

The +405 GG variant of vascular endothelial growth factor polymorphism is associated with poor prognosis in patients undergoing coronary artery bypass graft surgery

Maciej Pastuszcak¹, Agnieszka Branicka², Bogdan Jakiela³, Ewa Stępień², Andrzej K. Jaworek⁴, Anna Wojaś-Pelc⁴, Bogusław Kapelak⁵, Jerzy Sadowski⁵

¹ Joseph Dietl Hospital, Kraków, Poland

² John Paul II Hospital, Kraków, Poland

³ 2nd Department of Medicine, Jagiellonian University School of Medicine, Kraków, Poland

⁴ Department of Dermatology, Jagiellonian University School of Medicine, Kraków, Poland

⁵ Department of Cardiovascular Surgery and Transplantation, Jagiellonian University School of Medicine, Kraków, Poland

KEY WORDS

cardiovascular surgery, coronary artery disease, gene polymorphism, prognosis, vascular endothelial growth factor (VEGF)

ABSTRACT

INTRODUCTION Coronary artery bypass graft (CABG) surgery is associated with systemic response and increased concentrations of numerous cytokines. Vascular endothelial growth factor (VEGF) related pathway also seems to be involved in inflammatory response induced by CABG.

OBJECTIVES The aim of this study was to analyze the association between the VEGF gene +405 G>C polymorphism (linked to serum VEGF production), and the short-term clinical outcome during the in-hospital period (30 days) in patients undergoing CABG.

PATIENTS AND METHODS Genotyping for VEGF gene +405 G>C polymorphism was performed in 64 patients with coronary artery disease at a mean age of 66 years (76.6% males), with a mean EuroSCORE (European System for Cardiac Operative Risk Evaluation) of 2.5 (0–2 points: 50% patients, 3–4: 25%, ≥5 points: 25%), who underwent CABG surgery.

RESULTS Twenty-one (33%) patients were homozygous for the +405 G allele, 40 (63%) were heterozygous, and 3 were homozygous for the +405 C allele. Ten patients died during the 30-day follow-up (7 subjects with +405 GG genotype, and the other 3 carriers of the +405 C allele). Using multivariate logistic regression analysis, the risk of death after CABG was increased in patients with +405 GG genotype (odds ratio [OR] = 6.7; 95% confidence interval [CI] 1.5–29.4) and with EuroSCORE ≥5 points (OR = 4.4; 95% CI 1.1–18.1).

CONCLUSIONS The VEGF gene +405 G>C polymorphism might be a prognostic factor of an adverse postoperative course in patients undergoing CABG surgery. Apart from its proangiogenic action, VEGF may have additional, possibly proinflammatory properties.

INTRODUCTION Coronary artery bypass graft (CABG) surgery is associated with an enhanced inflammatory state. Rapid changes in circulating levels of lipid mediators (such as leukotriene B₄, thromboxane B₂), proinflammatory cytokines (such as interleukin [IL]-6), soluble cytokine receptors (IL-1R), and hematopoietic growth factors (e.g., macrophage colony-stimulating factor

[M-CSF] and granulocyte-CSF), which occur during and after CABG surgery, reflect the systemic inflammatory response, and could be involved in the pathogenesis of postoperative complications.^{1,2}

Moreover, it has been proved that those changes are not solely a result of an unspecific inflammatory state. Other cytokines, including leukemia

Correspondence to:

Maciej Pastuszcak, MD,
Szpital Specjalistyczny im. J. Dietla,
ul. Skarbowa 4, 31-121 Kraków,
Poland, phone: +48-12-687-63-30,
fax: +48-12-421-38-00,
e-mail: mpastuszcak@wp.pl

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inhibitory factor, GM-CSF, and soluble cytokine receptors (such as soluble IL-6 receptor), remain unchanged during and after CABG surgery.^{3,4}

Elevated plasma concentrations of the vascular endothelial growth factor (VEGF) during and after CABG suggest that angiogenesis pathways could also participate in the systemic response associated with CABG surgery.⁵ Moreover, Denizot et al.⁶ showed that postoperative plasma VEGF levels were higher in patients with cardiovascular and hematological disorders.

