A microsatellite polymorphism in the heme oxygenase-1 gene promoter is associated with increased bilirubin and HDL levels but not with coronary artery disease

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Summary
Heme oxygenase 1 (HO-1) is involved in the generation of the endogenous anti-oxidant bilirubin which exerts beneficial effects against arteriosclerosis. A (GT) repeat polymorphism in the HO-1 promoter region modulates HO-I expression in response to oxidative stress. Recently, this polymorphism has been reported to protect from coronary artery disease in Orientals. We intended to confirm this observation in Caucasians.

We studied 649 individuals with myocardial infarction (n=258), stable coronary artery disease (n=180) and controls without coronary artery disease (n=211). Carriers of short alleles (<25 repeats) had higher bilirubin levels (median 0.66 mg/dL, IQR 0.49 to 0.91) compared to non-carriers (median 0.61 mg/dL, IQR 0.45 to 0.82; p=0.03) and a more favourable lipid profile (HDL median 47 mg/dL, IQR 40 to 50 vs. median 45, IQR 37 to 55, p=0.01; triglycerides median 118 mg/dL, IQR 87 to 174 vs. median 132, IQR 97 to 191, p=0.03). However, no significant differences of the genotype distribution were observed between the three groups in this Caucasian study population (p=0.94).

Although potentially beneficial effects of the short HO-1 allele on lipid profile and serum bilirubin were observed, in contrast to Orientals, the HO-1 genotype was not associated with coronary artery disease in Caucasians.

Keywords
Heme oxygenase 1, promoter polymorphism, coronary artery disease, bilirubin, Caucasians

Introduction
Over the past decade, increasing evidence has emerged supporting the hypothesis of a “free radical attack” as an underlying pathomechanism in atherosclerotic vascular disease, and sustained efforts have been made to determine the cardioprotective role of antioxidants (1). Increased expression of endogenous specific stress proteins including heme oxygenase (HO) is part of the physiologic response to oxidative stress to prevent further cell damage. HO is the rate limiting enzyme in the degradation of heme to biliverdin releasing free iron and carbon monoxide (CO)(2, 3). The reduction of biliverdin by biliverdin reductase...
leads to the generation of bilirubin, a potent endogenous antioxidant. Heme oxygenase-1 (HO-1), the inducible isoform of the enzyme, is involved in the intracellular antioxidant defense mechanism and modulates vascular function via the release of CO and biliverdin. Endothelium derived CO diffuses to subjacent smooth muscle cells and activates soluble guanylyl cyclase (4, 5) leading to vasodilatation (6), whereas bilirubin protects LDL from oxidative modification potentiating the effect of exogenous antioxidants such as tocopherol or ascorbic acid (7, 8). Interestingly, bilirubin has been shown to inhibit the activity of protein kinase C in human fibroblasts (9). Since many effects of proatherogenic agents are mediated by protein kinase C (10) the inhibition of this enzyme by bilirubin might also exert protective effects apart from its known antioxidant properties.

HO-1 expression in atherosclerotic lesions (11) as well as in endothelial and smooth muscle cells (12, 13) is increased in response to oxidized LDL. This adaptive response contributes to the maintenance of vascular tone and patency in atherosclerotic vessels (1). Aside of exogenous influences on HO-1 expressions, such as oxidative stress, cytokines, heavy metals, hypoxia or heme, genetic variability may determine the individual HO-1 response to exogenous stimuli. Indeed, Yamada et al. (14) observed that a frequent (GT) dinucleotide repeat polymorphism in the promoter region of the HO-1 gene modulates the HO-1 response to exogenous stimuli. In vitro, short HO-1 alleles (<25 GT repeats) showed an increased promoter activity compared to longer alleles upon stimulation with H$_2$O$_2$. Additionally, a decreased susceptibility to emphysema in carriers of the short allele was demonstrated in smokers (14).

