

Research Article

COMT-Val158Met-Polymorphism Is Not a Risk Factor for Acute Kidney Injury after Cardiac Surgery

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Background. Cardiac surgery-associated acute kidney injury (CSA-AKI) depicts a major complication after cardiac surgery using cardiopulmonary bypass (CPB). **Objective.** CSA-AKI has clearly been linked to increased perioperative morbidity and mortality. Dysregulations of vasomotor tone are assumed to be causal for CSA-AKI. While catechol-O-methyltransferase (COMT) is involved in metabolizing catecholamines, a single-nucleotide polymorphism (SNP) in the COMT gene leads to different enzyme activities according to genotype. Pilot studies found associations between those COMT genotypes and CSA-AKI. **Methods.** We prospectively included 1741 patients undergoing elective cardiac surgery using cardiopulmonary bypass (CPB). Patients were genotyped for COMT-Val158Met-(G/A) polymorphism (rs4680). **Results.** Demographic characteristics and procedural data revealed no significant differences between genotypes. No association between COMT genotypes and the RIFLE criteria could be detected. A multiple linear regression analysis for postoperative creatinine increase revealed highly significant associations for aortic cross-clamp time ($P < 0.001$), CPB time ($P < 0.001$), norepinephrine ($P < 0.001$), and age ($P < 0.001$). No associations were found for COMT genotypes or baseline creatinine. With an $R^2 = 0.39$ and a sample size of 1741, the observed power of the regression analysis was >99%. **Conclusions.** Based on our results, we can rule out an association between the COMT-Val158Met-(G/A) polymorphism and the appearance of CSA-AKI.

1. Introduction

Cardiac surgery-associated acute kidney injury (CSA-AKI) depicts a major complication in the postoperative course after cardiac surgery using cardiopulmonary bypass and has been linked to increased mortality and morbidity [1, 2]. An individual preoperative risk assessment could offer crucial information to clinicians and finally lead to improved outcomes. The emergence of perioperative genomics has enabled the detection of potential genetic risk factors in order to individualize and optimize therapy [3–7].

Dysregulations of vasomotor tone have been assumed to be causal for CSA-AKI [8]. The catechol-O-methyltransferase (COMT) is one of the enzymes essential for metabolizing

circulating serum catecholamines and thus is involved in the regulation of vascular resistance. The enzyme coding region contains a well-investigated single-nucleotide-polymorphism (SNP) in codon 158 (rs4680), in which valine (Val) is substituted to methionine (Met) through a substitution of guanine to adenine. Three genotype groups (homozygous Val158Val, heterozygous Val158Met, and homozygous Met158Met) result from this substitution, which subsequently leads to different enzyme activities based on changes in thermostability. The Met/Met-genotype has a 3-4-fold reduced enzymatic activity compared to the Val/Val-genotype [9]. Considering the crucial role of catecholamine therapy during the perioperative period, we assumed that differences in COMT activities triggered by different genotypes in

the COMT-*Val158Met*-polymorphism subsequently result in a lower or higher risk for CSA-AKI.

The COMT-*Val158Met*-polymorphism has been intensively studied. Associations have been found with the susceptibility and appearance of cognitive phenotypes, psychiatric disorders and changes in brain activation and structure, and cancer susceptibility [10, 11]. Furthermore, links between COMT genotypes and increased risk of coronary events or the outcome of patients with ischemic heart disease have been revealed [12–14].

In a recent study enrolling 260 patients, an association of the COMT genotype with the appearance of CSA-AKI was described. The authors showed that different COMT genotypes were correlated with varying perioperative plasma catecholamine levels. The COMT-Met/Met homozygosity was identified to be an independent risk factor for shock, length of hospital stay after cardiac surgery, and CSA-AKI [15].

In this study, we sought to investigate the influence of the COMT-*Val158Met*-polymorphism on CSA-AKI in a group of 1741 patients undergoing cardiac surgery with CPB.