Until now, there have been 15 single nucleotide polymorphisms identified within the 5' untranslated region of the VEGF gene.⁹ One of them, namely the +405 G>C VEGF polymorphism (rs2010963) seems to have a functional significance because the GG genotype correlated with higher VEGF protein production in healthy individuals.⁷

The aim of our study was to assess whether there is an association between the VEGF gene +405 G>C polymorphism and clinical outcome in patients with coronary artery disease (CAD) undergoing CABG surgery.

PATIENTS AND METHODS **Patients** The study comprised 64 patients (49 males, 76.6%), at a mean age of 66 years, undergoing CABG surgery due to advanced CAD (more than 50% stenosis of the left main coronary artery and disease of all three coronary vessels, or disease of two coronary arteries with a significant narrowing of the left anterior descending artery). All fatal cases (n = 10) were selected from a group of 300 patients who underwent CABG. The remaining 54

patients were randomly selected. Half of patients (50%) in the studied group had 0–2, 25% 3–4, and 25% ≥5 EuroSCORE points. Peripheral blood samples for genotyping and routine laboratory tests, including hemoglobin, lipid profile, glucose, fibrinogen, and prothrombin time, were assayed before surgery. Demographic data, present medical status, and clinical history of patients were recorded. Patients gave their informed written consent and the study was approved by the Jagiellonian University Bioethics Committee.

Genotyping Genomic DNA was extracted from frozen peripheral blood samples using QIAmp Blood Mini Kit (Qiagen Inc., Valencia, California, United States). Genotyping for VEGF gene +405 G>C polymorphism (rs2010963) was performed using polymerase chain reaction (PCR)-restriction fragment length polymorphism method. A fragment of 5'UTR region of VEGF gene was amplified using the following primers: 5'-ATTTATTTTGTCTGCCATT-3' and 5'-GTCTGTCTGTCTGTCCGTC-3' (Tib Molbiol, Poznań, Poland). This results in a 304 bp product. In the presence of +405 G allele PCR product was cleaved by the BsmFI restriction enzyme (Fermentas, Vilnius, Lithuania) in 193 and 111 bp fragments.⁸

Statistical analysis All statistical analyses were performed with Statistica 7.1 PL package (StatSoft, Inc. Tulsa, Oklahoma, United States). Data are expressed as medians (min–max), or otherwise stated. The Kolmogorov-Smirnov test was used to determine whether the data were normally

TABLE 1 Characteristics of study subjects: demographic data and results of laboratory tests

	GG n = 21	GC + CC n = 43	P
age, years	61 (42–77)	66 (48–77)	NS
men, n (%)	17 (81%)	32 (74.4%)	NS
laboratory tests			
hemoglobin, (g/dl)	14.4 (13–16.9)	14.2 (11.1–17.6)	NS
hematocrit, (%)	42.8 (37.6–49.9)	41.5 (32.7–49.2)	NS
RBC, ($\times 10^6/\mu\text{l}$)	4.8 (4.05–5.9)	4.7 (3.63–5.6)	NS
WBC, ($\times 10^3/\mu\text{l}$)	7.3 (3.5–12.1)	7.1 (4.7–21.3)	NS
platelets, ($\times 10^3/\mu\text{l}$)	239 (140–312)	230 (117–387)	NS
INR	1.02 (0.91–1.23)	1.08 (0.92–1.6)	NS
aPTT, (s)	30.8 (22.2–36.5)	30.7 (24.8–44.7)	NS
fibrinogen, (g/l)	4.6 (2.55–5.8)	4.1 (2.4–8.2)	NS
total cholesterol, (mmol/l)	5.4 (4.3–6.7)	4.8 (3.4–6.5)	0.008
LDL-C, (mmol/l)	3.7 (2.4–4.7)	2.9 (1.9–5.0)	0.02
HDL-C, (mmol/l)	1.3 (0.9–1.6)	1.3 (0.9–1.8)	NS
triglycerides, (mmol/l)	1.5 (0.9–2.4)	1.4 (0.7–2.7)	NS
glucose, (mmol/l)	6.3 (4.7–13.7)	5.2 (4.0–10.3)	0.0001

Data are presented as medians (min–max), unless otherwise stated.

