

## Association Between the Paraoxonase-1 192Q>R Allelic Variant and Coronary Endothelial Dysfunction in Patients With Early Coronary Artery Disease

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**OBJECTIVE:** To test the hypothesis that allelic variants of the paraoxonase-1 gene are associated with endothelial dysfunction, an early stage of atherosclerosis.

**PATIENTS AND METHODS:** We assessed 192Q>R and 55L>M allelic variants of the paraoxonase gene and coronary endothelial function in response to intracoronary acetylcholine in 99 patients (52 with homozygous QQ, 47 with homozygous RR or heterozygous QR). The study was conducted from September 1, 2002, through November 30, 2004.

**RESULTS:** Of 52 homozygous QQ patients, 39 (75%) had endothelial dysfunction vs 20 (43%) of the 47 RR/QR patients ( $P=.001$ ), and this association remained significant after adjustment in a multivariable linear regression model ( $P=.005$ ). In homozygous QQ vs RR/QR patients, epicardial arterial diameter decreased more (percent change in diameter,  $-22\pm 21\%$  vs  $-9\pm 16\%$ , respectively,  $P=.002$ ), coronary blood flow increased less ( $+37\pm 77\%$  vs  $+75\pm 75\%$ ,  $P=.02$ ) in response to acetylcholine, and oxidized LDL levels were higher. The 55L>M allelic variant was not significantly associated with endothelial dysfunction and had no effect on the association between endothelial dysfunction and the 192Q>R allelic variant.

**CONCLUSION:** The 192Q>R allelic variant of the paraoxonase-1 gene is associated with coronary endothelial dysfunction. The current study provides further information regarding the potential mechanisms by which this allelic variant contributes to early atherosclerosis in humans.

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APV = average peak velocity; CBF = coronary blood flow; HDL = high-density lipoprotein; LDL = low-density lipoprotein; oxLDL = oxidized LDL

Endothelial dysfunction is considered an early stage in the atherogenic process; however, the precise pathogenesis of transition from normal to abnormal endothelial function remains unknown. Although traditional cardiac risk factors, such as hypertension and hyperlipidemia, are associated with endothelial dysfunction, the magnitude of endothelial dysfunction in patients with similar risk factors is highly variable.<sup>1-3</sup> Novel risk factors, such as oxidative stress and genetic heterogeneity, could contribute to this process, possibly mediating between traditional coronary artery disease risk factors and endothelial dysfunction.

Oxidative stress, which represents an imbalance between oxidant and antioxidant processes, can occur systemically or locally in the vessel wall.<sup>4</sup> Oxidation of low-density lipoprotein (LDL) in the arterial wall is a key event

in the pathophysiology of atherosclerosis.<sup>5,6</sup> The mechanisms by which high-density lipoprotein (HDL) exerts its antiatherogenic influence are multifactorial and include the reverse cholesterol transport pathway<sup>7</sup> and the antioxidant properties of HDL.<sup>8</sup> These antioxidant properties are related in part to the presence of HDL-associated enzymes, such as paraoxonase-1.<sup>5</sup>

The effect of paraoxonase on atherosclerosis could be related to its allelic variants, to its binding to HDL, and to HDL levels.<sup>9-12</sup> Two allelic variants commonly occur in the paraoxonase-1 coding region: leucine is replaced by methionine at codon 55 (55L>M), and glutamine is replaced by arginine at codon 192 (192Q>R).<sup>13</sup> The 55L>M single-nucleotide allelic variant modulates paraoxonase-1 concentration; the 192Q>R allelic variant, paraoxonase-1 activity.<sup>14</sup> Conflicting results have been reported by epidemiological studies exploring the association between allelic variants of the paraoxonase-1 gene and the risk of coronary artery disease.<sup>15-20</sup> Furthermore, the role of allelic variants of the paraoxonase gene in early coronary atherosclerosis and in endothelial dysfunction remains unclear.<sup>21</sup>

Our study aimed to test the hypothesis that allelic variants of paraoxonase-1 are related to the presence of coronary endothelial dysfunction in humans. To address this hypothesis, we assessed the association between coronary endothelial function in response to intracoronary administration of the endothelium-dependent vasodilator acetylcholine and cardiovascular risk factors, 55L>M and 192Q>R paraoxonase-1 allelic variants, and oxidized low-density lipoprotein (oxLDL) levels in patients without occlusive coronary artery disease.