2. Methods

From December 2006 to July 2009, a total of 1741 consecutive patients undergoing cardiac surgery with CPB were included. In patients who underwent multiple surgeries with CPB, only the first surgery was considered. Patients with cardiogenic shock due to endocarditis ($n = 3$), patients after renal transplantation ($n = 3$), patients after nephrectomy ($n = 2$), and patients with preoperative requirement of dialysis ($n = 12$) were excluded. All patients received antifibrinolytic treatment according to the protocol of our institution to minimize the risk of postoperative bleeding. No patient within the study group was treated with monoamine oxidase (MAO) or COMT inhibitors.

The study was approved by the local ethics committee (888/03). Written informed consent was obtained from all participating patients. After admission, genomic DNA was purified from drawn blood samples using the DNeasy blood and tissue kit (QIAGEN, Hilden, Germany) according to the manufacturer's recommendation. The COMT-*Val158Met*-(*rs4680*) polymorphism was detected by fluorescence-based real-time PCR analysis and subsequent melting curve analysis on a LightCycler 1.5 (Roche, Mannheim, Germany). The following primers and probes were used (TIB MOLBIOL, Berlin, Germany): forward primer 5' GGG CCT ACT GTG GCT ACT CA 3', reverse primer 5' GGC CCT TTT TCC AGG TCT G 3', sensor probe 5' ATT TCG CTG GCA TGA AGG ACA AG-fluorescein (specific for the 158Met allele), and anchor probe 5' LC640-TGT GCA TGC CTG ACC CGT TGT CA 3'.

Genomic DNA (1 μ L) was amplified in a total volume of 10 μ L with 0.4 U FastStart *Taq* polymerase (ROCHE) in the presence of 50 mM Tris/HCl, 10 mM KCl, 5 mM (NH₄)SO₄ pH 8.3, 2.5 mM MgCl₂, BSA (0.5 mg/mL), dNTPs (0.2 mM each), 650 nM of primers, and 188 nM of probes using the following conditions: 10 min at 95°C to activate *Taq*

polymerase followed by 35 cycles with heating to 95°C and 57°C for 10 sec and 72°C for 10 sec.

After amplification, the PCR fragment was subjected to a melting curve analysis. The reaction was heated to 95°C, cooled down to 40° for 2 min, and slowly heated to 80°C at a ramp rate of 0.1°C/sec with continuous recording of the fluorescence signal which was plotted against the temperature, thereby yielding the respective melting points T_m of either allele. The T_m for the Val and Met alleles were approximately 60.5°C and 66.5°C, respectively.

According to the melting curve analysis, patients were distributed into three genotype groups. These groups were analyzed for an association of genotype with an overall increase of postoperative creatinine and the frequency of acute postoperative kidney injury according to RIFLE criteria [16]. RIFLE groups were classified according to postoperative creatinine levels—"risk": increased creatinine $\times 1.5$ – 2.0 ; "injury": increased creatinine $\times 2$ – 3 ; "failure": increased creatinine $\times 3.0$; "loss": complete loss of kidney function > 4 weeks; "ESRD": end stage renal disease (complete loss of kidney function > 3 months). Due to length of hospital stay, the groups "loss" and "ESRD" (end stage renal disease) could not be evaluated.

Statistical tests were run with IBM SPSS Statistics (version 20; IBM, Armonk, NY, USA); the power analysis was performed with StatPages.org. For continuous variables mean values \pm standard deviation, for ordinally scaled variables numbers and corresponding percentages were listed. For comparison of group mean values, an analysis of variance (ANOVA) was used. For comparative analyses of categorical variables, an χ^2 -test was run. Pearson correlation coefficients were calculated for the evaluation of bivariate correlations. A multiple linear regression analysis evaluated the influence of age, norepinephrine, CPB time, aortic cross-clamp time, creatinine at baseline, and Met/Met genotype on postoperative creatinine increase. An explorative, two-sided P value of less than 0.05 was considered significant for all results. There is no correction for the issue of multiple testing due to the screening nature of the study. In addition, this is a conservative interpretation for no-association results.