Abbreviations: aPTT – activated partial thromboplastin time, INR – international normalized ratio, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, NS – nonsignificant, RBC – red blood count, WBC – white blood count

TABLE 2 Characteristics of study subjects: clinical data (medical history, intake of medications)

	GG n = 21	GC + CC n = 43	P
ejection fraction, (%)	50 (30–70)	50 (30–70)	NS
peripheral artery disease, n (%)	7 (33.3%)	7 (16.3%)	NS
hypertension, n (%)	18 (85.7%)	34 (79.1%)	NS
history of MI, n (%)	19 (90.5%)	33 (76.7%)	NS
history of stroke, n (%)	2 (9.5%)	2 (4.7%)	NS
diabetes, n (%)	10 (47.6%)	10 (23.3%)	0.047
AF, n (%)	6 (31.6%)	7 (16.7%)	NS
COPD, n (%)	2 (9.5%)	5 (11.6%)	NS
BAV, n (%)	2 (9.5%)	0 (0%)	NS
smoking, n (%)	8 (38.1%)	12 (27.9%)	NS
ACEI, n (%)	17 (81%)	31 (72.1%)	NS
β -blockers, n (%)	20 (95.2%)	34 (79.1%)	NS
statins, n (%)	20 (95.2%)	38 (88.4%)	NS

Data are presented as frequencies (%), except for ejection fraction (median, range).

Abbreviations: ACEI – angiotensin-converting enzyme inhibitors, AF – atrial fibrillation, BAV – bicuspid aortic valve, COPD – chronic obstructive pulmonary disease, MI – myocardial infarction, others – see [TABLE 1](#)

distributed. Between-group comparisons and associations between individual parameters were done with the Mann-Whitney U-test or χ^2 test. To identify independent factors, we used a multivariate logistic regression analysis. A *P* value <0.05 was considered statistically significant.

RESULTS Out of 64 patients who were enrolled into the study, 21 (33%) subjects were homozygous for the +405 G allele, 40 (63%) were heterozygous, and 3 were homozygous for the +405 C allele. Thus, the minor allele (C) frequency of +405 G>C polymorphism was 36%. Genotype frequencies significantly deviated from Hardy-Weinberg equilibrium (*P* <0.01). To analyze the influence of the VEGF gene +405 G>C polymorphism on the clinical outcome after CABG, the study subjects were further divided into 2 groups: group 1 comprised +405 GG homozygotes (*n* = 21), and group 2 carriers of the +405 C allele (*n* = 43)

Detailed clinical characteristics of the +405 GG and +405 GC/CC groups are shown in [TABLE 1](#) and [TABLE 2](#). The studied groups did not differ with respect to demographic data, the majority of laboratory tests, and medication. In comparison to +405 GC/CC genotype group, patients with GG genotype had significantly higher preoperative levels of total cholesterol, low-density lipoprotein cholesterol, and fasting glucose ([TABLE 1](#)), and a higher frequency of diabetes ([TABLE 2](#)).

The studied groups did not differ with respect to the operative risk (EuroSCORE – European System for Cardiac Operative Risk Evaluation), the number and type of bypass grafts, and other surgery-related parameters ([TABLE 3](#)).

The selected group of 64 patients comprised 54 individuals who recovered after CABG and 10 who died postoperatively during the 30-day follow-up due to cardio-respiratory failure. Out of all fatal cases, 7 subjects had +405 GG genotype, and

TABLE 3 Coronary artery bypass graft surgery – related data and clinical outcome

	GG n = 21	GC + CC n = 43	P
EuroSCORE	2 (0–7)	3 (0–7)	NS
number of bypasses	2 (1–3)	2 (1–4)	NS
LAD-LIMA, n (%)	17 (81%)	34 (79.1%)	NS
urgent surgery, n (%)	2 (9.5%)	2 (4.7%)	NS
IABC, n (%)	4 (19%)	2 (4.7%)	NS
ECC, n (%)	16 (76.2%)	27 (62.8%)	NS
postoperative MI, n (%)	9 (42.9%)	15 (34.9%)	NS
death, n (%)	7 (33.3%)	3 (7%)	0.01

Data are presented as medians (min–max) or frequencies.

