Association of a functional polymorphism in the *CYP4A11* gene with systolic blood pressure in survivors of myocardial infarction

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Objective **Survivors of myocardial infarction (MI) are known to have a high prevalence of arterial hypertension which, at the same time, imposes a major risk to such patients. Genetic variants of the arachidonic acid monooxygenase *CYP4A11* may result in decreased synthesis of 20-hydroxyeicostatetraenoic acid (20-HETE), experimental hypertension and elevated blood pressure levels in humans. The present study aimed to investigate the impact of the functionally relevant T8590C polymorphism of this gene on blood pressure and the prevalence of hypertension in MI patients.**

Methods **Survivors of MI from the MONICA Augsburg MI registry ($n = 560$) were studied after a mean of 5.6 years after the acute event. Participants were examined by standardized anthropometric and echocardiographic measurements, as well as genotyping for *CYP4A11* T8590C allele status.**

Results **Genotype frequencies in MI patients (TT = 71.8%, CT = 26.2%, CC = 2.0%) did not differ from those in population-based controls ($n = 1363$; TT = 75.4%, CT = 22.5% and CC = 2.1%, $P = 0.22$). MI survivors with the CC genotype displayed higher systolic blood pressure levels (CC: 143.4 ± 4.9 mmHg versus CT: 134.5 ± 1.3 mmHg and TT: 131.1 ± 0.8 mmHg; $P = 0.02$) and a non-significant trend towards higher diastolic blood pressure levels (CC: 88.4 ± 3.0 mmHg versus CT: 84.9 ± 0.8 mmHg and TT: 83.9 ± 0.5 mmHg; $P = 0.17$) in multivariate models. Accordingly, the C allele was related to elevated odds ratios for hypertension in a recessive [4.14; 95% confidence interval (CI) = 1.07–15.96, $P = 0.04$] and in a dominant model (1.50; 95% CI = 1.03–2.20, $P = 0.04$), respectively. No blood pressure-independent association of the T8590C polymorphism with echocardiographic parameters of left ventricular function and/or geometry was found.**

Conclusion **The data obtained in the present study strengthen the evidence of an association of the *CYP4A11* T8590C polymorphism with blood pressure levels and hypertension prevalence. Particularly, the risk of arterial hypertension is substantially higher in MI patients homozygous for the CC allele. By contrast, no evidence was obtained for an association between this genotype and MI.** ***J Hypertens*** **24:1965–1970 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Arterial hypertension markedly increases the mortality of patients with a history of myocardial infarction (MI) [1]. Thus, it is important to identify conditions that increase the prevalence of hypertension in MI survivors. In addition to environmental factors, blood pressure levels in MI patients may be modulated by genetic variants [2–5]. Mutations with profound implications for blood pressure regulation have been found predominantly in exceptional families [6] but none of these mutations has been studied in MI patients to date. Moreover, some frequent polymorphisms have displayed consistent

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effects on blood pressure in the overall population [3,7–12]. In such cases, no or only limited information is available regarding their implications for blood pressure levels after MI. Likewise, the *CYP4A11* T8590C polymorphism repeatedly displayed substantially elevated blood pressure levels in healthy individuals homozygous for the C allele [11,12]. The present study reports on the implications of this polymorphism in patients surviving a MI. First, the study aimed to reproduce the association with the CC genotype of the *CYP4A11* gene with elevated blood pressure in a patient sample with a high prevalence of hypertension. Moreover, the potential implications of this interesting variant in the complex phenotype MI were investigated.