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## PATIENTS AND METHODS

The study was approved by the Mayo Clinic Institutional Review Board, and informed consent was obtained from patients. Conducted from September 1, 2002, through November 30, 2004, the study included 100 consecutive patients undergoing diagnostic coronary angiography who were referred for evaluation of coronary endothelial function. Patients were excluded if they had substantial epicardial coronary artery stenosis (ie, stenosis >30%) or compounding medical conditions such as cancer, anemia, and renal disorders. Angiography was performed after overnight fasting; all vasoactive medications affecting cardiovascular hemodynamics and antioxidant vitamins were discontinued at least 48 hours before the study.

Patients were considered to have diabetes mellitus if they had either a history of diabetes (controlled by diet or by oral hypoglycemic agents or insulin) or a fasting plasma glucose value of 126 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0555).<sup>22</sup> Patients who had smoked within the past month were considered smokers.<sup>23</sup>

### CORONARY VASOREACTIVITY ASSESSMENT

After diagnostic angiography and exclusion of patients with substantial obstructive coronary artery disease, a 6F or 7F guiding catheter was placed into the left main coronary artery. Coronary vasoreactivity responses were studied as we have previously described.<sup>23-25</sup> In brief, a Doppler-tipped guidewire (Volcano Therapeutics, Rancho Cordova, CA) was positioned within a coronary-infusion catheter (Ultrafuse; SciMed Life System, Minneapolis, MN) in the midportion of the left anterior descending coronary artery. Velocity signals were instantaneously obtained from the Doppler wire by online fast Fourier transform analysis, and average peak velocity (APV) was determined. This method was previously validated,<sup>24,25</sup> and analysis of data from our laboratory show that the variation in repeated measurements  $\pm$  SD is  $8\% \pm 3\%$ .

Intracoronary bolus injections of adenosine were given either in incremental doses (18-60  $\mu$ g) until maximal hyperemia was achieved or in the highest dose to evaluate endothelium-independent microvascular coronary flow reserve. Coronary flow reserve was calculated by dividing the APV after adenosine injection by the APV at baseline.

Subsequently, to assess endothelium-dependent vasoreactivity, the endothelium-dependent vasodilator acetylcholine was selectively infused at increasing concentrations ( $10^{-6}$ ,  $10^{-5}$ , and  $10^{-4}$  M) for 3 minutes at each concentration into the left anterior descending coronary artery.<sup>23</sup> Coronary artery diameter and APV were measured and coronary blood flow (CBF) calculated after each infusion of acetyl-

choline. Endothelium-dependent changes in CBF were calculated with the following equation:  $[(\text{CBF After Intracoronary Acetylcholine} - \text{Resting CBF}) / \text{Resting CBF}] \times 100 (\%)$ . Finally, endothelium-independent epicardial coronary artery function was determined by the change in coronary artery diameter in response to intracoronary administration of a 100- $\mu$ g bolus of nitroglycerin.

Coronary artery diameter in the segment 5 mm distal to the tip of the Doppler wire was measured offline by an independent technician using a quantitative coronary angiography program (Medis, Leiden, the Netherlands), as was previously described.<sup>26</sup> Coronary blood flow was calculated from the Doppler-derived time velocity integral and vessel diameter using a previously derived formula<sup>25</sup>:  $\pi \times (\text{Coronary Artery Diameter}/2)^2 \times (\text{APV}/2)$ . Endothelium-dependent coronary flow response was calculated as the percent change in CBF in response to acetylcholine. On the basis of our previous studies,<sup>24,25</sup> we defined coronary epicardial endothelial dysfunction as a greater than 20% decrease in diameter in response to the maximum dose of acetylcholine. Microvascular endothelial dysfunction is defined as a 50% or greater increase in CBF in response to the maximal dose of acetylcholine compared with baseline CBF.<sup>24,25</sup> Endothelial dysfunction is defined as either microvascular or epicardial endothelial dysfunction, both of which are associated with increased risk of future cardiac events.<sup>24</sup>

