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Original Paper

Relevance of Endothelial Cell-Specific Molecule 1 (Endocan) Plasma Levels for Predicting Pulmonary Infection after Cardiac Surgery in Chronic Kidney Disease Patients: The Endolung Pilot Study

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Keywords
Biomarkers · Endocan · Pulmonary infection · Sepsis · Cardiovascular surgery

Abstract
Objectives: This pilot study aimed to evaluate the relevance of endocan plasma levels for predicting pulmonary infection after cardiac surgery in patients with chronic kidney disease (CKD). ***Methods:*** Serum collected in a previous prospective cohort study (from 166 patients with preoperative CKD who underwent cardiac surgery) was used. Five patients with postoperative pulmonary infection were compared with 15 randomly selected CKD patients with an uneventful outcome. Blood samples were tested at 4 time points (preoperatively and 6, 12, and 24 h after the end of surgery). Endocan, procalcitonin, and C-reactive protein plasma levels were compared between the two groups. ***Results:*** At 6 h, the patients with pulmonary infection had significantly higher levels of endocan than the patients without pulmonary infection (24.2 ± 15.6 vs. 6.4 ± 3.2 ng/mL; $p = 0.03$). A receiver operating characteristic curve analysis showed 80% sensitivity and 100% specificity for endocan to predict pulmonary infection (area under the curve 0.84), with a cutoff value of 15.9 ng/mL. The time saved by assessment of the endocan dosage compared to a clinical diagnosis of pulmonary infection was 47 h. ***Conclusion:*** This pilot study showed that a specific study to assess the link between endocan plasma levels and pulmonary infection after cardiac surgery in CKD patients is of potential utility.

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Introduction

The incidence of postoperative pulmonary infection after cardiac surgery ranges between 5.7 and 21.6% [1], and such an infection can lead to death in up to 31.9% of cases [2–4]. The diagnosis of postoperative pulmonary infection is often obtained late because of several confounding factors due to perioperative inflammation and because of the poor diagnostic performance of current infection markers in the immediate postoperative period.

Endocan (also called endothelial cell-specific molecule 1 or ESM-1) is a proteoglycan that can be detected in human blood and is produced and secreted by endothelial cells, mainly from the lung and to a lesser extent from the kidney [5, 6]. The selective expression by lung endothelial cells is governed by a proximal region of its promoter. Endocan can take part in molecular interactions with a wide range of biologically active moieties, which are essential for the regulation of biological processes such as cell adhesion, migration, proliferation, and neovascularization [7]. Endocan binds to leukocyte function-associated antigen 1 (LFA-1) on human leukocytes and inhibits LFA-1 binding to endothelial intercellular adhesion molecule 1 (ICAM-1), and is thus able to modulate leukocyte migration from blood flow into the tissues [8, 9]. The synthesis and secretion of endocan are upregulated by proinflammatory cytokines like TNF-α or interleukin-1b and lipopolysaccharides [5].

Endocan has been shown to provide promising results in the early detection of acute lung injury after major trauma or in septic shock patients [10, 11]. Kao et al. [12] reported in a recent study that endocan was reliable in evaluating the severity of community-acquired pneumonia. Güzel et al. [13] found a correlation between plasma endocan levels and thromboembolism. Endocan has been shown to be correlated with the estimated glomerular filtration rate and, as such, may indicate the stage of chronic kidney disease (CKD) [14]. Indeed, it has been hypothesized that endocan could become a useful marker for differentiating acute kidney injury from CKD [15]. To date, endocan has never been tested in cardiac surgery for the early detection of postoperative pulmonary infection, although other biomarkers have been shown to be of interest in this context. Procalcitonin (PCT) has already been tested in cardiac surgery to detect postoperative infection, but its role remains controversial. Some authors clearly describe a relation between PCT and the onset of postoperative infection [16] and also ventilator-associated pneumonia [17]. Other authors, such as Chakravarthy et al. [18], found no significant difference in serum PCT levels between patients with and those without bacterial infection after cardiac surgery. Secondly, C-reactive protein (CRP), another widely used marker, is reportedly less specific and peaks later than PCT [19, 20].