Methods

Study populations

Patients suffering from MI prior to the age of 60 years were identified through the Augsburg MONICA (Monitoring trends and determinants in Cardiovascular disease) MI register. Starting in 1984, this clinical register has collected information on all these patients in the urban and surrounding areas of the Bavarian city of Augsburg. The diagnosis of MI was established according to the MONICA diagnostic criteria [13]. In June 1996, a total of 1187 patients who were alive and had suffered from premature MI were registered. Between 1996 and 1997, all individuals with living siblings were contacted and, after providing their informed consent, invited to participate in the study (KORA-B study). A total of 606 MI patients (529 men, 77 women) were studied by physical examination, blood testing and a standardized interview, including medical history, physical activity, medication and personal habits. Resting blood pressure was taken according to MONICA guidelines using random zero sphygmomanometers after patients had been resting in a sitting position. The mean of the second and third recording was calculated and employed to define hypertension as a blood pressure $\geq$ 140/90 mmHg. The standard treatment after myocardial infarction included angiotensin-converting enzyme (ACE)-inhibitors and β-blockers in most patients because of their positive effects on the remodelling process. However, because these agents also have antihypertensive effects, the majority of patients (82.7%) in the present population formally received by definition antihypertensive medication, although elevated blood pressure might not be the leading indication in most cases. Therefore, the intake of antihypertensive medication did not comprise part of the definition of 'hypertension' in the present study. Body weight (kg) and height (m) were determined when patients were wearing light clothing. Written informed consent was obtained from all patients, and a local ethical committee approved the study protocol.

Patients from the echocardiographic substudy (n = 1397) of the third population-based MONICA/KORA Augsburg survey 1994/5 served as a control group. The association of *Cyp4A11* with blood pressure in this population has recently been reported [12]. A total of 34 individuals with MI were excluded, leaving 1363 controls for the final analyses.

Echocardiographic measurements

A two-dimensionally guided M-mode echocardiogram recorded on strip-chart paper at 50 mm/s was performed for each subject. Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters, septal wall (IVS) and posterior wall (PWD) thickness were measured according to the recommendations of the American Society of Echocardiography (ASE) [14]. Left ventricular mass (LVM) was calculated using the formula $\text{LVM (g)} = 0.8 \times 1.04[(\text{LVEDD} + \text{IVS} + \text{PWD})^3 - \text{LVEDD}^3] + 0.6$ as described by Devereux *et al.* [15] LVM was indexed to body surface area (BSA). Left-ventricular end-systolic and end-diastolic volumes (LVESV and LVEDV) were calculated according to the Teichholz equations [16]. The ejection fraction was calculated as EF = (LVEDV – LVESV)/LVEDV.

Genotyping

Genotyping of the T8590C polymorphism was performed as described previously [12]. Ten percent of all genotypes were repeated in independent polymerase chain reactions to check for consistency and to ensure intra- and inter-plate genotype quality control. No genotyping discrepancies were detected between the repeated samples. For the present study, 561 post-MI patients and 1397 controls [12] were successfully genotyped.

Statistical analysis

To determine whether the genotypes of the *CYP4A11* T8590C polymorphism conformed with Hardy–Weinberg equilibrium, the equivalence test proposed by Wellek [17] was used (equivalence level 5%). To evaluate whether the effect of the genotype on blood pressure and left ventricular mass measurements, the prevalence of hypertension and the risk of MI was independent of conventional risk factors, multivariate models were used for analyses. Based on our previous results [12], the effect of the genotype on systolic and diastolic blood pressure in a recessive model (CC versus CT + TT) was tested primarily. Least square means for systolic and diastolic blood pressure adjusted for age, body mass index (BMI), gender and diabetes were calculated for all genotype groups. The relationship between continuous variables and dependent variables was modelled using fractional polynomials [18]. The intake of antihypertensive medication (dichotomous: yes versus no) was also tested, but revealed $P \geq 0.05$. Similarly, if each class of antihypertensive medication (ACE-inhibitors, β-blockers, diuretics and Ca^{2+}-antagonists) was tested separately in the models, they

were not significant covariates at the 5% level. Similarly, the number of antihypertensive agents taken by each patient showed $P \geq 0.05$ for both systolic and diastolic blood pressure.

P-values of a two-tailed *t*-test for independent groups for a recessive model (CC versus CT + TT) and exploratory *P*-values for a dominant model (CC + CT versus TT) are reported.