3. Results

The distribution of homozygous and heterozygous groups was in accordance with the Hardy-Weinberg equilibrium. Group I (Val/Val) consisted of 417 patients, group II (Val/Met) of 850 patients, and group III (Met/Met) of 474 patients. Baseline characteristics were equally distributed across genotype groups (Table 1). The overall gender distribution was 1214 (69.73%) males to 527 (30.27%) females. Mean age in Val/Val was 66.33 ± 11.62 years, and in Val/Met 66.01 ± 11.67 years, in Met/Met 66.08 ± 12.28 years.

Surgical procedures were distributed into "CABG" (coronary artery bypass grafting), "valve," "CABG + valve," and others. There was no difference between genotype groups. Detailed perioperative data are given (Table 2).

Baseline creatinine in Val/Val was 1.01 ± 0.38 mg/dL, in Val/Met 1.00 ± 0.38 mg/dL, and in Met/Met 0.98 ± 0.31 mg/dL, $P = 0.556$. Peak postoperative creatinine during

TABLE 1: Demographics.

	Val/Val 417 (24.0%)	Val/Met 850 (48.8%)	Met/Met 474 (27.2%)	<i>P</i>
Age (years)	66.33 ± 11.62	66.01 ± 11.67	66.08 ± 12.28	0.901
Male	295 (70.7%)	596 (70.1%)	323 (68.1%)	0.661
Weight (kg)	80.00 ± 14.74	80.16 ± 14.21	78.87 ± 13.11	0.293
Height (cm)	171.54 ± 9.23	171.3 ± 9.3	171.5 ± 8.2	0.871
LVEF*	57.83 ± 14.10	57.79 ± 14.83	58.57 ± 15.11	0.474
PAD**	23 (5.6%)	55 (6.6%)	23 (4.9%)	0.460
COPD***	25 (6.1%)	63 (7.6%)	29 (6.2%)	0.521
Previous cardiac surgery	38 (9.2%)	71 (8.5%)	37 (7.9%)	0.736
PMI****	62 (15.1%)	108 (12.9%)	75 (16.2%)	0.252
Atrial fibrillation	74 (24.3%)	148 (22.9%)	84 (22.9%)	0.789
Cardiovascular risk factors				
Arterial hypertension	289 (77.1%)	586 (75.9%)	327 (75.9%)	0.897
Diabetes	79 (24.5%)	156 (18.4%)	97 (24.9%)	0.655
Tobacco smoking habit	88 (21.1%)	157 (18.5%)	77 (16.2%)	0.706
Hyperlipidaemia	125 (37.4%)	267 (38.1%)	149 (38.0%)	0.971
Preoperative medication				
Beta-blockers	154 (37.5%)	333 (40.0%)	185 (39.8%)	0.676
Diuretics	154 (37.5%)	324 (38.8%)	184 (39.6%)	0.811
ACE inhibitor*****	101 (24.6%)	225 (27.0%)	145 (31.2%)	0.081
Statins	111 (26.6%)	239 (28.1%)	136 (28.7%)	0.776
Nitrates	20 (4.8%)	37 (4.4%)	27 (5.7%)	0.551
Preoperative laboratory findings				
Hemoglobin (g/dL)	13.59 ± 1.56	13.59 ± 1.52	13.64 ± 1.53	0.908
Urea (mg/dL)	45.82 ± 24.78	43.01 ± 22.03	43.17 ± 23.67	0.242
Creatinine (mg/dL)	1.01 ± 0.38	1.0 ± 0.38	0.98 ± 0.31	0.556

*LVEF: left ventricular ejection fraction.

**PAD: peripheral arterial disease.

***COPD: chronic obstructive pulmonary disease.

****PMI: previous myocardial infarction.

*****ACE: angiotensin converting enzyme.

TABLE 2: Procedural and perioperative data.