### BLOOD SAMPLES AND GENETIC ANALYSIS

Before the coronary angiogram, fasting blood samples were drawn for analysis of oxLDL levels and genomic DNA and for routine clinical laboratory tests (lipid profile and C-reactive protein). Plasma oxLDL levels were assessed by enzyme-linked immunosorbent assay (ELISA) (Merckodia, Uppsala, Sweden).<sup>27</sup> Genomic DNA was extracted from white blood cells according to standard methods. The 192Q>R and 55L>M allelic variants were measured using a multiplex method, ie, direct allelic variant analysis of DNA amplified by the polymerase chain reaction. The DNA was amplified in 2 multiplex reactions using a biotinylated primer within each primer set to later bond each amplicon to a streptavidin-coated NanoChip microarray chip. The amplified DNA was hybridized with oligonucleotide probes specific for the normal and polymorphic variants and was read in a Nanogen Reader, using laser-excited 2-color fluorescence detection. Wild-type, heterozygous, or variant genotypes were identified by the fluorescence pattern observed at increasing temperatures.<sup>28</sup> To validate the assays, we designed different primer sets, making separate PCR amplicons for direct DNA sequencing in both directions using the 3730xl DNA Analyzer (Applied Biosystems, Foster City, CA).

We further validated our results with a Luminex-based method (Luminex 100 xMAP; Luminex, Austin, TX).<sup>29</sup>

### STATISTICAL ANALYSES

Patients were divided into groups according to allelic variant (192Q>R vs 55L>M). Continuous variables with normal distribution are presented as mean  $\pm$  SD; skewed variables, as median and interquartile range. Discrete variables are presented as numbers and percentages. The baseline characteristics of groups were compared using the *t* test or 2-sided Wilcoxon signed rank test for continuous variables and by the  $\chi^2$  statistic for categorical variables. Single-predictor and multivariable linear regression models were used to calculate the association between the 192Q>R allelic variant and coronary endothelial dysfunction. The dependent variables were the degree of epicardial and microvascular endothelial dysfunction. Independent variables found to show marginal association ( $P<.2$ ) with endothelial dysfunction in the single-predictor analysis were used in the multivariable model. Lipid levels were included in the model because of their possible effect on paraoxonase. Also, because interaction between the effects of the 192Q>R and 55L>M allelic variants is possible, we evaluated the effect of this interaction in the model as well as the effect of diabetes mellitus and smoking. Only linear associations were considered.  $P<.05$  was used to determine statistical significance.

### RESULTS

One hundred patients completed the study, but DNA extraction failed in samples from 1 patient. Among the remaining 99 patients, similar results were obtained using the Nanogen- and Luminex-based methods. Patients were divided into groups according to their paraoxonase-1 allelic variant. Genotype frequencies for the 192Q>R allelic variant were as follows: QQ (n=52), RR (n=7), and QR (n=40). The R allele carriers were grouped together for the analysis because several in vitro and epidemiological studies suggest that their HDL is less protective against oxidative modification of LDL and that they are more likely to have cardiovascular events than homozygous QQ patients.<sup>30,31</sup> Genotype frequencies in the 55L>M allelic variant were as follows: LL (n=41), MM (n=7), and LM (n=51). Like the carriers of the 192Q>R allelic variant, the M allele carriers (MM and LM) were grouped together.<sup>31</sup> Because the association with coronary artery disease in previous studies is less compelling for the 55L>M than for the 192Q>R allelic variant, we focused primarily on the 192Q>R allelic variant.

