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C-reactive Protein Predicts Postoperative Delirium Following Vascular Surgery

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Background: The etiology of postoperative delirium (POD) following vascular surgery is generally unknown. The incidence, however, can be as high as 35%. A possible neuroinflammatory basis for delirium is likely and C-reactive protein (CRP) as a marker for inflammation can possibly play a predictive role.

Methods: Between March 2010 and September 2012, 277 consecutive elective vascular surgery patients were prospectively evaluated for the diagnosis of POD. Various potential risk factors, including postoperative CRP values, were collected.

Results: The mean age of the patients was 69 ± 11 years (range 21–92). The mean hospital length of stay was 6 ± 4 days (range 1–33). Sixteen patients (6%) developed POD during hospital stay. Univariate analysis revealed multiple comorbidities ($P = 0.001$), postoperative elevated CRP levels ($P = 0.001$), intensive care unit admittance ($P = 0.01$), and open aortic surgery or amputation procedures ($P = 0.0001$) to be significantly related to the diagnosis POD. Multivariate logistic regression analysis confirmed the relationship between an elevated CRP value and POD (odds ratio [OR] 1.01, 95% confidence interval 1.00–1.03, $P = 0.04$). The sensitivity analyses yielded essentially similar results. Based on OR, it can be calculated that the risk of POD is increased by approximately 35% if the CRP concentration is 50 mg/L, and by approximately 90% if the CRP concentration is 100 mg/L (compared with a CRP concentration of 5 mg/L). Thirty-one percent (5/16) of patients with POD needed a long-stay care facility after discharge ($P = 0.0001$).

Conclusions: In this study, CRP can be used as a marker for an increased risk of POD after vascular surgery. In addition, it was found that POD was associated with a 10-fold increase in the need of long-stay care after discharge.

INTRODUCTION

Postoperative delirium (POD) is defined as an acute disorder of attention and cognition and is characterized by fluctuating symptoms of inattention and

disturbance of consciousness.¹ Not only does it affect approximately 11–24% of elderly patients during hospital stay, it is also associated with longer hospitalization and institutionalization, higher medical costs, persistent functional decline, and even

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death.^{1–7} POD incidences are similar to that of acute myocardial infarction or sepsis making it a serious complication after surgery.⁸ The long-term prognosis of POD is largely unknown and underexposed. Nevertheless, there is growing understanding of the fact that POD has major implications on cognitive and functional decline as well as further postdischarge institutionalization.^{5,9} Although POD is already a very costly complication, preventing further institutionalization may render an important contribution in controlling healthcare costs.

POD is a common complication after vascular surgery with an incidence of more than 35%.¹ The etiology of POD after vascular surgery is generally unknown, and preemptively predicting its occurrence is found to be difficult. Inouye et al.^{8,10} stated that POD is a multifactorial syndrome consisting of a complex interaction of precipitating factors related to surgery and hospitalization with baseline vulnerabilities. Various prevalence studies have identified risk factors for the occurrence of POD, including C-reactive protein (CRP).^{11–15} The effect of CRP on postoperative cognition is only partially known. Current data suggest a pathway of inflammation that culminates in higher concentrations of various inflammatory markers in peripheral blood.^{16,17} Despite the selective regulation of the blood–brain barrier, the brain is directly influenced by peripheral cytokines through activation of vascular endothelial cells and perivascular cells in the brain. By propagating the inflammatory cascade, this may then lead to neuron injury.¹⁵ This neuroinflammatory response may cause neurocognitive behavioral abnormalities.¹⁸ The aim of this study was to analyze the relationship between CRP and POD in a common vascular surgery population. We hypothesized that elevated CRP values, as a marker for inflammation, are independently associated with POD and that the occurrence of POD increases the need for discharge to a long-stay care facility.