	Val/Val 417 (24.0%)	Val/Met 850 (48.8%)	Met/Met 474 (27.2%)	<i>P</i>
CABG*	120 (28.8%)	251 (29.50%)	134 (28.3%)	
Valve	128 (30.7%)	266 (31.3%)	141 (29.7%)	0.931
CABG + valve	71 (17.0%)	147 (17.3%)	93 (19.6%)	
Others	98 (23.5%)	186 (21.9%)	106 (22.4%)	
Aortic cross clamp time (min)	75.1 ± 29.6	72.2 ± 27.3	74.2 ± 29.5	0.346
Bypass time (min)	109.3 ± 44.24	106.6 ± 38.2	108.57 ± 42.4	0.482
IABP**	9 (2.2%)	9 (1.1%)	6 (1.3%)	0.289
Transfused blood (mL)	624 ± 1409	610 ± 1341	576 ± 1086	0.845
Postop. ventilation time (h)	15.4 ± 32.6	15.68 ± 52.9	15.66 ± 19.6	0.640
Postop. need of norepinephrine	347 (83.2%)	701 (82.5%)	395 (83.3%)	0.828
Duration of norepinephrine (d)	2.73 ± 6.25	2.61 ± 5.64	2.36 ± 3.66	0.573
Peak creatinine (mg/dL)	1.22 ± 0.83	1.20 ± 0.84	1.17 ± 0.74	0.600

*CABG: coronary artery bypass grafting.

**IABP: Intra-aortic balloon pump.

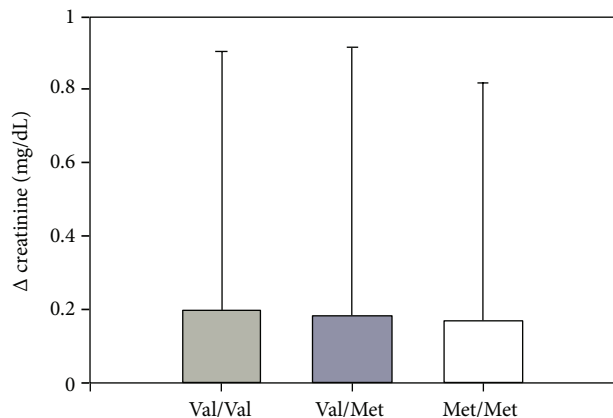


FIGURE 1: Postoperative creatinine increase (mg/dL) as stratified to genotype groups showed no statistical difference.

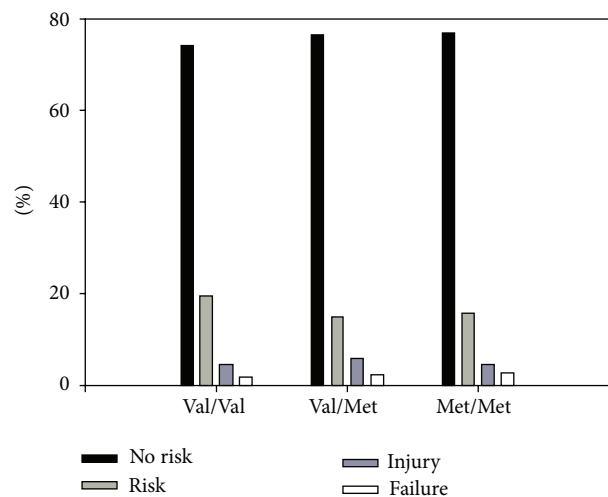


FIGURE 2: Distribution of RIFLE groups as stratified to genotype groups. Between genotypes, no statistical difference was seen.

hospital stay in Val/Val was 1.22 ± 0.83 mg/dL, in Val/Met 1.20 ± 0.84 mg/dL, and in Met/Met 1.17 ± 0.74 mg/dL, $P = 0.600$. Differences between baseline and peak creatinine levels between groups were not significant (Tables 1 and 2).