Previous studies from our group indicated functional importance of this polymorphism and a protective influence of the <25 allele on aortic arteriosclerosis leading to a lower prevalence of abdominal aortic aneurysms in carriers of the <25 allele (15). Similarly, the <25 allele is associated with protective effects in local vascular inflammation after percutaneous transluminal angioplasty resulting in a lower frequency of restenosis (16, 17).

Up to now, two studies revealed a possible role of the HO-1 (GT) promoter polymorphism on the development of coronary artery disease (CAD) and myocardial infarction (MI) especially in high risk patients in Orientals (18, 19), while the association of the HO-1 promoter polymorphism and CAD has not been studied in Caucasians as yet. To test whether a different ethnic and environmental background might result in different results in Caucasians, we performed a cross-sectional study on 649 consecutive patients referred for evaluation of coronary artery disease. Furthermore, we studied the association between the HO-1 promoter polymorphism and intermediate phenotypes which by themselves represent independent cardiovascular risk factors, e.g. total serum bilirubin, HDL and LDL cholesterol and serum triglycerides.

**Patients and methods**

**Patients**

After exclusion of 20 individuals of whom no DNA samples were available, we studied 649 consecutive patients referred to the Department of Cardiology, University of Vienna for evaluation of coronary artery disease (CAD). Patients were divided in three groups according to clinical findings, patients’ history and coronary angiography: The first group (MI group) consisted of 258 patients (59 female, 199 male, median age 60.5 years IQR 53-71) who had a history of myocardial infarction (MI) according to WHO criteria or presented with this clinical diagnosis. MI was defined by either one of the following criteria: 1) Typical rise and fall of biochemical markers of myocardial necrosis (CK-MB, troponin) with at least one of the following: a) ischemic symptoms; b) development of pathologic Q waves on the ECG; c) ECG changes indicative of ischemia (ST segment elevation or depression); in case of acute MI whereas established MI was determined by the following criteria: 1) Development of new pathologic Q waves on serial ECGs. 2) Pathologic findings of a healed or healing MI (20). The second group (stable CAD) included 180 individuals (49 female, 131 male, median age 64 years IQR: 57-72) with stable clinically relevant CAD without history of instable angina or MI. Clinically relevant CAD was defined as an exercise-induced ischemic ST-segment depression >0.1 mV (21) and/or a history of coronary intervention (coronary artery bypass or percutaneous transluminal coronary angioplasty). In 211 patients (108 female, 103 male, median age 58 years IQR: 48-67) the presence of CAD was excluded by angiography, where indicated, or other tests to prove coronary ischemia (exercise stress test and/or thallium-persantin scintigraphy) (non CAD group). Non CAD patients suffered from different diseases including valvular heart disease, non-ischemic cardiomyopathy, infectious diseases and non ischemic arrhythmias.

All patients were questioned for established cardiovascular risk factors including diabetes, smoking (>20 cigarettes for more than 5 years), hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >80 mmHg at repeated measurements or a known history of hypertension and treatment with antihypertensive drugs), body mass index (BMI) and family history of cardiovascular disease (Table 1). Hypercholesterolemia was defined as baseline cholesterol levels above 200 mg/dl or serum LDL levels above 130 mg/dl and hypertriglyceridemia as triglyceride levels above 180 mg/dl after overnight fasting and was considered to be present in all patients receiving lipid lowering medication. DM was considered present in patients with a known history of diabetes and in patients with a fasting glucose >126 mg/dl according to ADA criteria (22). The study was approved by the local ethic committee and all individuals participating in the study gave their written informed consent.
HO-1 genotype assessment