In addition, the association with hypertension (presence versus absence of hypertension) was reported descriptively. A logistic regression model with genotype, age, and BMI, gender, and diabetes as explanatory variables was developed, and odds ratios (ORs) and 95% Wald confidence intervals (CI) are reported. Based on our previous results [12], the genotype was coded for a recessive effect (CC versus CT + TT). For comparison, a dominant model (CC + CT versus TT) was considered. Two-tailed exploratory *P*-values of the Wald χ^2-test are reported.

Echocardiographical data according to 8590TT, 8590CT and 8590CC genotypes were descriptively compared using multiple linear regression with genotype, age, BMI, systolic blood pressure, gender, antihypertensive medication, and diabetes as explanatory variables. Exploratory *P*-values for a dominant model (CC + CT versus TT) and a recessive model (CC versus CT + TT) are reported. Furthermore, ORs and 95% Wald type CI for MI were calculated using logistic regression analyses with age, gender, BMI, smoking status, low-density lipoprotein (LDL) cholesterol, systolic blood pressure, diabetes, and genotype as explanatory variables, and odds ratios and 95% Wald type CI, as well as exploratory *P*-values, are reported.

Results

In total, 561 MI patients were genotyped successfully. One individual was excluded due to missing BMI values, leaving 560 patients (489 men, 71 women) for the final analysis. The allele frequencies of the 8590T and 8590C allele were 84.9 and 15.1%, respectively, and the 8590TT, 8590CT and 8590CC genotypes were found in 71.8, 26.2 and 2.0% of cases. These frequencies did not deviate from those predicted by Hardy–Weinberg equilibrium and were similar to those reported in previous studies [11,12]. The baseline characteristics of the study population, stratified by hypertension status, are shown in Table 1. In total, 228 MI patients (40.7%) were hypertensive. Age, BMI, the prevalence of diabetes and the intake of antihypertensive medication, stratified by T8590C genotype, are shown in Table 2. The prevalence of diabetes was not significantly elevated in individuals with CC genotype ($P = 0.079$ in a recessive model).

Table 1 Baseline characteristics of post myocardial infarction patients

	Normotensive	Hypertensive
N	332	228
Male, *n* (%)	287 (86.4)	202 (88.6)
Age (years)	56 ± 8	57 ± 7
BMI (kg/m^2)	28.0 ± 3.6	29.1 ± 3.9
SBP (mmHg)	122 ± 10	147 ± 14
DBP (mmHg)	78 ± 7	93 ± 9.0
Diabetes (%)	48 (14.5)	40 (17.5)

For continuous variables, mean ± SD is presented and, for binary variables, the number of individuals (percentage) is given. SBP, Systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Association of the T8590C polymorphism with blood pressure

The effect of the factors age, BMI, gender and diabetes on systolic and diastolic blood pressure is shown in Table 3. Adding the genotype to these models yields the effect of the genotype adjusted for the risk factors (Table 4). Compared to individuals with the TT genotype, C-allele carriers displayed higher systolic (SBP) levels and showed a tendency towards higher diastolic blood pressure (DBP) levels, in a recessive model as well as in a dominant model (Table 5). When assuming a recessive effect of the C allele, the OR of having hypertension with the CC genotype compared to CT and TT genotype was 4.14 (95% CI = 1.07–15.96) in the entire study population. Assuming a dominant effect of the C allele, there was still a significant association of the C allele with the prevalence of hypertension in the entire study group (OR = 1.50; 95% CI = 1.03–2.20) (Table 6).