METHODS

Design of the Study

Between March 2010 and October 2011, a total of 277 consecutive elective vascular surgery patients were prospectively evaluated. All vascular surgery patients admitted and/or operated in an elective setting, regardless of age or comorbidity, were included. Eligible surgical procedures included open and endovascular aortic repair, peripheral bypass surgery, amputation procedures, and percutaneous endovascular interventions (angioplasty and stenting procedures). All patients were examined both

pre- and postoperatively. Blood tests for determining CRP values were part of the postoperative work-up. Because patients were initially enrolled in a previous study, they gave oral consent to participate in this study.¹⁵ Our institutional review board (Medical Ethical Committee of the University Medical Center Groningen) provided a formal written waiver for both this study and the choice of oral informed consent. Patient data were processed and electronically stored according to the declaration of Helsinki - Ethical principles for medical research involving human subjects. All research was conducted in the Netherlands at our university hospital.

Postoperative Delirium

The primary outcome variable was the incidence of POD. The work-up with regard to cognitive and psychosocial assessment has been described in a previous publication by our group.¹⁵ In short, demographic data known to predispose to the occurrence of POD were collected prospectively from the medical records. Clinical awareness was increased by informing the nursing staff on the aims of this study and on the specific signs of POD, and when suspicion for POD was high, further assessment was done by using the Delirium Observation Screening Scale. A geriatrician was consulted when delirium was present or suspected and the diagnosis was confirmed according to the DSM-IV-TR criteria.¹⁹ Secondary outcomes were postoperative morbidity, hospital length of stay (HLOS), and type of care facility after discharge.

C-reactive Protein

CRP values were determined postoperatively on a Roche Modular analyzer (Roche Diagnostics, Almere, The Netherlands). These values were considered elevated when >5 mg/L. Postoperatively, the highest value within the first 5 days was recorded for analysis. As the incidence of delirium is also highest within these first few postoperative days, this timeframe was chosen. For the sake of completeness, of the available preoperative CRP values, a similar analysis was performed.

Other Variables

During admission, routine clinical data were recorded pre-, intra-, and postoperatively. Preoperatively, the Groningen Frailty Indicator (GFI) was obtained at the surgical outpatient clinic.¹⁵ As preoperative cognitive impairment and depression are known risk factors for POD, these were also measured using the GFI and further used for risk

assessment for POD in a logistic regression model. The GFI is a simple questionnaire consisting of 15 items, classified in 8 separate groups, consistent with the domains of functioning. The GFI has already been proven to predict POD after vascular surgery.¹⁵ In addition to CRP, the following predictors were investigated: preoperative predictors: age, sex, American Society of Anesthesiologists score (ASA), hemoglobin level, and impaired renal function (estimated glomerular filtration rate <60 mL/min $\times 1.73$ m²); intraoperative predictors: estimated blood loss, type of surgical procedure, and type of anesthesia; postoperative predictors: intensive care unit (ICU) admittance. All medical and surgical complications and deaths were identified and classified according to a system proposed by Clavien and associates.^{20,21} For a proper comparison in binary analysis, this is presented as mean $\pm$ standard deviation (SD).

Medical comorbidity was quantified using the Charlson Comorbidity Index (CCI).²² In this index, each medical condition was assigned a weighted score (range 0–19). Based on these comorbidities, the CCI predicts the 1-year mortality.²³

Statistical Analyses

Normally distributed continuous variables are presented as mean (SD). Skewed continuous variables are shown as median (interquartile range). Differences between numerical variables were tested with Student's 2-tailed *t*-test (normally distributed data) or, if appropriate, Mann–Whitney *U*-test (skewed data). Differences between categorical variables were tested with Pearson's χ^2 test. The association of POD (yes/no) with CRP (mg/L) was analyzed by logistic regression analysis adjusting for age (years), gender, number of comorbidities, cognitive impairment (yes/no), depression (yes/no), type of procedure (open aortic surgery or amputation versus other), and ICU admittance (yes/no). In addition, 2 sensitivity analyses were performed in which we used ASA classification and GFI, respectively, as a measure of comorbidity (instead of the CCI). Two-tailed *P* values were used throughout and significance was set at *P* < 0.05. All statistical analyses were done with the SPSS version 16.0.1 (Chicago, IL, 2007), when appropriate (>10 patients) confidence intervals (CI) were calculated using a method proposed by Altman et al.²⁴

