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European Journal of Cardio-thoracic Surgery 40 (2011) e50—e54

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

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Tumor necrosis factor-α —863 C/A promoter polymorphism affects the inflammatory response after cardiac surgery☆,☆☆

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Received 10 August 2010; received in revised form 2 January 2011; accepted 5 January 2011; Available online 29 March 2011

Abstract

Objective: Cardiac surgery using cardiopulmonary bypass (CPB) initiates an inflammatory response that shows a wide inter-individual range and determines postoperative morbidity. Previous research suggests that genetic diversity contributes to individual susceptibility to perioperative trauma and stress. Nevertheless, the genetic triggering of the tumor necrosis factor-alpha (TNF-α) release remains unclear. We tested two genetic single-nucleotide polymorphisms (SNPs) from the promoter region of the TNF-α gene for associations with perioperative TNF-α level after CPB. **Methods:** We prospectively included 122 patients, who underwent elective coronary artery bypass grafting (CABG). Patients were genotyped for TNF-α —863 C/A (rs1800630) and TNF-α —308 G/A (rs1800629). Plasma level of TNF-α was obtained preoperatively, at the end of CPB, 6 h postoperatively, and on the first postoperative day (POD). **Results:** Demographic characteristics and operative data revealed no significant differences between the different genotypes. Multiple linear regression analyses revealed significant associations for the TNF-α 863 C/A polymorphism: the major —863 CC variant was associated with higher TNF-α level preoperatively ($p = 0.003$), after CPB ($p = 0.005$), and 6 h postoperatively ($p = 0.010$), independently from CPB time, left ventricle (LV) function and age. Contrarily, the AA allele had lower TNF-α level preoperatively ($p = 0.008$), after surgery ($p = 0.024$) and 6 h postoperatively ($p = 0.001$). For the TNF-α 308 G/A polymorphism, only few significant associations could be observed: —308 GG carriers were associated with lower TNF-α level immediately after CPB ($p = 0.020$), whereas 308 AA carriers were significantly associated with elevated TNF-α level preoperatively ($p = 0.032$) and immediately after CPB ($p = 0.05$). No heterozygote variant of both SNPs revealed any significant associations with perioperative TNF-α level. **Conclusions:** The current study suggests that the major —863 CC variant determines elevated TNF-α level preoperatively and throughout the postoperative course after CPB.

Keywords: Cardiopulmonary bypass; Genetic polymorphisms; TNF-α; Inflammation

1. Introduction

Coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB) initiates an inflammatory response that shows a wide inter-individual range and determines postoperative morbidity [1]. Previous research suggests a significant genetic contribution to individual susceptibility to perioperative trauma and stress [2]. Former studies have analyzed various genetic single-nucleotide polymorphisms (SNPs) of different gene loci with post-CABG cytokine level, and subsequently found associations with adverse postoperative events [2—6].

Tumor necrosis factor alpha (TNF-α), a pro-inflammatory cytokine, plays a key role in the post-CABG inflammatory response [7—9]. TNF-α level increases in response to CPB with a peak shortly after surgery and faces rapid degradation afterwards. Excessive production of TNF-α may lead to organ dysfunction or death [10,11].

TNF-α production shows high inter-individual variations, which have been assigned to inherited factors [12]. For the TNF-α 308 G/A polymorphism, former research shows conflicting results regarding associations with post-CABG-TNF-α level, with some authors finding significant associations of the minor —308 AA variant with elevated TNF-α level [7,13] and others who did not [14].

Furthermore, Skoog et al. [15] identified a C/A exchange at position —863 of the TNF-α gene promoter and found higher transcriptional activity of the major —863 CC variant

☆ Parts of the article have been presented on the 39th Annual Meeting of the German Society of Cardiothoracic and Vascular Surgery 2010 in Stuttgart, Germany.

☆☆ Financial support was provided solely from Deutsches Herzzentrum Muenchen.