Abbreviations: ECC – extracorporeal circulation, EuroSCORE – European System for Cardiac Operative Risk Evaluation, IABC – intraaortic balloon counterpulsation, LAD-LIMA – bypassed left artery descendent with the left internal mammary artery, others – see [TABLES 1](#) and [2](#)

TABLE 4 Characteristics of fatal and nonfatal cases

	Fatal cases n = 10	Nonfatal cases n = 54	P
age, years	66.5 (58–77)	66 (42–75)	NS
men, n (%)	9 (90)	40 (74.1)	NS
laboratory tests			
hemoglobin, (g/dl)	14.7 (13–15.7)	14.3 (11.1–17.6)	NS
hematocrit, (%)	42.3 (37.6–48.2)	41.8 (32.7–49.9)	NS
RBC, ($\times 106/\mu\text{l}$)	4.7 (4.1–5.4)	4.7 (3.6–5.9)	NS
WBC, ($\times 103/\mu\text{l}$)	8.4 (6.3–12.1)	7.1 (3.5–21.3)	NS
platelets, ($\times 103/\mu\text{l}$)	251 (140–282)	230 (117–387)	NS
INR	1 (1–1.2)	1 (0.9–1.6)	NS
aPTT, (s)	31 (22.2–34.9)	30.1 (24.8–43.7)	NS
fibrinogen, (g/l)	4.5 (2.9–5.3)	4.3 (2.4–8.2)	NS
total cholesterol, (mmol/l)	5.7 (3.5–6.7)	5.2 (3.4–6.5)	NS
LDL-C, (mmol/l)	3.8 (2.4–4.7)	3.1 (1.9–5.0)	NS
HDL-C, (mmol/l)	1.2 (0.9–1.5)	1.3 (0.9–1.8)	NS
triglycerides, (mmol/l)	1.5 (0.9–2.0)	1.4 (0.7–2.7)	NS
glucose, (mmol/l)	5.9 (4.6–13.7)	5.4 (4.0–10.3)	NS
cardiovascular status			
ejection fraction, (%)	50 (35–70)	50 (30–70)	NS
peripheral artery disease, n (%)	2 (20)	12 (22)	NS
hypertension, n (%)	6 (60)	45 (83.3)	NS
history of MI, n (%)	7 (70)	44 (81.5)	NS
diabetes, n (%)	6 (60)	14 (25.9)	0.04
AF, n (%)	3 (30)	10 (18.9)	NS
COPD, n (%)	2 (20)	5 (9.4)	NS
BAV, n (%)	1 (10)	0	0.03
smoking, n (%)	4 (40)	16 (30)	NS
ACEI, n (%)	7 (70)	40 (74)	NS
β -blockers, n (%)	9 (90)	44 (81.5)	NS
cardiosurgical status			
number of bypasses	2 (2–3)	2 (1–4)	NS
LAD-LIMA, n (%)	7 (70)	43 (79.6)	NS
urgent surgery, n (%)	2 (20)	2 (3.7)	NS
postoperative MI, n (%)	3 (30)	20 (37)	NS
VEGF GG, n (%)	7 (70)	14 (25.9)	0.01

Data are presented as medians (min–max) or frequencies

Abbreviations: see TABLES 1, 2, and 3

the other 3 were carriers of +405 C allele (TABLE 3). Therefore, patients with VEGF +405 GG genotype had a higher frequency of death (33.3% vs. 7% in GC/CC group, $P = 0.002$) during the 30-day follow-up (TABLE 3).

Patients who died had a higher prevalence of diabetes ($P = 0.04$), bicuspid aortic valve ($P = 0.03$), EuroSCORE ≥ 5 ($P = 0.03$), and VEGF +405 GG genotype ($P = 0.01$). There were no significant differences in the remaining variables between the groups stratified by the outcome (fatal vs. nonfatal cases in TABLE 4).

The multivariate logistic regression analysis including significant associations (shown above)

revealed that the factors which independently increased the risk of death were the VEGF +405 GG genotype (odds ratio [OR] = 6.7; 95% confidence interval [CI] 1.5–29.4) and EuroSCORE ≥ 5 (OR = 4.4; 95% CI 1.1–18.1), ($P = 0.003$ for the whole model).