RESULTS

This study included 277 patients, 207 men (75%) and 70 women (25%), with a mean age of

69 $\pm$ 11 years (range 21–92). Baseline characteristics are listed in Table I. Operations performed included 13% open aortic surgery (*n* = 36), 26% endovascular procedures (*n* = 74), 31% peripheral bypass surgery (*n* = 85), 15% percutaneous interventions (*n* = 43), 11% amputations (*n* = 30), and 3% miscellaneous (*n* = 9). Postoperatively, 55 patients (20%) were admitted to the ICU. The mean HLOS was 6 $\pm$ 4 days (range 1–33).

Postoperative Delirium

Overall, the incidence of POD was 6% (Table II). However, the incidence was highly dependent on the type of surgery. The highest incidence rates (95% CI) were found after open aortic surgery and amputation surgery, 17% (4–29) and 20% (5–35), respectively. The lowest incidence rates (95% CI) were found after endovascular procedures, peripheral bypass surgery, and percutaneous interventions, 5% (0–11), 0% (2–13), and 0% (0–8) respectively (Table III). The mean number of complications (*n* $\pm$ SD) that occurred was equally divided between the POD and non-POD group (2.1 $\pm$ 0.9 and 1.8 $\pm$ 1.1, *P* = 0.22), respectively.

The outcome after discharge was considerably worse in patients with POD. Thirty-one percent (95% CI: 14–56) of patients with POD needed long-term care institutionalization after discharge compared with 3% (95% CI: 2–6) without POD (*P* = 0.0001).

C-reactive Protein and Delirium

Univariate analysis revealed multiple comorbidities (*P* = 0.001), elevated CRP levels (*P* = 0.001), ICU admittance (*P* = 0.01), and open aortic surgery or amputation procedures (*P* = 0.0001) to be significantly related to the diagnosis of POD. Preexisting cognitive impairment and depression were significantly associated with the occurrence of POD (*P* = 0.006 and *P* = 0.02, respectively) (Table III). Multivariate logistic regression analysis confirmed that an elevated CRP value (odds ratio [OR] 1.01, 95% CI: 1.01–1.04, *P* = 0.04) was the variable most closely correlated with the diagnosis POD (Table IV). The sensitivity analyses yielded essentially similar results. In the full model, the odds ratio of CRP was 1.01 (95% CI: 1.00–1.02, *P* = 0.04) if comorbidity was measured as ASA, and 1.01 (95% CI: 1.00–1.02, *P* = 0.03) if comorbidity was measured as GFI. Based on the odds ratio, it can be calculated that the risk of POD is increased by approximately 35% if the CRP concentration is 50 mg/L, and by approximately 90% if the CRP concentration is 100 mg/L (compared with a CRP concentration of

Table I. Patient characteristics and demographic data

Parameter	
Number (%)	277 (100)
Age (years)	69 ± 11 (21–92)
Gender	
Men	207 (75)
Women	70 (25)
Comorbidities ^a	5 ± 2
Impaired renal function ^b	29 (10)
ASA ^c	3 ± 0.5 (1–4)
Type of procedure	
Open aortic surgery	36 (13)
Endovascular procedures	74 (27)
Peripheral bypass surgery	85 (31)
Percutaneous interventions	43 (15)
Amputation surgery	30 (11)
Miscellaneous	9 (3)
Preoperative hemoglobin (mg/L)	8.8 ± 5.7 (3.6–12.1)
Intraoperative blood loss (mL)	100 (0–500)
ICU admittance	55 (20)
C-reactive protein (mg/L)	108 (27–188)
Postoperative delirium incidence	16 (6)

Data are expressed as number (percentage) or mean ± standard deviation or mean ± standard deviation (range) or median (interquartile range).