Table 2 Age, body mass index (BMI), prevalence of diabetes, and intake of antihypertensive medication stratified by T8590C genotype

	TT	CT	CC
N	402	147	11
Age (years), mean ± SD	56 ± 7	56 ± 7	60 ± 4
BMI (kg/m^2) mean ± SD	28.3 ± 3.9	29.0 ± 3.5	27.2 ± 1.9
Diabetes, *n* (%)	64 (16.0)	20 (13.7)	4 (36.4)
Antihypertensive medication, *n* (%)	332 (82.6)	121 (82.3)	10 (90.9)
Number of antihypertensive agents (mean ± SD)	1.44 ± 0.9	1.44 ± 0.9	1.45 ± 0.9

Table 3 Linear regression models with systolic and diastolic blood pressure as dependent variables including age, body mass index (BMI), gender and diabetes as explanatory variables

	Systolic blood pressure			Diastolic blood pressure		
	β	SE	*P*	β	SE	*P*
Age	0.48	0.09	< 0.001	−0.03	0.06	0.605
BMI	0.95	0.19	< 0.001	0.662	0.11	< 0.001
Gender	0.12	2.08	0.941	−3.09	1.28	0.016
Diabetes	−1.23	1.93	0.524	3.99	1.18	0.001

Table 4 Linear regression models with systolic and diastolic blood pressure as dependent variables including age, body mass index (BMI), gender, diabetes, and *Cyp4A11* genotype (recessive model, CC versus CT + TT) as explanatory variables

	Systolic blood pressure			Diastolic blood pressure		
	β	SE	*P*	β	SE	*P*
Age	0.46	0.09	< 0.001	−0.03	0.06	0.557
BMI	0.97	0.18	< 0.001	0.63	0.11	< 0.001
Gender	0.04	2.07	0.999	−2.96	1.29	0.014
Diabetes	−0.89	1.92	0.645	4.11	1.18	0.001
Cyp4A11 (CC versus CT + TT)	11.43	4.99	0.022	3.44	3.09	0.169

Association of the T8590C polymorphism with left ventricular mass measurements

In 554 individuals (483 men, 71 women) echocardiograms of sufficient quality were available. The C-allele was associated with trends towards higher left ventricular mass index, septal and posterior wall thickness, and with an increase of the end-diastolic diameter, although the *P*-value reached statistical significance only for the posterior wall thickness in a recessive model (Table 7).

Association of the T8590C polymorphism with myocardial infarction

The genotype distribution of T8590C polymorphism was not significantly different between post-MI patients (TT = 71.8%, CT = 26.2%, CC = 2.0%) and controls from a population-based sample (TT = 75.4%, CT = 22.5%, CC = 2.1%). Likewise, in a multivariate model adjusted for age, gender, BMI, smoking status, LDL cholesterol, SBP and diabetes, no elevated ORs were obtained for MI, neither in a dominant (OR = 1.20; 95% CI = 0.92–1.57; $P = 0.18$), nor in a recessive model (OR = 1.41; 95% CI = 0.61–3.25; $P = 0.42$; Table 8).

Discussion

The *CYP4A11* arachidonic acid monooxygenase oxidizes endogenous arachidonic acid to 20-hydroxyeicostatetraenoic acid (20-HETE) which can act as a pro- or antihypertensive metabolite [19–22]. Screening for genetic variants revealed a cytosine for thymidine transition at nucleotide 8590 in exon 11, which results in a non-synonymous phenylalanine (F) to serine (S) substitution at residue 434 of *CYP4A11* [11]. The less frequent 8590C genotype, which corresponds to the 434S variant on protein level, affects the catalytic activity of the 20-HETE synthase through a loss-of-function mechanism [11]. In the present study, a statistically significant association is reported between the C allele of the T8590C polymorphism of the *CYP4A11* gene with elevated systolic blood pressure in survivors of premature MI. The results are consistent with a blood pressure-elevating effect of the less frequent C allele, as previously described in three independent healthy population samples [11,12].

In comparison with homozygous T allele carriers (i.e. those with normal enzymatic activity [11]), heterozygous CT allele carriers had blood pressure levels elevated by 3 mmHg SBP and 1 mmHg DBP. The relatively rare CC genotype was associated with a substantially larger increase of blood pressure of approximately 12 mmHg SBP and 4 mmHg DBP. This elevation in SBP and DBP was much larger than that observed with most other hypertension-related polymorphisms [3,23,24], suggesting profound implications of the impaired functional activity of the enzyme.