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1010-7940/$ — see front matter
doi:10.1016/j.ejcts.2011.01.084

in reporter gene assays. This polymorphic site was associated with TNF-α level in healthy people [15], Alzheimer's disease [16] or chronic obstructive pulmonary disease (COPD) [17], but has not been tested in the context of CPB so far. The current study analyses these two polymorphisms from the promoter region of the TNF-α gene, TNF-α −863 C/A and the TNF-α −308 G/A, for associations with post CABG TNF-α level and major adverse events after surgery.

2. Methods

Patients undergoing elective CABG were prospectively recruited. After approval by the local Ethics Committee, written informed consent was obtained from all participating patients. A total of 122 consecutive patients, who underwent elective CABG, were included. Exclusion criteria included previous cardiac operation and emergency surgery.

2.1. Patient management

Anesthesia was performed with sufentanil and midazolam supplemented with sevoflurane inhalation; neuromuscular blockade was achieved by either pancuronium bromide or rocuronium. All patients received antifibrinolytic therapy. CABG was performed on all patients by cannulation of the right atrium and ascending aorta. CPB was performed via standard technique using a membrane oxygenator, an open cardiotomy reservoir, and uncoated tubing systems.

2.2. Genotyping

DNA was extracted from peripheral blood by using the commercial E.Z.N.A.® Blood DNA II Kit (PEQLAB Biotechnologie GmbH, Erlangen, Germany). Genotyping was performed as previously described [18], using LightCycler technology (Roche) by using the following primers for TNF-α 863 C/A: (5′-CCTCTGGGGAGATGTGACCA-3′), (5′-AGGTCCTGGAGGCTCTTTCAC-3′), (5′-LC Red640-ACCCCCACTTAACGAAGACAG-3′), and the anchor probe (5′-CAGGGCTATGAAAGTCGAGTATGGG-3′) were used. The primers for TNF-α 308 G/A were: (5′-GGCAATAGGTTTTGAGGGCCCAT-3′) and (5′-CCTCCCTGCTCCGATTCCG-3′).

2.3. Inflammation parameters

Plasma level of TNF-α was obtained preoperatively, after cessation of surgery, 6 h postoperatively and on the first postoperative day (POD).

2.4. Statistics

Statistical tests were performed with SPSS software 18.0 (SPSS Inc., Chicago, IL, USA). Comparisons between the three different genotypes were performed with analysis of variance (ANOVA) or Kruskal–Wallis *H*-test for quantitative data and a χ^2 test with two degrees of freedom for discrete data, as appropriate. Multiple linear regression analyses were performed to assess associations between different genotypes and TNF-α level preoperatively, after CPB, 6 h postoperatively, and 1 POD (Tables 6 and 7) considering clinical parameters as possible confounders. Any *p*-values given are two-sided and a *p*-value <0.05 was considered statistically significant.

3. Results

Genotyping results are outlined in Table 1 and showed similar frequencies as previously described [18]. The different genotypes of both polymorphisms did not show significant differences regarding demographic characteristics, preoperative medications, laboratory results, and cardiovascular risk factors (Tables 2 and 3). Furthermore, no differences regarding operative data and clinical outcome could be observed for TNF-α −863 C/A (Table 4) and TNF-α 308 G/A (Table 5). The frequencies for the different genotypes of the TNF-α −863 C/A polymorphism were consistent with the Hardy–Weinberg equilibrium (HWE). Although the frequencies for TNF-α 308 G/A were comparable to previous studies [12–14], they were not consistent with the HWE.

Table 1. Genotyping results for TNF-α −863 C/A, TNF-α 308 G/A, and haplotypes.

TNF 863 C/A (rs1800630)	CC	CA	AA
	n = 84 (68.9%)	*n* = 33 (27.0%)	*n* = 5 (4.1%)
TNF 308 G/A (rs1800629)	GG	GA	AA
	n = 83 (68.0%)	*n* = 31 (24.6%)	*n* = 8 (6.6%)

Table 2. Demographics by patient genotypes for TNF-α −863 C/A.