Genomic DNA was isolated from whole blood using the Puregene DNA isolation kit (Gentra Systems, Minneapolis, MN). PCR amplifications of the HO-1 (GT)n repeat length polymorphism were performed essentially as described previously (15, 16). In brief the 59-flanking region of the HO-1 gene containing a poly (GT)n repeat was amplified by the polymerase chain reaction (PCR) using a sense primer (HO-1GTFW 5-AGAGCCTGCAGCTTCTCAGA-3) and an antisense primer (HO-1GTR 5-ACAAAGTCTGGCCATAGGAC-3). Amplifications were performed in a Perkin Elmer 9700 thermocycler (Perkin Elmer Cetus, Emeryville, CA, USA). A 10-minute denaturation at 95°C was followed by 41 cycles of 40 seconds at 93°C, 40 seconds at 51°C, and 30 seconds at 70°C. A final extension at 72°C for 5 minutes completed the reaction. The sizes of PCR products were analyzed by gel electrophoresis on Spreadex EL 400 S-26 minigels (Elchrom Scientific, Zurich, Switzerland) at 170 V for 90 minutes. After staining with SybrGreen (Molecular Probes, Eugene, OR, USA) for 20 minutes and destaining with aqua bidest for 40 minutes, the bands were visualized on an ultraviolet transilluminator at 306 nm and photographed with a Polaroid camera. Selected samples were sequenced on a Perkin Elmer 310 automated DNA sequencer. Samples with 25 GT repeats were included as size markers in every electrophoresis run. The dinucleotide repeat length was evaluated by 2 independent observers. Allelic repeats were divided into two subclasses according to data from transfection studies. Significant induction of the HO-1 promoter/luciferase fusion gene by oxidative stress was observed only in (GT)n repeats <25, whereas the expression of the fusion gene carrying more GT repeats (class L allele) remained at control level (14).

We therefore divided allelic repeats into two subclasses: short repeats, with <25 (GT)n, were designated as allele class S (short), and long repeats with 25 (GT)n or more as allele class L (long). Homozygous class S and heterozygous class S were grouped together and compared to homozygous class L carriers. The rationale for this group classification was an observation that both homozygous and heterozygous carriers of the class S allele exhibited a reduced inflammatory response after vascular injury (17).

Statistical analysis

For statistical analyses the SPSS 10.0 software package (SPSS Inc., Chicago, USA) was used. Continuous data are presented as the median and the interquartile range (IQR, range from the 25th to the 75th percentile). Discrete data are given as counts and percentages. Univariate analysis was performed using a non-parametric Kruskall Wallis Test for continuous variables and Chi square tests for dichotomous variables as adequate. Multivariate linear regression analysis was used to assess the association between HO-1 genotype (carriers vs. non-carriers of the class S allele) and bilirubin as well as lipid parameters (laboratory values were log-transformed before being entered into the model). Multivariate logistic regression analysis was applied to assess the association of the HO-1 genotype and the group classification and to adjust for potentially confounding variables and test for interactions. Regression diagnostics were performed according to standard recommendations: the logit assumption was checked for continuous variables, an analysis of residuals was performed, global goodness of fit testing was performed using the Hosmer Lemeshow test, and interactions were evaluated using multiplicative interaction terms and log likelihood ratio Chi Square tests. Results of the logistic regres-
sion models are given as the odds ratio (OR) and the 95% confidence interval (95% CI). A two sided p-value<0.05 was considered statistically significant. The Bonferroni-Holm method was used to adjust for multiple comparisons. A sample size calculation revealed that with a sample size of 650 patients and 1.5 increase in risk could be detected (with alpha set at 0.05 and beta at 0.80).

Results

The distribution of established risk factors such as hyperlipidemia, hypertension, diabetes and smoking were significantly imbalanced between the three patient groups (Table 1). The stable CAD group and the MI group contained significantly more male patients and the individuals were older compared to controls.

HO-1 genotypes
Within the total population, 41 of 649 (6.3%) individuals were homozygous class S allele carriers, 263 of 649 (40.5%) were heterozygous class S allele carriers and 345 of 649 (53%) were class S allele non-carriers. Genotype frequencies were within the Hardy Weinberg equilibrium in all groups (Table 2).