In order to evaluate the relevance of plasma endocan levels for predicting pulmonary infection after cardiac surgery in patients with CKD, we used blood samples collected in a previous prospective study (NGAL study) [19]. In this study, 5 CKD patients presented with a postoperative pulmonary infection. These patients were compared to 15 randomly selected CKD patients from the same study who had an uneventful outcome. Endocan, PCT, and CRP levels were measured for all patients from blood samples taken during the perioperative period.

Patients and Methods

In a previous prospective cohort study (NGAL study [21]), 166 adult patients with preoperative CKD who underwent cardiac surgery with or without the use of cardiopulmonary bypass (CPB) were enrolled. CKD was defined as a creatinine clearance <60 mL/min (Cockcroft-Gault equation). Patients undergoing emergency operations, patients with ongoing inflammatory, infectious, or oncologic pathologies, pregnant women, adults under legal protection, and individuals who refused consent were excluded. Blood samples were taken in EDTA containers at 4 time points, namely, at induction of general anesthesia (baseline), as well as 6, 12, and 24 h after the end of surgery. The blood samples were centrifuged at 2,250 ± 250 rpm for 13 ±

2 min at room temperature (18–25°C), and plasma was aliquoted in 0.5-mL tubes (Eppendorf, Le Pecq, France) and frozen at –20°C for later analysis.

Nosocomial pneumonia was diagnosed based on the presence of all of the following criteria: fever >38.8°C, rales, leukocytosis (>11,000/μL), detection of new or progressive lung infiltrate(s) not explained otherwise, and confirmation by purulent respiratory secretion yielding the growth of a relevant pathogen. A positive culture of blood, pleural fluid, or bronchoalveolar lavage was regarded as additional proof of nosocomial pneumonia.

In the NGAL study, 5 patients presented with postoperative pulmonary infection. For the purposes of this analysis, we randomly selected 15 additional patients from the same study who had an uneventful outcome. There were no statistical differences in age, sex, or renal function between the two groups.

Endocan, PCT, and CRP were measured from blood samples. Endocan was measured using the Lunginnov ELISA kit (EndoMark® H1), which is based on an immunoenzymatic assay (Lunginnov SAS, Lille, France). The measurement range is from 0.625 to 5 ng/mL. During the study period, the between-assay imprecision was 12%, based on a quality control sample targeted at 3.5 ng/mL. PCT and CRP were measured on Roche cobas® 8000 analyzers (Roche Diagnostics, Meylan, France), using the PCT immunoassay kit (BRAHMS Thermo Fisher Scientific, Asnières-sur-Seine, France) and the CRP Gen3 immunoturbidimetric kit (Roche Diagnostics), respectively. The laboratory where the analyses were performed complied with all recommended quality controls (internal and external quality controls) for all routinely tested biomarkers during the study period.

We analyzed the ability of each biomarker individually to detect early postoperative infectious complications, as well as the diagnostic performance of associations of biomarkers.

Statistical Analysis

Continuous variables are presented as mean ± SD, and categorical variables as number (percentage). Quantitative variables were compared by the Student *t* test and the Mann-Whitney U test, according to their distribution. The associations of the different biomarkers were compared using receiver operating characteristic curve analysis. The reliability of the analysis was tested by calculating the area under the curve, cutoff value, sensitivity, and specificity. The validity of each biomarker (individually or in association) as an adequate diagnostic predictor was assessed by the Youden index. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

The average age of the 5 patients with pulmonary infection was 78 ± 10 years, and those with an uneventful outcome were 77 ± 7 years old ($p = 0.49$). Between the patients who presented with postoperative infection and those with an uneventful course, there were no significant differences in BMI (31 ± 10 vs. 24 ± 3; $p = 0.12$), diabetes mellitus (2 patients [40%] vs. 1 patient [7%]; $p = 0.14$), left ventricular ejection fraction (60 ± 12 vs. 57 ± 14; $p = 0.55$), and preoperative creatinine clearance (44 ± 13 vs. 47 ± 9 mL/min/1.73 m^2; $p = 0.67$). All patients (100%) with pulmonary infection and 6 patients (40%) with an uneventful outcome were male ($p = 0.04$). The kinetics of the endocan blood levels showed a progressive increase over time both in the patients with pulmonary infection and in the patients with an uneventful outcome (Table 1).