No significant difference in the degree of coronary artery disease was observed between groups. Mean left ante-

TABLE 1. Baseline Patient Characteristics by Allelic Variant<sup>a,b</sup>

Characteristic	QQ (n=52)	QR/RR (n=47)	P value <sup>c</sup>
Age (y)	49 $\pm$ 11	51 $\pm$ 13	.65
Male sex	20 (38)	14 (30)	.40
Hypertension	23 (44)	28 (60)	.16
Hyperlipidemia	34 (65)	35 (74)	.38
Diabetes mellitus	7 (13)	5 (11)	.76
Smoker	9 (17)	6 (13)	.58
Body mass index (kg/m <sup>2</sup> )	28.7 $\pm$ 5.3	27.7 $\pm$ 6.1	.40
Total cholesterol (mg/dL) <sup>d</sup>	180 $\pm$ 38	180 $\pm$ 37	.94
LDL	102 $\pm$ 33	101 $\pm$ 31	.87
HDL	49 $\pm$ 13	51 $\pm$ 15	.30
Triglycerides <sup>e</sup>	122 (95-161)	113 (78-159)	.30
High-sensitivity CRP (mg/L)	0.85 $\pm$ 1.2	0.74 $\pm$ 1.4	.68
Statin use	27 (52)	20 (43)	.42

<sup>a</sup> CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

<sup>b</sup> Values are number (percentage) for categorical variables and mean  $\pm$  SD for continuous values, unless otherwise indicated.

<sup>c</sup> P values were derived using the *t* test for continuous variables (with the exception of the 2-sided Wilcoxon signed rank test used for triglycerides) and the  $\chi^2$  test for categorical variables.

<sup>d</sup> SI conversion factor: To convert total cholesterol, LDL, and HDL values to millimoles per liter, multiply by 0.0259; to convert triglyceride values to millimoles per liter, multiply by 0.0113.

<sup>e</sup> Values for triglycerides are expressed as median (interquartile range).

rior descending stenosis was 15% $\pm$ 12% in homozygous QQ patients vs 12% $\pm$ 13% in carriers of the R allele ( $P=.24$ ). The clinical characteristics of the patients according to the 192Q>R allelic variant are outlined in Table 1. The prevalence of risk factors for coronary artery disease and endothelial dysfunction, specifically those that could affect paraoxonase activity, such as smoking and HDL levels, were similar in both groups. C-reactive protein levels were not associated with endothelial function. Supplemental vitamins had been taken in the past by 21 patients. No significant associations or trends were observed between prior consumption of antioxidant vitamins and the presence or degree of endothelial dysfunction or level of oxLDL. The frequency of statin therapy was also the same in both groups. Despite similar levels of LDL cholesterol, oxLDL levels were significantly higher in homozygous QQ patients than in R allele carriers (71.8 $\pm$ 19.4 U/L vs 62.7 $\pm$ 16.4 U/L, respectively;  $P=.01$ ) (Figure 1).

Hemodynamic data were similar in both groups. Mean arterial pressure  $\pm$  SD at baseline was 97 $\pm$ 17 mm Hg in carriers of the QQ allele vs 97 $\pm$ 14 mm Hg in carriers of the QR/RR allele ( $P=.94$ ), and coronary flow reserve  $\pm$  SD to adenosine was 2.8 $\pm$ 0.7 in both groups ( $P=.80$ ). The increase  $\pm$  SD in coronary artery diameter after intracoronary administration of nitroglycerin was also similar (12% $\pm$ 19% [QQ] vs 16% $\pm$ 17% [QR/RR];  $P=.27$ ).

In response to acetylcholine, carriers of the QQ allele had a more pronounced decrease in coronary artery diameter and a smaller increase in CBF than did carriers of the

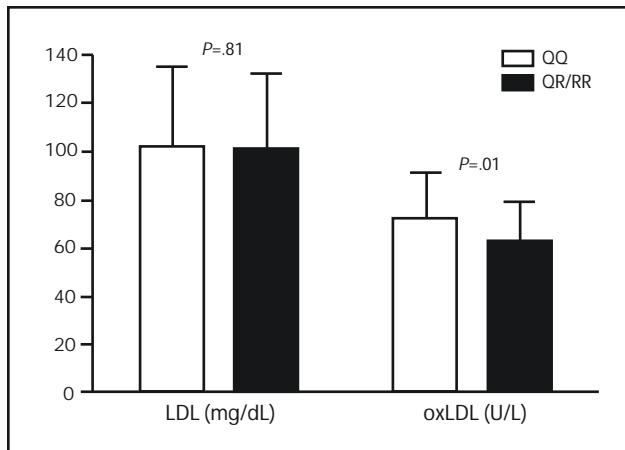


FIGURE 1. Low-density lipoprotein (LDL) and oxidized LDL (oxLDL) levels according to paraoxonase 192Q>R allelic variant.