HO-1 genotype and cardiovascular risk factors
Demographic data and clinical characteristics of patients and controls according to the HO-1 genotype (class S allele carriers vs. non-carriers) are presented in Table 3. There was a significant association between class S allele carrier status and parameters of the lipid profile as well as bilirubin values: carriers of the class S allele had significantly higher total serum bilirubin levels compared to non-carriers. Although the observed differences are small, and bilirubin ranges of both groups are well within the normal range, the accuracy of our measurement method was sufficient to discriminate such small differences (CV=2.2%). Furthermore, carriers of a short allele had lower serum triglycerides, higher HDL cholesterol and a lower total cholesterol/HDL ratio, whereas no differences were observed within LDL cholesterol or total cholesterol levels (Table 3). After adjustment for sex and patient group the observed associations between HO-1 genotype and total bilirubin (p=0.044), HDL cholesterol (p=0.01) and total cholesterol/HDL ratio (p=0.02) remained essentially unchanged. However, no significant association was observed between serum triglycerides and HO-1 genotype after adjustment for gender and group (p=0.2). Other cardiovascular risk factors such as smoking, DM, hypertension, age or male sex were not significantly imbalanced between carriers and non-carriers of the class S allele (Table 3).

HO-1 genotype and coronary heart disease
No significant differences in genotype frequency (Table 2) or allele frequency (Table 1) between the three patient groups (controls, stable CAD, MI) were observed in these patients. We then applied a multivariate model to adjust for possible confounding effects and to test for interaction between the HO-1 genotype and traditional cardiovascular risk factors (Table 4). To evaluate possible interactions of the HO-1 genotype and known cardiovascular risk factors (male sex, age, hypercholesterolemia, hypertriglyceridemia, hypertension, diabetes and smoking), in a first step we compared all (stable and unstable) CAD patients to the control group, and in a second step the stable CAD group versus MI patients. As expected, cardiovascular risk factors were significantly

<table>
<thead>
<tr>
<th>HO-1 Genotype</th>
<th>Controls (n=211)</th>
<th>Stable CAD (n=180)</th>
<th>MI (n=258)</th>
<th>Total (n=649)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous S (S/S)</td>
<td>16 (7.6%)</td>
<td>12 (6.7%)</td>
<td>13 (5.0%)</td>
<td>41 (6.3%)</td>
</tr>
<tr>
<td>Heterozygous S (S/L)</td>
<td>83 (39.3%)</td>
<td>74 (41.1%)</td>
<td>106 (41.1%)</td>
<td>263 (40.5%)</td>
</tr>
<tr>
<td>Homozygous L (L/L)</td>
<td>112 (53.1%)</td>
<td>94 (52.2%)</td>
<td>139 (53.9%)</td>
<td>345 (53.2%)</td>
</tr>
<tr>
<td>$X^2$ test for HWE</td>
<td>p=0.99</td>
<td>p=0.88</td>
<td>p=0.45</td>
<td>p=0.62</td>
</tr>
</tbody>
</table>

CAD denotes stable coronary artery disease
MI denotes myocardial infarction
HWE denotes Hardy Weinberg Equilibrium
S denotes <25 GT repeats in the HO-1 gene promoter
L denotes \geq25 GT repeats in the HO-1 gene promoter

No significant differences between the three patient groups with respect to the HO-1 class S allele frequency (p=0.84)
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associated with CAD. However, in both comparisons we found no significant association between the HO-1 genotype and CAD or MI, respectively. Furthermore, no significant interactions between the HO-1 genotype, cardiovascular risk factors and CAD / MI was observed, indicating that also in subgroups of high risk patients (e.g. diabetes) no association between the HO-1 genotype and CAD can be found in these patients.

### Discussion

We found that the HO-1 polymorphism is associated with favourable changes in serum bilirubin and HDL, but not with an increased risk for CAD in Caucasians.

The inducible form of HO, HO-1 is transcriptionally up-regulated by a variety of pathophysiological conditions or

### Table 3: Heme oxygenase-1 (HO-1) class S allele (<25GT repeats) is associated with various favorable changes in the lipid profile and in total serum bilirubin levels.