^aCharlson Comorbidity Index, a weighted index which measures the burden of comorbidities and predicts 1-year mortality (range 0–19 indicating no comorbidities to considerable comorbidities).

^bDefined as estimated glomerular filtration rate <60 mL/min × 1.73 m².

^cAmerican Society of Anesthesiologists score (assesses the fitness of patients before surgery: 1 = a normal healthy patient and 5 = a moribund patient who is not expected to survive without the operation).

5 mg/L). The additional analysis on preoperative CRP values provided basically the same results in the full model (OR 1.05, 95% CI: 0.98–1.12, *P* = 0.19). However, because of underfitting of the model, based on low number of incident cases and available data, this did not reach statistical significance.

DISCUSSION

This study shows that CRP is positively correlated with the diagnosis of POD after vascular surgery and might be considered as an important biomarker for POD. This is the first study that not only focuses specifically on the role of CRP and the occurrence of delirium after vascular surgery, but also demonstrates a correlation between the two. Our results further show that this association is independent of known risk factors such as age, preexisting comorbidity, cognitive impairment, and depression

Table II. Risk of postoperative delirium dependent on the type of surgical procedure

Type of procedure	Number of patients	Postoperative delirium		
		Number	Risk (%)	95% CI
Open aortic surgery	36	6	17	8–32
Endovascular procedures	74	4	5	2–13
Peripheral bypass surgery	85	0	0	0–4
Percutaneous interventions	43	0	0	0–8
Amputation surgery	30	6	20	9–37
Miscellaneous	9	0	0	0–30
Total	277	16	6	4–9

or type of surgery. This study also shows that with an increase in CRP level to 100 mg/L, the risk of POD is increased by almost 90%.

In a recent review on the association of atherosclerosis and delirium, inflammation appeared to play a key role in the occurrence of POD, an outcome that is confirmed by this study.²⁵ A second report, specifically focusing on inflammation in the pathogenesis of delirium within another high-risk group, found a similar association between inflammatory processes and the development of delirium.¹³

Although the pathophysiological processes have not yet been fully elucidated, current data suggest a pathway of inflammation that culminates in higher concentrations of various markers in peripheral blood.^{13,14} The cause of this increase seems 2-fold. First, the surgical stress itself can lead to a rise in inflammatory and proinflammatory cytokines. Second, vascular surgery patients have a high burden of atherosclerosis. Atherosclerosis is no longer considered a mere lipid storage disease but involves an ongoing inflammatory response.¹⁷ Studies focusing on inflammatory markers as predictor for delirium confirm that patients who developed delirium had significantly elevated levels of interleukins 6 and 8.^{26–28} There is increasing evidence that aging is associated with increased neuroinflammation, manifested as increased levels of activated microglia, the immune cells of the brain.¹⁴ This increased baseline inflammation in the elderly has a priming effect resulting in an enhanced response to peripheral stimuli such as surgery.²⁹ CRP is an acute phase protein and a nonspecific marker for inflammation, which can give important information and insight in this process and the associated risks. Two studies on CRP and postoperative outcome showed that an elevated CRP value was

Table III. Univariate analysis of possible risk factors of postoperative delirium

Variable	Delirium present	Delirium absent	P value
Number	16	261	N/A
Age (year)	74 ± 9	68 ± 11	0.42
Male gender	15 (93%)	192 (74%)	0.07
Comorbidities ^a	6.7 ± 1.8	5.1 ± 1.9	0.001
Cognitive impairment	3 (19)	19 (7)	0.006
Depression	10 (62)	123 (47)	0.02
ASA score >2 ^b	11 (68%)	147 (56%)	0.13
Hemoglobin (mg/L)	7.8 ± 1.7	8.9 ± 5.8	0.11
Impaired renal function ^c	3 (18%) ^d	13 (5%) ^d	0.27
Postoperative C-reactive protein (mg/L)	175 (127–246)	89 (24–176)	0.001
Open aortic surgery or amputation	12 (75)	54 (21)	<0.001
Intraoperative blood loss (mL)	350 (0–3000)	100 (0–500)	0.40
ICU admittance	7 (43%)	48 (19%)	0.01
Complications	2.1 ± 0.9	1.8 ± 1.1	0.22

Data are expressed as number (percentage) or mean ± standard deviation or median (interquartile range).