Diagnostic Performance of the Tested Biomarkers

The patients with pulmonary infection had significantly higher levels of endocan 6 h postoperatively than the patients with an uneventful outcome ($p = 0.03$) (Table 1). For these patients, the diagnosis of pneumonia was established on average 53 ± 20 h after the operation, and antibiotic treatment was initiated after an average of 62 ± 27 h. The receiver operating characteristic curve for endocan at 6 h showed the best diagnostic performance for the detection of pulmonary infections, with an area under the curve of 0.84, as well as 80% sensitivity and 100% specificity, at a cutoff value of 15.9 ng/mL (Fig. 1a). The PCT levels showed no relevant differences between the infected and the uninfected patients. The CRP levels at 6 and 12 h were related to postoperative pulmonary infection, with *p* values of 0.01 and 0.03,

Table 1. Preoperative and 6-, 12-, and 24-h endocan, PCT, and CRP plasma levels according to subsequent pulmonary infection

Biomarker	Timing	Pulmonary infection	Mean ± SD	*p* value
Endocan, ng/mL	Preoperatively	No	3.07±2.37	0.69
		Yes	2.21±1.47	
	6 h	No	6.44±3.16	0.03
		Yes	24.16±15.64	
	12 h	No	9.79±7.18	0.07
		Yes	25.27±14.35	
	24 h	No	13.17±6.68	0.63
		Yes	15.14±15.29	
PCT, ng/mL	Preoperatively	No	0.05±0.03	0.26
		Yes	0.11±0.12	
	6 h	No	0.90±1.70	0.11
		Yes	4.32±7.03	
	12 h	No	1.32±2.43	0.22
		Yes	6.13±9.65	
	24 h	No	2.04±3.15	0.6
		Yes	6.49±11.08	
CRP, mg/L	Preoperatively	No	3.38±4.91	0.19
		Yes	16.81±29.41	
	6 h	No	15.18±9.39	0.01
		Yes	48.54±41.29	
	12 h	No	51.83±18.09	0.03
		Yes	102.8±65.21	
	24 h	No	137.91±51.03	0.1
		Yes	197.76±89.29	

PCT, procalcitonin; CRP, C-reactive protein.

respectively. There was no significant difference in creatinine clearance between the patients with postoperative pulmonary infection and those without 6, 12, 24, or 48 h after surgery (p = 0.40, 0.22, 0.20, and 0.23, respectively).

Diagnostic Performance of Combined Biomarkers

The association of biomarkers showed that endocan and PCT taken together present a sensitivity of 100% and a specificity of 87% at 6 h, with cutoff values of 8.28 ng/mL for endocan and 0.65 ng/mL for PCT (Fig. 1b). The association of endocan with CRP had a sensitivity of 100% and a specificity of 93% at 6 h, with cutoff values of 12.24 ng/mL for endocan and 18.08 mg/L for CRP (Fig. 1c).

Discussion

Nosocomial infection still remains a diagnostic and therapeutic challenge in the care of cardiac surgery patients, affecting both morbidity and mortality. The early diagnosis and treatment of postoperative infections is considered very important for the patient's outcome [1]. The diagnosis of nosocomial infection in this patient population is sometimes difficult, since clinical and laboratory signs of inflammation may be caused not only by infection but also by tissue injury, or mainly by the systemic inflammatory response syndrome associated with CPB. It has been reported that CRP levels are not clearly helpful in differentiating between the postoperative presence and absence of infection in patients [19, 20]. In addition, surgical patients usually receive systemic antibiotics, thus negatively influencing blood culture. An