	CC (*n* = 84)	CA (*n* = 33)	AA (*n* = 5)	*p*
Weight (kg)	79.3 ± 13.3	79.4 ± 13.1	81.6 ± 8.9	n.s.[a]
Height (cm)	170.7 ± 7.8	170.6 ± 7.3	172.2 ± 5	n.s.
Age (years)	67.1 ± 9.9	69.8 ± 8.3	72.6 ± 9.6	n.s.
NYHA (preoperatively)	2.7 ± 0.5	2.6 ± 0.5	2.8 ± 0.4	n.s.
Ejection fraction (%)	57.7 ± 15.9	58.2 ± 12.5	53.6 ± 13.1	n.s.
Previous myocardial infarction	23 (27.3%)	8 (24.2%)	3 (60%)	n.s.
Sinus rhythm	78 (92.6%)	31 (93.4%)	5 (100%)	n.s.
COPD[b]	5 (6.0%)	2 (6.1%)	0	n.s.
Previous stroke	3 (3.6%)	0	1 (20%)	n.s.
Preoperative medication				
Nitrate	71(84.5%)	28 (84.8%)	4 (80%)	n.s.
β-blockers	69 (82.1%)	24 (72.7%)	2 (40%)	n.s.
ACE-inhibitors	10 (11.9%)	7 (21.2%)	2 (40%)	n.s.
Diuretics	48 (57.1%)	19 (57.6%)	2 (40%)	n.s.
Statins	70 (83.3%)	28 (84.8%)	4 (80%)	n.s.
Cardiovascular risk factors				
Diabetes	16 (19.0%)	11 (33.3%)	2 (40%)	n.s.
Family history	9 (10.7%)	4 (12.1%)	0	n.s.
Hyperlipidemia	44 (52.4%)	19 (57.6%)	2 (40%)	n.s.
Hypertension	71 (84.5%)	30 (90.9%)	5 (100%)	n.s.
Smoking	18 (21.4%)	8 (24.2%)	0	n.s.
Preoperative lab				
WBC[c] (10^9/l)	7.2 ± 1.6	7.7 ± 2.6	7.0 ± 2.4	n.s.
Hemoglobin (mg/dl)	13.6 ± 1.5	13.5 ± 1.8	12.8 ± 2.0	n.s.
Creatinine (mg/dl)	1.00 ± 0.33	1.04 ± 0.33	1.24 ± 0.20	n.s.
Platelets (10^9/l)	258.9 ± 72.9	251.1 ± 101.4	234.0 ± 46.0	n.s.

[a] n.s. – not significant.
[b] COPD – chronic obstructive pulmonary disease.
[c] WBC – white blood count.

Table 3. Demographics by patient genotypes for TNF-α 308 G/A.