N/A, not applicable.

^aCharlson Comorbidity Index, a weighted index which measures the burden of comorbidities and predicts 1-year mortality (range 0–19 indicating no comorbidities to considerable comorbidities).

^bAmerican Society of Anesthesiologists (assesses the fitness of patients before surgery: 1 = a normal healthy patient and 5 = a moribund patient who is not expected to survive without the operation).

^cDefined as estimated glomerular filtration rate <60 mL/min × 1.73 m².

^dDifferent total number because of missing data.

independently related with the occurrence of complications as well as an impaired mental status.^{13,30}

Thus, it seems that the effect of CRP is much greater than just the occurrence of POD. In vascular surgery, it has been shown that CRP is associated with an increased severity of peripheral arterial disease at presentation and independently predicts adverse postoperative events, including cardiovascular, contralateral limb, and graft-related end points after lower extremity bypass surgery.³¹ Second, it is associated with an increased risk of perioperative myocardial damage and early adverse cardiovascular events in patients undergoing elective vascular surgery.³² CRP also plays an important role in the composition and progression of atherosclerotic lesions.^{33,34} There is growing evidence of a link between plasma CRP and the degree of atherosclerosis suggesting that inhibition of plasma CRP may represent a therapeutic modality for the treatment of cardiovascular disease and possibly POD.³⁵ The current results support the important role of inflammation after (vascular) surgery and provide the opportunity for a future intervention.

This is the first study that demonstrates the large differences in risk of POD in vascular surgery with the highest incidence rates (95% CI) found after open aortic surgery and amputation surgery. An important finding that has not yet been demonstrated to date is the major difference in POD incidence between open and endovascular aortic

aneurysm repair (EVAR). EVAR has become a good alternative to open repair with benefits such as shorter hospitalization time, less morbidity, and 30-day mortality. A lower POD incidence further contributes to these benefits and can be of decisive importance in the treatment of elderly, vulnerable patients.

The occurrence of POD in this study is associated with a statistically significant risk of subsequent long-term care. These findings are in line with the current literature and further emphasize the far-reaching consequences of POD. POD has a poor prognosis when it comes to persistent cognitive decline and increased risk of dementia.^{5,35} Frail, elderly patients frequently require discharge to an institutional care facility and this study shows that POD adds a significant contribution to this already increased risk. A systematic review on outcome after POD confirms our results that POD has serious adverse effects on both HLOS and institutionalization.³⁵

The level of CRP may be related to the number or severity of complications, such as postoperative infection. Also, the occurrence of complications is considered a potential risk factor for POD.³⁶ Even in a prospective study such as ours, it is difficult to reliably determine the cause and effect relationship among CRP, complications, and POD. However, with an equally divided mean number of complications between the POD and non-POD group, it is less likely that this has influenced the outcome

Table IV. Multiple logistic regression analysis of the risk of postoperative delirium on CRP

Variable	Model 1			Model 2			Model 3			Model 4		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Postoperative C-reactive protein (mg/L)	1.01	1.00–1.11	0.003	1.01	1.01–1.02	0.02	1.01	1.00–1.04	0.007	1.01	1.00–1.04	0.04
Age (year)	—			1.05	0.98–1.12	0.16	1.04	0.96–1.12	0.29	1.05	0.97–1.14	0.20
Gender (male versus female ^a)	—			0.34	0.04–2.83	0.32	0.26	0.03–2.24	0.22	0.24	0.03–2.33	0.22
Comorbidities ^b	—			—			1.12	0.83–1.51	0.46	1.10	0.77–1.55	0.60
Cognitive impairment ^c (yes versus no ^a)	—			—			2.86	0.79–10.35	0.11	2.91	0.74–11.50	0.13
Depression ^c (yes versus no ^a)	—			—			1.10	0.73–1.65	0.66	0.97	0.61–1.53	0.90
Type of procedure (open aortic surgery or amputation versus other ^a)	—			—			—			5.39	1.11–26.26	0.04
ICU admittance (yes versus no ^a)	—			—			—			0.60	0.13–3.25	0.65

^aReference category (no or other procedure).^bCharlson Comorbidity Index.^cAs determined by item 9 and 10 of the Groningen Frailty Indicator.

