C/C	331	9.8± 0.3	0.12	17.6± 0.4	0.30
	C/T	595	8.2± 0.2		15.5± 0.3	
	T/T	228	8.6± 0.3		16.2± 0.5	
$(CA)_n$	S/S	757	8.9± 0.2	0.88	16.4± 0.2	0.60
	S/L	393	8.7± 0.2		16.4± 0.3	
	L/L	43	8.6± 0.8		15.4± 1.0	
rs1256034	G/G	1064	8.9± 0.2	**0.007**	16.5± 0.2	**0.01**
	G/A	70	7.1± 0.6		13.2± 0.8	
rs1256031	T/T	304	10.2± 0.3	0.17	18.0± 0.4	0.48
	T/C	601	8.3± 0.2		15.6± 0.3	
	C/C	280	8.7± 0.3		16.4± 0.4	

LS mean, least square estimate of the mean adjusted for age, sex, weight, height, diabetes, total/HDL cholesterol ratio, triglycerides, fasting glucose, smoking within past 6 hours, prevalent cardiovascular disease, menopausal status and hormone replacement therapy (in women), lipid-lowering medication, hypertension medication and systolic ejection period.

Table 6

Summary

What is known about this topic: • Aortic stiffness has been identified as a cardiovascular disease risk factor in three large, independent, community-based cohorts.[1–3] • Estrogen is known to play an important role in endothelial function in both men and women. • Genetic variations of the major proteins involved in estrogen conversion and receptor function have been shown to be associated with the increased risk of myocardial infarction[17] and coronary artery disease,[18–20] elevated blood pressure,[21] altered lipoprotein particles concentrations,[22, 23] adiposity, [24] and left ventricular mass.[25–27]
What this Study adds: • This 1261 unrelated Framingham Offspring Study participants shows that variation in *ESR1* and *ESR2*, but not *CYP19A1* may predispose to excess pressure wave reflection, which may contribute to morbidity from several complex diseases. • Finding genes associated with excess wave reflection may help elucidate hemodynamic mechanisms of disease pathogenesis and enhance our ability to favorably manipulate vascular responses in genetically susceptible individuals before clinical manifestations occur.