QR or RR alleles (Figure 2, top), indicating both epicardial and microvascular endothelial dysfunction in carriers of the QQ allele. Endothelial dysfunction was found in 39 (75%) of the 52 patients with the QQ allele compared with 20 (43%) of the 47 patients with QR/RR alleles ( $P=.001$ ). Patients with endothelial dysfunction had higher levels of oxLDL ( $70.3 \pm 18.3$  U/L vs  $63.8 \pm 18.5$  U/L;  $P=.08$ ), and oxLDL levels were associated with both the epicardial and microvascular response to acetylcholine. The results of single predictors of endothelial dysfunction and multivariable models are shown in Table 2. After adjustment for important variables, the QQ allele remained an important and significant predictor of epicardial and microvascular coronary endothelial dysfunction ( $P=.03$ ), whereas the association between endothelial dysfunction and oxLDL level was not significant ( $P=.29$  and  $P=.42$ , respectively).

The association between the 55L>M allelic variant and coronary endothelial dysfunction was not significant (Table 2; Figure 2, bottom) and was unaffected by adjustments for sex, body mass index (calculated as the weight in kilograms divided by height in meters squared), and lipid and oxLDL levels ( $P=.70$ ). Endothelial function was unaffected by interactions between the effects of 192Q>R and 55L>M allelic variants. Smoking status, diabetes mellitus, and HDL and LDL levels had no significant effect on the association between the 192Q>R allelic variant and endothelial function.

## DISCUSSION

The current study shows that the presence of the paraoxonase-1 192Q>R allelic variant in patients with early atherosclerosis is associated with epicardial and microvascular endothelial function as well as with increased oxLDL levels.

By preventing oxidation of LDL, paraoxonase affects lipid metabolism.<sup>32</sup> However, the exact role of paraoxonase in LDL oxidation and atherosclerosis and its association with paraoxonase allelic variants are unclear. The activity of paraoxonase depends on the studied substrate and the assay used for measurements.<sup>11</sup> Patients with 192QQ and 55MM are presumed to have the greatest protective capacity against LDL oxidation, but their paraoxonase hydrolytic activity is weaker compared with 192RR and 55LL.<sup>32,33</sup> Interestingly, Marathe et al<sup>34</sup> observed that paraoxonase preparations are contaminated by platelet-activating factor acetylhydrolase and that paraoxonase has no phospholipase activity. According to recent reports, paraoxonase does not affect the accumulation of phosphatidylcholine oxidation products, bringing into question its role in lipid oxidation.<sup>35,36</sup>

Another controversy regards the role of paraoxonase allelic variants and the risk of atherosclerosis and cardiovascular disease. Conflicting results have been reported by