<table>
<thead>
<tr>
<th></th>
<th>Class S allele carriers (n=384)</th>
<th>Class S allele non-carriers (n=345)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Sex</td>
<td>209 (48.3%)</td>
<td>224 (51.7%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Age</td>
<td>64 (52-70)</td>
<td>61 (54-71)</td>
<td>0.59</td>
</tr>
<tr>
<td>Triglycerides [mg/dL]</td>
<td>118 (87-174)</td>
<td>132 (97-191)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total cholesterol [mg/dL]</td>
<td>203 (168-230)</td>
<td>201 (171-234)</td>
<td>0.43</td>
</tr>
<tr>
<td>LDL-Cholesterol [mg/dL]</td>
<td>124 (99-153)</td>
<td>126 (101-154)</td>
<td>0.46</td>
</tr>
<tr>
<td>HDL-Cholesterol [mg/dL]</td>
<td>47 (40-59)</td>
<td>45 (37-55)</td>
<td>0.01</td>
</tr>
<tr>
<td>TC/HDL ratio</td>
<td>4.1 (3.4-5.1)</td>
<td>4.6 (3.5-5.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Total bilirubin [mg/dL]</td>
<td>0.66 (0.49-0.91)</td>
<td>0.61 (0.45-0.82)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes present</td>
<td>107 (45.5%)</td>
<td>128 (54.5%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hypertension present</td>
<td>178 (47.3%)</td>
<td>198 (52.7%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Smokers</td>
<td>93 (44.3%)</td>
<td>117 (55.7%)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Continuous data are given as median and interquartile range (IQR, range from the 25th to the 75th percentile, discrete variables are given as counts and percentage.

### Table 4: Multivariate logistic regression analysis comparing the HO-1 genotype distribution (carriers vs. non-carriers of the class S allele) in CAD patients and controls as well as in CAD and MI patients.

<table>
<thead>
<tr>
<th></th>
<th>CAD vs controls</th>
<th>MI vs stable CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Male sex</td>
<td>4.2 (2.8-6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (in tertiles)</td>
<td>2.3 (1.8-3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2.7 (1.8-4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>2.3 (1.4-3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.9 (1.3-2.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.9 (1.8-4.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.2 (0.8-1.8)</td>
<td>0.3</td>
</tr>
<tr>
<td>Carrier of the HO-1 &lt;25 allele</td>
<td>1.0 (0.7-1.5)</td>
<td>0.8</td>
</tr>
</tbody>
</table>
substances involved in the pathogenesis of CAD and MI such as hypoxia (23), ischemia (24), hypertension (25), proinflammatory cytokines or oxidized LDL (26). The heme oxygenase reaction, which is the rate limiting step of heme degradation in mammals, mediates the conversion of heme to biliverdin, carbon monoxide and free iron (3). The elimination of prooxidant heme and the production of these metabolites are proposed to provide cytoprotective roles against different pathophysiological stresses in the vascular wall (27, 28).

Oxidative modification of lipoproteins in the vascular wall is believed to be essential for the initiation and development of atherosclerosis. In this context beneficial effects of HO-1 recently could be shown in an animal model (29, 30). Additionally, Yamada et al. (14) observed that the individual HO-1 response is genetically determined by a (GT) repeat polymorphism in the promoter region of the HO-1 gene. In vitro the HO-1 short allele (<25 (GT) repeats) shows a significantly higher HO-1 expression in response to oxidative stress compared to non-carriers of the class S allele. Putting these findings together, it seemed reasonable to speculate that increased HO-1 upregulation in patients with short GT repeat alleles may exert a protective effect against atherosclerotic lesion formation via an enhanced release of antioxidant bilirubin. Consistently, we could demonstrate a presumably protective effect of the class S allele against the formation of abdominal aortic aneurysms (15).