(Table III). It seems therefore plausible that the inflammatory response through the surgery leads to the increased risk of POD, a finding which to date has not been demonstrated.

This study has some limitations. As in our previous publication on POD after vascular surgery, the incidence of delirium is much lower than that reported in the literature. Therefore, we were limited in the number of variables in our multiple logistic regression analysis. However, the incidence in our study was also strongly dependent on the type of surgery, resulting in a large variance between the various operations. The incidence rate in our study was comparable with the incidence rates in large prospective studies and it is generally acknowledged that large studies yield the most reliable estimates.^{37,38} In a large prospective cohort study by Marcantonio et al.,³⁷ POD occurred in only 117/1341 (9%) patients older than 50 years. The same goes for a large international study by Rudolph et al.³⁸ in which a large group of patients were daily assessed for delirium after noncardiac surgery. Again, only 8% of patients developed POD. So although we describe a “high-risk” group, a relatively low POD incidence is not uncommon. Proactive geriatric consultation has been proven to reduce both delirium incidence and severity after surgery and, as it is readily available in our hospital, this could have led to a low delirium incidence.^{39,40}

Postoperative CRP increase should be considered a risk factor for the occurrence of POD. However, if one speaks in terms of prevention and determining the risk of POD at the earliest possible stage, the preoperative CRP value is preferable. In half of our patients, a preoperative CRP value was determined, and although the same risk estimate was achieved with regard to the occurrence of POD, this did not reach statistical significance in the final model because of underfitting.⁴¹ Although various cytokines (including interleukins and tumor necrosis factors) appear to have an even greater sensitivity in the pathogenesis of POD, its use in daily practice is impractical and expensive.^{13,14} The use of CRP fits into the pathophysiological hypothesis and can easily be applied in every surgical clinic.

Preoperative cognitive impairment and depression are known risk factors for the occurrence of POD.⁴² In this study, we corrected for these variables by making use of 2 items of the GFI. By the use of these subgroups, one can easily correct for 2 important risk factors. Furthermore, clinical subtypes such as hypoactive delirium or the unclassified type which account for, respectively, 29% and 7% of delirium subtypes could have been missed, thus leading to an underestimation of the POD

incidence.³ However, the clinical relevance of these subtypes remains questionable and usually they have no therapeutic consequence.

Although CRP alone is not sufficient as a target for prevention in a multifactorial disease as POD, evidence is growing of (neuro)inflammation as a common final pathway in the occurrence of POD. This study adds relevant information to the growing understanding of this pathway. However, in this process, there are several factors which influence the onset of POD and there is certainly a balance between the degree of neuroinflammation and the vulnerability of the patient. Multivariate models, such as proposed by Böhner et al.,⁴³ are needed to truly predict POD and develop preventive strategies. Their model also showed CRP to be significantly associated with POD, but unfortunately, this high quality prospective study failed to further explore this unexpected outcome. Further research may strengthen the relationship between CRP and POD and may as well provide better insights into its etiology.

In conclusion, elevated CRP levels, as a measure of inflammation, should be considered a marker for an increased risk of POD. Whether preoperative CRP values can also be used as a predictor for POD cannot be concluded based on these findings and should be further investigated. The occurrence of POD has major implications for the subsequent care facility after discharge. Patients with elevated CRP values should be considered eligible for active geriatric consultation given the risk of POD and subsequently the need for postdischarge institutionalization.

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