Correspondingly, differences in postoperative creatinine increase did not reach statistical significance (0.20 ± 0.71 mg/dL in Val/Val, 0.19 ± 0.73 mg/dL in Val/Met, and 0.17 ± 0.65 mg/dL in Met/Met) (Figure 1). Genotype groups were tested for the occurrence of acute kidney injury according to the RIFLE classification.

AKI occurred in 103 (26.1%) patients in group I Val/Val (“risk”: 77 (19.5%), “injury”: 18 (4.6%), and “failure”: 8 (2%)); in 190 (23.4%) patients in group II Val/Met (“risk”: 123 (15.1%), “injury”: 46 (5.7%), and “failure”: 21 (2.6%)); in 105 (23.3%) patients in group III Met/Met (“risk”: 71 (15.7%), “injury”: 21 (4.7%), and “failure”: 13 (2.9%)). The analysis revealed no significant differences in the incidence of acute kidney injury, $P = 0.532$ (Figure 2).

TABLE 3: Linear regression analysis for postoperative creatinine increase.

	Regression coefficient	Standard error	<i>P</i>
(Constant)	-0.591	0.102	<0.001
Met/Met	-0.008	0.034	0.810
Creatinine	-0.006	0.044	0.898
Aortic cross clamp time	-0.005	0.001	<0.001
CPB time*	0.004	0.001	<0.001
Norepinephrine	0.056	0.003	<0.001
Age	0.008	0.001	<0.001

*CPB: cardiopulmonary bypass time.

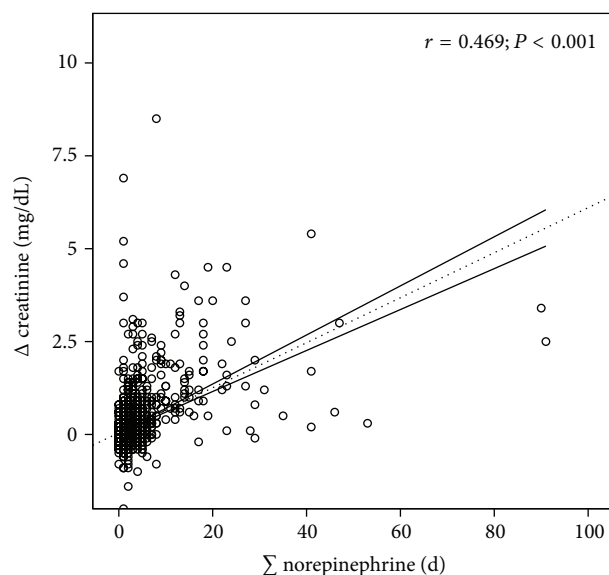


FIGURE 3: Correlation of the amount of applied norepinephrine in days with the postoperative creatinine increase ($r = 0.469$; $P < 0.001$). Dashed line indicates trend; solid lines indicate 95% confidence interval.

The following parameters showed significant linear correlations with a postoperative increase of creatinine in both the univariate and the multivariate analyses: age ($r = 0.205$; $P < 0.001$), bypass time ($r = 0.131$; $P < 0.001$), aortic clamp time ($r = 0.058$; $P = 0.017$), amount of transfused blood ($r = 0.450$; $P < 0.001$), and amount of applied norepinephrine ($r = 0.469$; $P < 0.001$) (Figure 3).

Neither Met/Met genotype nor baseline creatinine was a risk factor for perioperative creatinine increase. With an $R^2 = 0.39$ and a sample size of 1741, the observed power of the regression analysis for delta creatinine was >99% (Table 3).

4. Discussion

CSA-AKI is a common complication following cardiac surgery using CPB and is associated with longer intensive care and hospital lengths of stay, decreased short- and long-term survival, and increased healthcare resource utilization [1, 2,

17, 18]. Although statistical models based on demographic and procedure-related parameters have proven to be useful in assessing perioperative risks, predictors often have poor predictive value for the individual patient.