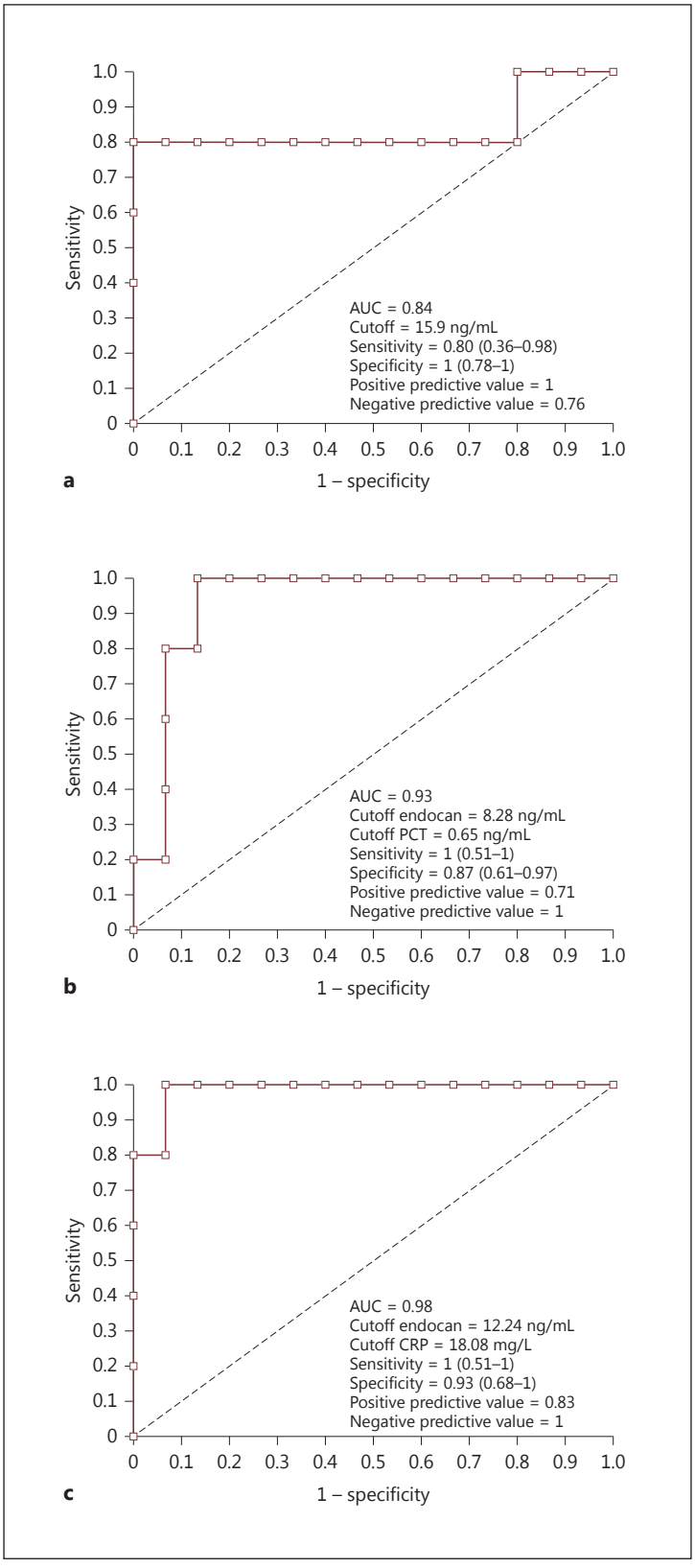

Fig. 1. Receiver operating characteristic curves of biomarker plasma levels 6 h after the end of surgery. **a** Endocan alone. **b** Association of endocan plus PCT. **c** Association of endocan plus CRP. PCT, procalcitonin; CRP, C-reactive protein; AUC, area under the curve.

increase in PCT values after CPB, in the absence of postoperative infection, has previously been reported by Meisner et al. [22]. Moreover, PCT values greater than 2 ng/mL can be observed in case of systemic inflammatory response syndrome after CPB, without any postoperative infectious complication [23, 24].

In our study, the endocan blood levels were significantly elevated in CKD patients with postoperative pulmonary infection. Endocan serum levels 6 h after the end of surgery (cutoff 15.9 ng/mL) were shown to predict postoperative pulmonary infections with a specificity of 100% and a sensitivity of 80%. CRP also showed an increase in case of postoperative infections, but we know from the literature that while both CRP and PCT are very sensitive in revealing bacterial infections [19, 20, 24], they suffer from a lack of specificity. Shehabi and Seppelt [25] stated that as a matter of pragmatism, no biomarker should ever be used in isolation for decision-making. It is just one tool in the clinician's armamentarium and must be considered in conjunction with clinical examination, other laboratory tests, and microbiological results. In line with this point of view, we tested endocan in association with CRP and PCT. Endocan associated with PCT or CRP serum levels at 6 h led to an increase in sensitivity, but at the cost of a decrease in specificity.