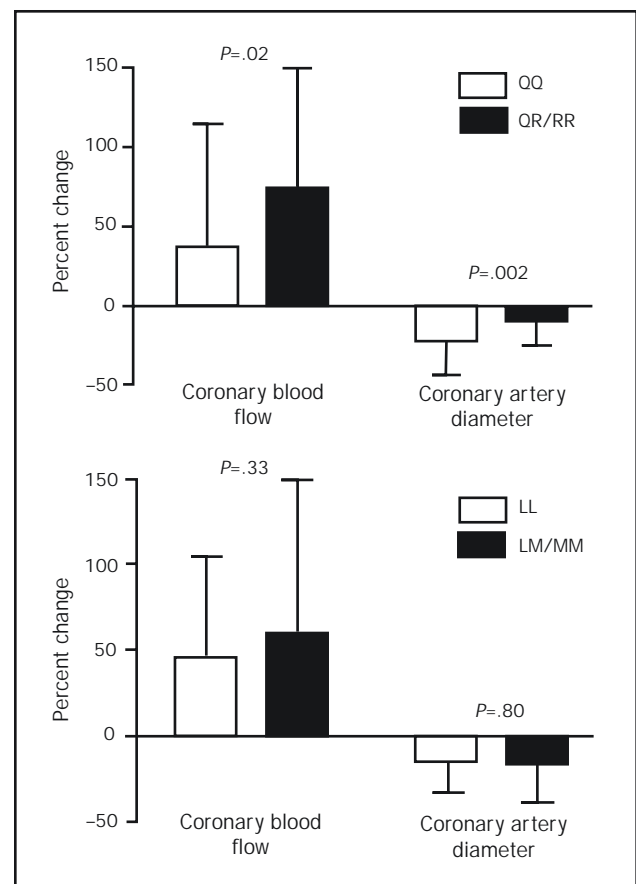


FIGURE 2. Changes in coronary artery diameter and coronary blood flow in response to intracoronary acetylcholine in patients undergoing coronary angiography who were categorized according to paraoxonase allelic variants. Top, 192Q>R allelic variant. Bottom, 55L>M allelic variant.

TABLE 2. Single-Predictor and Multivariable Analysis of Vascular Response to Acetylcholine<sup>a</sup>

	Coronary artery diameter response				Coronary blood flow response			
	Single predictor		Multivariable		Single predictor		Multivariable	
	PE	P value	PE	P value	PE	P value	PE	P value
Age	-0.11	.51	...	...	-0.64	.33	...	...
Sex	-3.47	.11	-3.18	.22	-4.05	.63	...	...
BMI	-0.47	.19	-0.36	.40	-2.71	.05	-1.48	.38
Hypertension	-0.69	.73	...	...	-1.01	.89	...	...
DM	-1.65	.60	...	...	-13.40	.27	...	...
Smoking	-1.07	.71	...	...	13.90	.21	...	...
LDL	-0.05	.40	0.01	.94	-0.23	.36	-0.01	.99
HDL	0.12	.42	-0.16	.43	0.33	.55	-0.10	.88
oxLDL	-0.25	.04	-0.18	.29	-0.87	.06	-0.54	.42
Vitamins <sup>b</sup>	-2.61	.35	...	...	-6.00	.58	...	...
QQ <sup>c</sup>	-6.30	.002	-5.14	.03	-18.40	.02	-19.5	.03
LL <sup>c</sup>	0.53	.80	...	...	-7.53	.35	...	...
QQ-LL <sup>c</sup>	-3.08	.30	...	...	-15.20	.29	...	...

<sup>a</sup> BMI = body mass index; DM = diabetes mellitus; HDL = high-density lipoprotein; LDL = low-density lipoprotein; oxLDL = oxidized LDL; PE = parameter estimate.

<sup>b</sup> Vitamins include vitamin C, E, or multivitamins.

<sup>c</sup> QQ and LL are paraoxonase allelic variants, and QQ-LL indicates an interaction between QQ and LL allelic variants.

studies examining the association between allelic variants of paraoxonase-1 and the risk of cardiovascular disease.<sup>37-40</sup> The effects of allelic variants are subtle and could be modified by environmental factors, perhaps explaining the discrepant results.<sup>41,42</sup> Studies of the association between genetic factors and phenotypic expression could be more enlightening before the development of overt clinical disease.<sup>42</sup> Such could be the case for coronary endothelial dysfunction and occlusive coronary artery disease, which share the same risk factors. Specifically, LDL oxidation impairs endothelial function<sup>43</sup> and is associated with coronary artery disease. Therefore, a stronger association can be plausibly assumed to exist between paraoxonase-1 allelic variants and endothelial dysfunction than between paraoxonase-1 allelic variants and occlusive coronary disease.