	GG (n = 83)	GA (n = 31)	AA (n = 8)	p
Weight (kg)	80.7 ± 13.6	76.3 ± 11.2	78.8 ± 11.3	n.s.[a]
Height (cm)	170.2 ± 7.5	172.5 ± 7.9	170.1 ± 6.1	n.s.
Age (years)	69.2 ± 8.4	65.3 ± 11.6	66.4 ± 10.6	n.s.
NYHA (preoperatively)	2.7 ± 0.5	2.6 ± 0.5	2.8 ± 0.4	n.s.
Ejection fraction (%)	57.9 ± 14.8	56.7 ± 15.9	61 ± 12.5	n.s.
Previous myocardial infarction	22 (26.5%)	9 (28.8%)	3 (37.5%)	n.s.
Sinus rhythm	79 (95.2%)	29 (93.5%)	5 (60%)	n.s.
COPD[b]	4 (4.8%)	1 (3.2%)	1 (12.5%)	n.s.
Previous stroke	3 (3.6%)	0	1 (12.5%)	n.s.
Preoperative medication				
Nitrate	68 (81.9%)	30 (96.8%)	5 (60%)	n.s.
β-blockers	62 (74.7%)	27 (87.1%)	6 (75)	n.s.
ACE-inhibitors	17 (20.5%)	2 (6.4%)	0	n.s.
Diuretics	45 (54.2%)	19 (61.3%)	5 (60%)	n.s.
Statins	68 (81.9%)	26 (83.9%)	8 (100%)	n.s.
Cardiovascular risk factors				
Diabetes	19 (22.9%)	9 (28.8%)	1(12.5%)	n.s.
Family history	7 (8.4%)	4 (12.8%)	2 (25%)	n.s.
Hyperlipidemia	42 (50.6%)	19 (61.3%)	4 (50%)	n.s.
Hypertension	73 (88.0%)	28 (90.3%)	5 (60%)	n.s.
Smoking	18 (21.7%)	6 (19.4%)	2 (25%)	n.s.
Preoperative lab				
WBC[c] (10^9/l)	7.1 ± 1.6	7.7 ± 2.6	6.1 ± 2.4	0.04
Hemoglobin (mg/dl)	13.6 ± 1.5	13.5 ± 1.8	12.8 ± 2.0	n.s.
Creatinine (mg/dl)	1.00 ± 0.33	0.94 ± 0.33	0.91 ± 0.20	0.03
Platelets (10^9/l)	258.9 ± 72.9	251.1 ± 101.4	234.0 ± 46.0	n.s.

[a] n.s. — not significant.
[b] COPD — chronic obstructive pulmonary disease.
[c] WBC — white blood count.

Table 4. Perioperative treatment and clinical outcome for TNF-α −863 C/A.

	CC (n = 84)	CA (n = 33)	AA (n = 5)	Total (n = 122)	p
Cross clamp time (min)	57.6 ± 18.1	56.5 ± 17.4	53.8 ± 13.6	57.2 ± 17.6	n.s.
CPB time (min)	85.3 ± 24.8	85.2 ± 24.2	80.0 ± 18.6	85.1 ± 24.3	n.s.
Ventilation time (h)	9.1 ± 4.3	9.3 ± 3.1	7.2 ± 3.6	9.1 ± 4.0	n.s.
Intra-aortic balloon pump	1 (1.2%)	0	0	1 (0.8%)	n.s.
Blood loss 24 h (ml)	680 ± 387	680 ± 495	664 ± 356	679 ± 414	n.s.
Rethoracotomy	2 (2.4%)	1 (3.0%)	0	3 (2.5%)	n.s.
Creatinine (maximum)	1.05 ± 0.43	1.14 ± 0.70	1.18 ± 0.26	1.08 ± 0.51	n.s.
Stroke	3 (3.6%)	1 (3.0%)	0	4 (3.3%)	n.s.
30 days mortality	2 (2.4%)	0	0	2 (1.6%)	n.s.

After risk adjustment to age, CPB time, and left ventricle (LV) function, multiple linear regression analyses revealed significant associations of the −863 CC variant with higher TNF-α level preoperatively (p = 0.003) (Table 6). In the postoperative period, we observed an increased TNF-α release with a peak immediately after CPB and 6 h after surgery (Fig. 1). During this period, the −863 CC variant was associated with elevated level after CPB (p = 0.005) (Table 6), and 6 h postoperatively (p = 0.010) (Table 6). In the later postoperative course, TNF-α level declined, and the differences of TNF-α level did not reach statistical significance any more. On the other hand, the minor −863 AA variant was associated with significant lower level preoperatively (Table 7), lower TNF-α level after surgery (p = 0.024) (Table 7), and 6 h postoperatively (p = 0.001) (Table 7).

Table 5. Perioperative treatment and clinical outcome for TNF-α 308 G/A.