DISCUSSION The significance of VEGF in cardiovascular diseases has recently become the subject of extensive research. Serum VEGF levels increase after acute myocardial infarction (MI).⁹ The results of the CAPTURE study¹⁰ indicate that elevated VEGF levels are associated with impaired prognosis during a 6-month follow-up after MI.

It has also been established that patients undergoing CABG, with postoperative cardiovascular or hematological disorders, had increased plasma VEGF levels after surgery.⁸ Nevertheless, preoperative circulating VEGF levels were not found to predict unfavorable prognosis in patients after CABG surgery because Denizot et al.⁸ did not show differences in preoperative plasma VEGF levels.

The aim of our study was to evaluate an association between the functional VEGF gene +405 G>C polymorphism and clinical outcome in patients undergoing CABG surgery. We analyzed 64 CAD patients selected from a larger group of CABG patients and showed that +405 GG variant of VEGF gene can increase the risk of death after the surgery.

Several other studies have supported the observations that VEGF +405 G>C polymorphism may affect clinical outcome in various angiogenesis-dependent diseases. Howell et al.¹¹ established an association between VEGF +405 CC genotype and slower growth rate of cutaneous malignant melanoma. Moreover, Stevens et al.¹² showed an increased responsiveness of breast cancer cells carrying VEGF gene +405 GG genotype to phorbol esters binding to the VEGF promoter. These studies suggest a functional significance of +405 G>C polymorphism, though the precise function of this polymorphism is still debated.

Until now, the influence of VEGF gene +405 G>C polymorphism on protein production has not been established. In the study of Watson et al.,⁹ who compared VEGF production in healthy subjects with different genotypes, the VEGF gene +405 GG genotype compared to +405 GC and CC was associated with higher production of VEGF (by 20% and 60%, respectively). However, this was analyzed in a relatively small group of healthy individuals whose peripheral blood mononuclear cells were incubated in vitro with lipopolysaccharide, and VEGF concentration was measured in culture supernatants. In contrast, Awata et al.¹³ analyzed VEGF concentration in sera of healthy subjects, but did not observe a similar association, and VEGF levels were higher in subjects carrying the CC genotype. Conflicting results may be explained by a different methodological approach used in these studies. VEGF originated mainly from resting leukocytes, aggregated platelets, and vascular endothelial cells, as observed by Awata et al.¹² or from activated leukocytes, as observed by Watson et al.⁹

In the present study, we found that patients undergoing CABG surgery carrying the VEGF gene +405 GG genotype are at a 6-fold higher risk of death on average during the first 30 days after operation in comparison to carriers of VEGF +405 C allele. Of note, the GG genotype group had a higher frequency of diabetes, which can worsen the prognosis; however, diabetes does not seem to be an independent predictor of death in the studied groups. Our observations are consistent with those of Metha et al.,¹⁴ who showed that

diabetes is associated rather with long-term than short-term (30 days) mortality after CABG.

VEGF expression is activated by the transcription factor hypoxia-induced factor-1. An increase in plasma VEGF levels is regarded as an early adaptation of the myocardium to deprivation in the blood flow.^{15,16} VEGF is regarded as proangiogenic factor, which seems to be beneficial for ischemic tissue.^{17,18} Lower VEGF levels could be associated with reduced proangiogenic effect and decreased tissue repair.¹⁹ This probably explains why patients with chronic heart failure who were included in the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) study,²⁰ and who were carriers VEGF gene +405 CC genotype (probably associated with lower VEGF production), had a poorer prognosis during 11-month follow-up.

It seems likely that unfavorable postoperative course in CABG patients who have elevated VEGF serum levels, does not result from proangiogenic properties of VEGF, but is associated with proinflammatory actions of VEGF, such as enhanced vascular permeability, upregulation of proinflammatory mediators, induced nitric oxide and prostacyclin release, and activation of endothelial cells.^{21,22}

Our study has several limitations. First of all, a relatively small group of patients resulted in a rather low statistical power. We also did not measure the plasma concentration of VEGF in different genotypes, thus a functional significance of VEGF gene +405 G>C polymorphism still awaits elucidation.