Our study is the first to show that the Q allele is associated with endothelial dysfunction in patients with minimal atherosclerosis. It concurs with previous reports of an association between paraoxonase-1 allelic variants and endothelial function in patients with established coronary or peripheral vascular disease. Bauters et al<sup>21</sup> analyzed the decrease in coronary artery diameter after intracoronary administration of serotonin in patients with overt coronary artery disease. They found that the reduction in lumen diameter was greater in patients with QQ alleles than in those with QR alleles. Pasqualini et al<sup>44</sup> studied the association between paraoxonase-1 allelic variants and brachial artery flow-mediated vasodilatation in patients with peripheral vascular disease. Patients with the R allele had higher flow-mediated dilatation than those with the Q allele. The results of our study extend these previous observations and show that this

association can be detected in the very early phase of atherosclerosis. Of the 2 single nucleotide allelic variants of paraoxonase-1 studied, 192Q>R was found to be associated with both epicardial and microvascular endothelial function. Genotype interaction between the studied allelic variants did not affect endothelial function.

Our observation is also supported by the finding that carotid intima-media thickness, another surrogate of early atherosclerosis, was lower among certain groups of R allele carriers.<sup>45</sup> In contrast, Yamane et al<sup>46</sup> recently reported that paraoxonase allelic variants did not play an important role in modulation of coronary endothelial function in a Japanese population. However, most of their patients carried the R allele, and carriers of the QQ and QR alleles were grouped together. Furthermore, a critical review of their results shows a trend toward a higher degree of endothelial dysfunction in the carriers of the QQ/QR allele compared with carriers of the RR genotype, a finding that could be consistent with our results. Hence, the combining of the QQ and QR groups and the relatively small number of patients in the study by Yamane et al (N=43) could account for the lack of differences in endothelial dysfunction noted between the groups. Our results are also supported by those of a study showing that the R allele is protective against LDL oxidation and is associated with fewer cardiac events in a Japanese population.<sup>47</sup> Our findings diverge from those of some epidemiological studies of paraoxonase and coronary artery disease<sup>18,37,38</sup> and from previous *in vitro* findings that relate paraoxonase activity to LDL oxidation.<sup>32</sup> However, the exact biological pathways by which paraoxonase protects against lipid oxidation are not well established. In fact, a recent report showed that the number of paraoxonase

peptides in HDL is actually higher in patients with coronary artery disease than controls.<sup>48</sup> Thus, systemic paraoxonase levels might not correlate with the effect of paraoxonase on HDL function in vivo.

The association between paraoxonase allelic variants and endothelial dysfunction in our study could be mediated by oxidation of LDL. We found that patients with the QQ allele had higher levels of oxLDL. Furthermore, oxLDL, a mediator of endothelial cell apoptosis,<sup>49</sup> was associated with the degree of endothelial dysfunction. However, in the multivariable model, only paraoxonase allelic variants remained a predictor of endothelial dysfunction. Paraoxonase allelic variants could affect endothelial function by binding to HDL, thereby hampering its local antioxidant activity. Indeed, a recent study shows that the amino acid 192 constitutes part of the HDL-anchoring surface and the active site of paraoxonase 1 and that the R isoenzyme better binds HDL and has greater antiatherogenic properties.<sup>12</sup> These findings could explain the association observed between the Q isoenzyme and endothelial dysfunction in our study.

Our study had several limitations. First, we did not measure paraoxonase activity. However, doing so might not have clarified the complex causal relationship between paraoxonase activity and early atherosclerosis. For example, paraoxonase decreased oxidative stress; however, oxidative stress can reduce paraoxonase expression and activity.<sup>50</sup> Furthermore, paraoxonase levels in serum might not correlate with lipoprotein-bound paraoxonase.<sup>12</sup> Genetic associations are more likely to clarify the causal relationship. Second, our study enrolled a relatively small number of patients. Nevertheless, a striking association between paraoxonase allelic variants and the degree of endothelial dysfunction was observed in our study and remained significant after adjustment. The evaluation of single-nucleotide allelic variants in cardiovascular diseases could lead to more precise risk stratification.<sup>51</sup> Although therapies specific to paraoxonase allelic variants are currently unavailable, genetic findings could very soon play an integral part in clinical decision making and be used for genetically directed therapies.

## CONCLUSION

Our study shows that coronary endothelial dysfunction in humans with early coronary atherosclerosis is associated with the paraoxonase-1 allelic variant 192Q>R. The exact mechanism by which paraoxonase affects coronary artery disease could involve oxLDL and remains to be explored.

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