In 2009, Haase-Fielitz et al. reported on an association of COMT genotype on postoperative kidney injury in 260 patients undergoing cardiac surgery with CPB [15]. The authors measured perioperative plasma norepinephrine levels across genotype groups. Patients with homozygous Met/Met COMT polymorphisms had significantly higher plasma levels of norepinephrine and revealed a significantly higher frequency of vasodilatory shock, longer duration of shock, and a higher frequency of acute kidney injury. Moreover, the homozygous genotype was independently associated with longer intensive care and hospital length of stay [15].

For the detection and classification of acute kidney injury, several models exist, whereas the RIFLE and AKIN classifications remain the two models used in clinical routine. In a large multicenter study including 16,784 patients from 303 intensive care units, Joannidis et al. found that RIFLE criteria showed better robustness and a higher detection rate of AKI [19]. Furthermore, RIFLE classification takes into account baseline creatinine that was routinely obtained from all of our patients' admission. For those reasons, we decided to use the RIFLE classification in our study and did not find significant associations with COMT genotypes.

Furthermore, Tolpin et al. showed that even subclinical changes in serum creatinine depict an independent risk factor for all-cause 30-day mortality after cardiac surgery [2]. In a retrospective cohort of 3914 patients undergoing cardiac surgery using CPB, those changes in creatinine that did not meet acute kidney injury criteria according to RIFLE or AKIN were independently associated with all-cause 30-day mortality [2]. These findings correlate well with an earlier study by Lassnigg et al., who also found an association between minimal serum creatinine changes in the perioperative period and mortality after cardiac surgery [1]. Additionally, a recent multicenter study revealed that perioperative creatinine levels are superior in detection of CSA-AKI in comparison with other parameters like cystatin C [20].

Therefore, we chose the perioperative creatinine change for multiple regression analysis and the subsequent power analysis (Table 3), and we did not find any association between the COMT genotypes and creatinine increase. This analysis had a statistical power >99%. While this most sensitive parameter for AKI after cardiac surgery was not associated with COMT genotypes, we can rule out deleterious effects of the COMT-Val158Met-polymorphism on CSA-AKI.

An assumed cause for CSA-AKI is the systemic inflammatory response syndrome (SIRS) [21]. In cardiac surgery, CPB triggers a complex immune response through different cascades including endogenous and exogenous toxins, damages through ischemia, reperfusion, and reactive oxygen species, resulting in disturbances of microcirculation and vasomotor tone [22–25]. Almost all patients after CPB have temporary vasodilatation with reduced peripheral vascular resistance. For maintenance of a sufficient perioperative blood pressure in defiance of adequate intravascular volume substitution and sufficient cardiac index, vasopressors are the treatment of

choice [26, 27]. Nevertheless, vasopressor use itself is a known risk factor for CSA-AKI, as well as the length of aortic cross-clamp and CPB times [28, 29].

Haase-Fielitz et al. described associations of COMT genotypes with duration of vasodilatory shock and the frequency of acute kidney injury [15]. The authors suppose that persistent vasodilatation may be caused by high circulating catecholamine levels via α -adrenoceptor downregulation and desensitization in vascular smooth muscle cells [30]. In our study, 82.8% of the patients received vasopressor therapy regardless of the COMT genotype (Table 2), and the duration of vasopressor therapy turned out to be a major risk factor for CSA-AKI (Table 3). Despite its assumed role in catecholamine metabolism and the high rate of patients who received vasopressor therapy, COMT genotypes did not turn out as a predictor for CSA-AKI. In comparison to Haase-Fielitz et al., we did not measure plasma catecholamine levels.

Developments in translational and personalized medicine are promising. Advances in next-generation sequencing technologies will rapidly facilitate substantial progress in the discovery of genetic risk factors. Nevertheless, the specific role of the COMT-Val158Met-polymorphism in renal catecholamine metabolism and local blood pressure regulation remains controversial. In conclusion, neither the RIFLE criteria nor the more sensitive creatinine changes during the postoperative period were influenced by COMT genotypes.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

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