	GG (n = 83)	GA (n = 31)	AA (n = 8)	p
Cross clamp time (min)	57 ± 19.0	58.8 ± 13.8	57.2 ± 17.7	n.s.
CPB time (min)	85.2 ± 25.3	88.1 ± 14.6	85.1 ± 24.4	n.s.
Ventilation time (h)	9.2 ± 3.9	8.4 ± 4.2	9.0 ± 4.0	n.s.
Intra-aortic balloon pump	1 (1.2%)	0	0	n.s.
Blood loss 24 h (ml)	702 ± 423	607 ± 415	643 ± 280	n.s.
Rethoracotomy	2 (2.4%)	1 (3.2%)	0	n.s.
Creatinine (maximum)	1.14 ± 0.4	1.18 ± 0.5	1 ± 0.0	n.s.
Stroke	2 (2.4%)	1 (3.2%)	1 (12.5%)	n.s.
30 days mortality	1 (1.2%)	0	1 (12.5%)	n.s.

Table 6. Multiple regression analyses for impact of TNF-α −863 CC on perioperative TNF-α level. p-values are listed below. p-values <0.05 were considered statistically significant.

	Preoperatively	After CPB	6 h postoperatively	1 POD
(Constant)	<0.001	<0.001	<0.001	<0.001
Bypass time		n.s.	0.049	n.s.
LV-function	n.s.	0.012	0.032	n.s.
Age	n.s.	0.026	0.004	n.s.
TNF 863 CC	0.003	0.005	0.010	n.s.

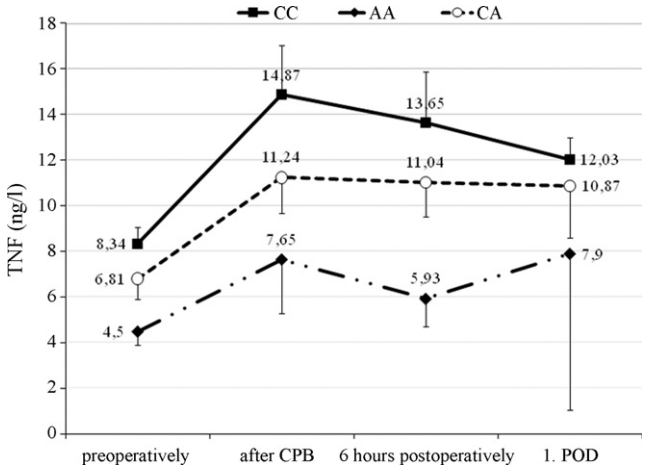

Fig. 1. Associations of TNF-α −863 C/A with plasma level of TNF-α: means and 95% confidence intervals. −863 CC carries were significantly associated with elevated and −863 AA carriers with lowered TNF-α level preoperatively, after CPB and 6 h postoperatively. −863 CA carriers did not show any significant associations.

Table 7. Multiple regression analyses for impact of TNF-α −863 AA on perioperative TNF-α level. *p*-values are listed below. *p*-values <0.05 were considered statistically significant.

	Preoperatively	After CPB	6 h postoperatively	1 POD
(Constant)	<0.001	<0.0001	<0.0001	<0.0001
Bypass time		n.s.	0.038	n.s.
LV-function	n.s.	0.010	0.019	n.s.
Age	n.s.	0.053	0.004	n.s.
TNF 863 AA	0.008	0.024	0.001	n.s.

Nevertheless, no significant associations between the different genotypes of TNF-α −863 C/A (Table 4) or TNF-α −308 G/A (Table 5) with major adverse postoperative events could be observed.

The TNF-α 308 G/A showed only few significant associations during the perioperative course: −308 GG carriers were associated with lower TNF-α level immediately after CPB ($p = 0.020$), whereas 308 AA carriers were significantly associated with elevated TNF-α level preoperatively ($p = 0.032$) and immediately after CPB ($p = 0.05$). Neither heterozygote carriers of the TNF-α −863 C/A nor heterozygote carriers of the TNF-α −308 G/A polymorphism showed significant associations with pre- or post-CABG TNF-α level.