The kinetics of blood endocan levels showed a progressive increase over time in patients with an uneventful outcome in our population of CKD patients. This is in line with a previous report by Yilmaz et al. [26] showing that plasma endocan levels increase in the presence of a decreasing estimated glomerular filtration rate, and are related to the risk of all-cause mortality and cardiovascular events. However, it remains unknown whether the mechanism for this rise is an increase in production or a reduction in clearance [27]. In our study, the increase in endocan could be due to the lung injury secondary to the proinflammatory systemic response induced by surgical aggression. In patients who went on to develop pneumonia, the increase in endocan levels was up to 12 times the basal value after only 6 h, testifying to the more severe lung injury independently of the underlying kidney disease. Even in patients with an uneventful outcome, endocan levels after cardiac surgery probably increase because of a proinflammatory systemic response to surgery and subsequent pulmonary dysregulation. Therefore, in addition to the relation between endocan and renal function, endocan may also be a marker of lung injury, and the mechanisms linking these two systems remain to be established.

Endocan has already been shown to be a marker of lung injury in different fields, but not in cardiac surgery until now. Mikkelsen et al. [11] evaluated endocan levels in major trauma patients at hospital admission and reported that low endocan levels were predictive of the occurrence of acute lung injury via endocan-mediated leukocyte blockage. Palud et al. [10] demonstrated that in patients presenting with septic shock, low endocan levels (<3.55 ng/mL) at admission to the ICU appeared to be predictive of acute respiratory dysfunction, justifying earlier specific therapies such as a protective ventilator strategy and use of antibiotics. We also found lower basal endocan levels in patients developing postoperative pulmonary infection than in patients showing no complications (2.21 ± 1.47 vs. 3.07 ± 2.37 ng/mL), and although the difference did not reach statistical significance, the trend suggests the same biological behavior as that described above by Palud et al. [10] and Mikkelsen et al. [11].

In our cohort of CKD patients undergoing cardiac surgery, pulmonary infection was diagnosed according to standard clinical criteria an average of 53 h after surgery, and the consequent antibiotic treatment was initiated on average 62 h after the operation. Elevated endocan levels 6 h after the intervention (i.e., much earlier) were shown to strongly correlate with postoperative pulmonary infection. This suggests that endocan can anticipate the diagnosis and treatment of pulmonary infection in these patients, with respective potential gains of 47 and 56 h, which clearly could play a major role in decreasing morbidity, mortality, and the length of hospital stay.

There are several limitations to this study. Firstly, due to the design of our original prospective study, all patients had chronic renal failure, with the result that our findings cannot be extrapolated to all cardiac surgery patients. Further confirmation in a non-CKD population is required. However, a previous study on CKD patients indicated that endocan maintains a good diagnostic performance, even in CKD patients [27]. Secondly, our sample size is small (pilot study), even if comparable to those of other studies on endocan [10, 11, 13]. We randomly selected 15 patients with an uneventful outcome for the purposes of comparison with the 5 patients with infection as we judged this to be a sufficient number for a pilot study. Lastly, the comparator patients were randomly selected, and there was no matching for age, sex, or renal function. However, the comparison between the two groups showed no statistical differences in these criteria.

This was a pilot study to test feasibility. A larger, prospective study on the same topic is registered with the ClinicalTrials.gov database under the number NCT02542423 and was initiated at our center in January 2016.

Conclusions

In this pilot study, we demonstrate that endocan is a potentially useful biomarker for the early detection of postoperative pulmonary infection in cardiac surgery patients with chronic kidney failure. Furthermore, it makes it possible to anticipate the diagnosis of postoperative pulmonary infection by 2 days as compared to clinical diagnosis. Our findings need to be confirmed in a larger, prospective study.

Statement of Ethics

The NGAL study was approved by the local ethics committee (CPP EST II, registered under the number 10/544) and was registered on the ClinicalTrials.gov database under the number NCT01227122. All participants provided written informed consent in which they gave consent to conserve and use their serum for other research purposes.

Disclosure Statement

No author has any conflict of interest to declare in relation to this manuscript.

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