In MI patients carrying the C allele, the relative risk for having arterial hypertension was elevated for both inheritance models assumed (i.e. dominant and recessive). This

Table 5 Systolic (SBP) and diastolic (DBP) blood pressure measurements, according the T8590C genotype, assuming a dominant and a recessive effect of the C allele

	TT	CT	CC	P^a	P^b
N	402	147	11		
SBP (mmHg)	131.1 ± 0.8	134.5 ± 1.3	143.4 ± 4.9	0.010	0.022
DBP (mmHg)	83.9 ± 0.5	84.9 ± 0.8	88.4 ± 3.0	0.192	0.169

Values are least square means ± SE adjusted for age, body mass index, gender and diabetes. [a]Two-tailed *P*-values from *t*-test for independent data for the recessive model (CC versus CT + TT). [b]Two-tailed exploratory *P*-values from *t*-test for independent data for the dominant model (CC + CT versus TT).

Table 6 Genotype distribution of the T8590C polymorphism stratified by presence or absence of hypertension and odds ratios (OR) for hypertension, assuming a dominant or recessive effect of the C allele

	Normotensive	Hypertensive
N	332	228
Genotype		
8590 TT, *n* (%)	250 (75.3)	152 (66.7)
8590 CT, *n* (%)	79 (23.8)	68 (29.8)
8590 CC, *n* (%)	3 (0.9)	8 (3.5)
8590 C allele frequency	0.13	0.18
OR (95% CI), P^a	4.14 (1.07–15.96), $P = 0.039$	
OR (95% CI), P^b	1.50 (1.03–2.20), $P = 0.036$	

OR [95% confidence interval (CI)] adjusted for age, body mass index, gender and diabetes. [a]Two-tailed exploratory *P*-values from Wald type χ^2-test; data for the recessive model (CC versus CT + TT). [b]Two-tailed exploratory *P*-values from Wald type χ^2-test; data for the dominant model (CC + CT versus TT).

Table 7 Effect of the T8590C polymorphism on left ventricular mass measurements in 554 post myocardial infarction patients

	TT	CT	CC	P^a	P^b
N	399	145	10		
LVMI (g/m^2)	120.7 ± 1.6	122.4 ± 2.7	137.6 ± 10.2	0.38	0.11
Septal wall (mm)	10.9 ± 0.1	11.0 ± 0.2	11.6 ± 0.7	0.74	0.36
Posterior wall (mm)	10.0 ± 0.1	10.0 ± 0.1	11.1 ± 0.5	0.89	0.027
LVEDD (mm)	55.1 ± 0.3	55.4 ± 0.6	56.6 ± 2.1	0.48	0.50
EF (%)	51.2 ± 0.5	49.8 ± 0.9	52.7 ± 3.5	0.21	0.60

Values are least square means ± SE adjusted for age, body mass index, and systolic blood pressure, gender, antihypertensive medication, and diabetes. [a]Two-tailed exploratory *P*-values from *t*-test for independent data for the recessive model (CC versus CT + TT). [b]Two-tailed exploratory *P*-values from *t*-test for independent data for the dominant model (CC + CT versus TT). LVMI, Left ventricular mass index; LVEDD, left ventricular end-diastolic diameter; EF, ejection fraction.

Table 8 Genotype distribution in post myocardial infarction patients and in controls and odds ratios (OR) and 95% confidence intervals (CI) for myocardial infarction (MI) assuming a dominant and a recessive effect of the C-allele

	Controls	Post-MI patients
All individuals	1363	560
Genotype		
8590 TT, *n* (%)	1028 (75.4)	402 (71.8)
8590 CT, *n* (%)	307 (22.5)	147 (26.2)
8590 CC, *n* (%)	28 (2.1)	11 (2.0)
8590 C allele frequency	0.13	0.15
OR (95% CI), P^a	1.41 (0.61–3.25); $P = 0.42$	
OR (95% CI), P^b	1.20 (0.92–1.57), $P = 0.18$	