Analyzing the haplotypes of the −863 CC genotypes with TNF-α −308 G/A variants, 53 patients had −308 GG, 23 patients −308 GA, and eight patients −308 AA. No significant associations between the different haplotypes and TNF-α level could be observed.

4. Discussion

The current study suggests that the −863 CC variant of the TNF-α −863 C/A polymorphism determines elevated TNF-α level throughout the perioperative course, independently from bypass time, LV function, and age. Accordingly, the observation that carriers of the minor −863 AA had lower TNF-α level meets the expectations. Factors influencing the inflammatory response such as bypass time or cross-clamp time did no differ between the different genetic variants (Tables 2 and 3). Furthermore, there was no difference in preoperative statin treatment that influences the inflammatory response according to a recently published study [19].

Our data suggest a prominent role of the C → A substitution for perioperative TNF-α level for TNF-α −863 C/A. Lower TNF-α baseline level was previously documented in healthy men carrying the −863 AA variant [15]. Furthermore, this genotype was associated with a 31% reduction in reporter gene transcriptional activity in hepatoblastoma cell lines compared to the −863 CC genotype. Other research suggests an association of the −863 AA variant with a later onset of Alzheimer's disease [16] and a lower risk of chronic obstructive pulmonary disease (COPD) [17]. In general, the −863 AA genotype seems to be somewhat 'protective' compared to the −863 CC variant. These findings correlate well with the results of the current study, which observed higher TNF-α level in −863 CC carriers (Fig. 1) and lower level in −863 AA carriers. Nevertheless, −863 CC carriers did not show an increased risk for major postoperative events in the current study. Given the small numbers of major adverse postoperative events in the current study, larger sample sizes are necessary to analyze the clinical impact of the current findings.

A number of association studies have been conducted to examine effects of the TNF-α −308 G/A polymorphism in patients undergoing CABG. The results, however, are somewhat contradictory: Bittar et al. found an association of the rare −308 AA variant with increased post-CABG TNF-α level. Nevertheless, only eight patients carrying the −308 AA variant were analyzed in this study [7]. These results, however, were confirmed in an Asian population [13], whereas all patients in the present study were Caucasians. Whether ethnic background affects the results regarding this special polymorphism is unclear. Another study found associations between the TNF-α 308 G/A polymorphism and prolonged mechanical ventilation [20], what we consider a relatively indifferent clinical parameter. Nevertheless, these findings could not be validated by Galinanes et al. [14] who neither did find associations between TNF-α 308 G/A carriers and perioperative TNF-α level nor observed associations with adverse postoperative events. Similar inconsistencies have been found for the association of the TNF-α 308 G/A with susceptibility and outcome of sepsis [21,22]. Our data suggest slight associations of the TNF-α −308 G/A promoter polymorphism: elevated levels in −308 AA carriers preoperatively and immediately after CPB and one significant association of −308 GG carriers with lowered levels after CPB. A further subgroup analysis of the haplotypes between the TNF-α 308 G/A polymorphism and the −863 CC variants did not show any significant associations with perioperative TNF-α level. In order to obtain more convincing results, larger sample sizes with more individuals carrying the rare −308 AA variant are necessary.

TNF-α shows a wide range of proinflammatory activities, and occupies a pivotal role in the initiation and amplification of the inflammatory cascade in various clinical conditions. For example, anti-TNF-α treatment has been shown to improve the clinical course in rheumatoid arthritis [23]. Accordingly, some investigators have suggested that aboli-

tion of TNF-α production in knockout mice reduce post-ischemic myocardial dysfunction [24]. Recent experimental research suggests that the devastating effects of TNF-α might depend on the amount of the cytokine produced [25].

As the current study suggests, an impact of the TNF-α — 863 C/A polymorphism on TNF-α level, genotyping of the polymorphic TNF gene, may be an important complementary tool to select patients at high risk of developing vital organ dysfunction after CPB.

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