Two independent studies reported that the HO-1 promoter polymorphism might also protect from CAD in Orientals (18, 31). However, in both studies the effect of the HO-1 genotype was restricted to selected subgroups of patients: Chen et al. (18) reported that in a Chinese population the association between CAD and the HO-1 genotype was restricted to patients with DM, whereas Kaneda et al. (31) found an association between the HO-1 genotype and CAD in Japanese patients with hyperlipidemia, DM and smoking. In the present study, we found an association between the HO-1 class S allele and slightly elevated total bilirubin levels, indicating that individuals carrying this allele might have higher levels of HO-1 and an increased production of the endogenous antioxidant bilirubin. Elevated serum bilirubin levels have been consistently reported to protect from CAD in several studies (32-34). However, it is likely that the changes in serum bilirubin levels observed in our study were far too low to exert a beneficial effect on the total risk for CAD or MI. Additionally, we found that carriers of the class S allele have slightly higher HDL levels and lower serum triglyceride levels, whereas total cholesterol and LDL levels were not different. This effect might be explained by the anti-inflammatory effect of HO-1. Inflammatory conditions have been consistently shown to influence HDL and triglyceride concentrations (35), an effect which may be counteracted by HO-1. However, analysing the possible association between the HO-1 promoter polymorphism and CAD in Caucasians we did not observe an association between CAD or MI and the HO-1 genotype neither in the total population nor in patients' subgroups with diabetes or hyperlipidemia, suggesting that the beneficial effects on bilirubin elevation and lipid profile improvement were too small to influence the risk for CAD and MI.

Our findings are in contrast to the observations made in Orientals. Although an explanation for these differing findings is currently missing, environmental risk profiles (Western lifestyle) probably in combination with the ethnic background might explain this phenomenon. The impact of several environmental risk factors such as DM or smoking on the individual risk for suffering CAD may significantly differ depending on the ethnic background. Nevertheless, even adjusting for environmental influences and established cardiovascular risk factors, we did not find a significant association between CAD and the HO-1 genotype.

**Limitations and comparability of the study**

Undoubtedly, the impact of a single nucleotide polymorphism on a complex disease such as CAD or MI, may be influenced by patient selection, ethnic background or sample size among others. Our collective represents a cross-sectional sample of survivors of MI and CAD. Patients with MI, who died of sudden cardiac death before reaching the hospital, could not be included in our study. Therefore, our findings can only be applied to survivors of MI.

Kaneda et al. (31) proposed a cut off point at <27 repeats in contrast to our study where we proposed a cut off at <25 GT repeats. However, since only few individuals carry alleles with 25 and 26 GT repeats (~5%) the obtained results should not differ significantly. In contrast, Chen et al (18) chose to divide the GT repeat alleles into three groups: <23 , 23-32 and >32 repeats. This results in 6 different genotypes of unknown clinical significance since the individual level of HO-1 expression in the various genotypes is unknown. Since there is evidence for an increased HO-1 response also in 23 and 24 GT repeats (17) we chose this cut off point for the current study. Given the different published criteria for defining “short” and “long” alleles of 22, 23 or 25 (14, 16, 18, 19) for short alleles and 27 or 30 for long alleles (14, 19), we decided to restrict our analysis to criteria previously published by our group, which proved to correlate with an intermediate phenotype (17) as well as with a clinical outcome parameter (16). Nevertheless, we are aware that we can thus only provide a rough information whether a long or short allele is present. Thus a direct comparison to the other studies is difficult. Another limiting point of our study is the sample size and thus changes in relative risk <1.5 fold might be missed. However, these small effects are likely to be of limited clinical relevance.

**Conclusion**

We observed some favourable differences in serum bilirubin levels and in the lipid profile in carriers of the class S allele in
the HO-1 gene promoter. However, these small alterations may not have been sufficient to exert a protective effect against the development and clinical severity of CAD. In contrast to Orientals, we found no association between the HO-1 (GT) repeat promoter polymorphism and CAD in Caucasians, neither in the unselected total collective nor after stratification for conventional risk factors. Thus, we conclude that in Caucasians screening for the HO-1 promoter polymorphism might not be indicated for the risk assessment for CAD.

References