In conclusion, GG genotype of VEGF gene +405 G>C polymorphism is associated with increased probability of short-term mortality after CABG. Both the analysis of long-term outcomes in CABG patients differing in VEGF gene +405 G>C genotype, and further evaluation of VEGF's role in the pathogenesis of CABG-related complications is required to validate prognostic significance of VEGF polymorphisms.

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Wariant GG polimorfizmu +405 genu czynnika wzrostu śródbłonka naczyniowego wiąże się z gorszym rokowaniem u pacjentów poddanych pomostowaniu aortalno-wieńcowemu

Maciej Pastuszczyk¹, Agnieszka Branicka², Bogdan Jakiela³, Ewa Stępień²,
Andrzej K. Jaworek⁴, Anna Wojaś-Pelc⁴, Bogusław Kapelak⁵, Jerzy Sadowski⁵

1 Szpital Specjalistyczny im. Józefa Dietla, Kraków

2 Krakowski Szpital Specjalistyczny im. Jana Pawła II, Kraków

3 II Katedra Chorób Wewnętrznych, Uniwersytet Jagielloński, Collegium Medicum, Kraków

4 Katedra Dermatologii, Uniwersytet Jagielloński, Collegium Medicum, Kraków

5 Klinika Chirurgii Serca, Naczyni i Transplantologii, Uniwersytet Jagielloński, Collegium Medicum, Kraków

SŁOWA KLUCZOWE

choroba niedokrwienna serca, czynnik wzrostu śródbłonka naczyniowego (VEGF), kardiologia, chirurgia, polimorfizm genu, rokowanie

STRESZCZENIE

WPROWADZENIE Zabieg pomostowania aortalno-wieńcowego (*coronary artery bypass graft* – CABG) wiąże się z reakcją systemową, w czasie której dochodzi do wzrostu stężenia wielu cytokin. W reakcji prozapalnej związanej z CABG może uczestniczyć szlak, którego głównym mediatorem jest czynnik wzrostu śródbłonka naczyniowego (*vascular endothelial growth factor* – VEGF).

CELE Celem pracy była analiza zależności pomiędzy polimorfizmem +405 G>C genu VEGF (związanym z produkcją surowiczego VEGF), a wynikiem klinicznym zabiegu CABG w krótkoterminowej obserwacji szpitalnej (30 dni).

PACJENCI I METODY U 64 pacjentów z chorobą niedokrwienną serca, w średnim wieku 66 lat, (76,6% mężczyzn), ze średnim wynikiem w skali EuroSCORE (European System for Cardiac Operative Risk Evaluation) 2,5 (0–2 punkty: 50% chorych, 3–4: 25% i ≥5 punktów: 25%) poddanych CABG wykonano genotypowanie polimorfizmu +405 G>C genu VEGF.

WYNIKI W badanej grupie stwierdzono 21 (33%) homozygot pod względem allelu +405 G genu VEGF, 40 (63%) heterozygot GC i 3 homozygoty +405 C. Dziesięciu pacjentów zmarło po CABG w czasie 30-dniowej obserwacji (7 osób z genotypem +405 GG i 3 nosicieli allelu +405 C). Wieloczynnikowa analiza regresji logistycznej wykazała, że prawdopodobieństwo zgonu po CABG jest zwiększone u pacjentów z genotypem +405 GG (OR = 6,7; 95% CI 1,5–29,4) i wynikiem w skali EuroSCORE ≥5 punktów (OR = 4,4; 95% CI 1,1–18,1).

WNIOSKI Polimorfizm +405 G>C genu VEGF może być czynnikiem rokowniczym niekorzystnego przebiegu pooperacyjnego u pacjentów poddanych CABG. Wydaje się, że VEGF poza swoim działaniem proangiogennym wykazuje dodatkowe działanie, prawdopodobnie o charakterze prozapalnym.

Adres do korespondencji:

lek. Maciej Pastuszczyk, Szpital Specjalistyczny im. J. Dietla, ul. Skarbowa 4, 31-121 Kraków, tel.: 012-687-63-30, fax: 012-421-38-00,

e-mail: mpastuszczyk@wp.pl

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