OR (95% CI) were adjusted for age, gender, body mass index, smoking status, low-density lipoprotein cholesterol, systolic blood pressure and diabetes. [a]Two-tailed exploratory *P*-values from Wald type χ^2-test; data for the recessive model (CC versus CT + TT). [b]Two-tailed exploratory *P*-values from Wald type χ^2-test; data for the dominant model (CC + CT versus TT).

issue remains controversial because Gainer *et al.* [11] reported a dominant effect of the C allele within non-diabetics, whereas our group previously demonstrated a recessive mode of inheritance for higher blood pressure levels in a population-based sample [12]. Additional analyses on this interesting variant are needed to clarify the precise genetic mechanism of blood pressure elevation. The present study lacks functional data to explain biochemically the regulatory mechanism mediating the association between the *CYP4A11* polymorphism and arterial blood pressure in survivors of MI. In this respect, Gainer *et al.* [11] demonstrated, in experiments performed *in vitro*, that the C allele of the T8590C polymorphism results in a phenylalanine to serine replacement that reduces the 20-HETE synthase activity of *CYP4A11* by more than half [11]. Verification of this finding *in vivo* would be of great interest. Unfortunately, the material available in the patients from the present study does not allow measurement of the 20-HETE activity in serum samples or total sodium excretion during 24 h after sodium challenge.

One potential bias in the interpretation of the data from the present study might arise from the fact that more than 80% of the patients who were evaluated in this study received antihypertensive medication. However, β-blockers and ACE-inhibitors may have been prescribed in many patients in accordance with guidelines of post-MI treatment rather than for treatment of hypertension. Therefore, hypertensive individuals were defined by blood pressure levels higher than 140/90 mmHg and not by intake of antihypertensive medication. Unfortunately, we cannot address the question of whether patients with elevated blood pressure levels, despite taking of β-blockers or ACE inhibitors, represent those who are more resistant to such medication. However, the findings of the present study clearly suggest the need for further studies on the potential pharmacogenetic effects of the CYP4A11 variant.

Candidate genes for hypertension may be also involved in the pathogenesis of MI. Several candidate gene polymorphisms have been shown to affect both diseases [2,5,10,25]. Therefore, the genotype distribution of the T8590C polymorphism was compared between MI survivors and population-based controls. However, allele and genotype frequencies did not differ significantly, either in a dominant, or in a recessive model. Moreover, our patient sample lacks a follow-up study so that the potential long-term effects of this variante in MI survivors cannot be studied. In complex diseases, several genes and environmental factors are involved in the etiology, and the modulatory effect of each single genetic variant may be small. It might be speculated that the effect of this variant on blood pressure is not strong enough to result in a statistically significant risk elevation for MI in the present sample. The trends observed in the present study may help in performing power calculations when planning larger investigations on this issue. Moreover, the present analysis focused on a sample of infarct survivors, resulting in a potential selection bias. Consequently, prospective analysis on this variant in cohort studies would be of great interest.

Phenotypic data of the KORA-B family heart study further allowed evaluation of the potential impact of the T8590C polymorphism on left ventricular geometry in MI survivors. By statistical means, the C-allele was not, or only marginally, significantly associated with elevations of left ventricular mass index, septal and posterior wall thickness, and end-diastolic diameter. These data are consistent with those obtained in a population-based sample demonstrating no strong effects of this polymorphism on left ventricular mass or geometry, regardless of whether a dominant or recessive mode of inheritance was assumed [12]. The mode of action, with renal expression of the gene and localization of the functional active metabolite 20-HETE in the proximal tubules but no evidence of cardiac expression, may explain these findings.

Taken together, our data allow us to assume that the *CYP4A11* T8590C polymorphism has a significant effect in regulation of blood pressure, which is still highly relevant in patients surviving MI. The substantially increased prevalence of hypertension in carriers of the *CYP4A11* C allele in this high-risk patient group requires further investigation to define the clinical relevance of this genetic marker.

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