Is Endocan a Diagnostic Marker for Pneumonia After Cardiac Surgery? The ENDOLUNG Study

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The development of postoperative pneumonia is a frequent complication after cardiac surgery and is associated with increased inhospital morbidity and mortality [1]. The prevalence of ventilator-associated pneumonia after cardiac surgery is estimated to be between 5.7% and 21.6% [2]. A more serious form of lung injury is acute respiratory distress syndrome (ARDS), affecting as many as 20% of patients, and associated with a mortality rate as high as 80% after cardiac surgery [3]. Various risk factors have been associated with the development of pulmonary complications in patients undergoing cardiac surgery, including the duration of mechanical ventilation, type of surgery, use of cardiopulmonary bypass, supine position during the first 24 hours, history of chronic obstructive pulmonary disease, and transfusion-related acute lung injury [1, 2, 4].

Cardiac surgery and cardiopulmonary bypass trigger an acute and nonspecific inflammatory reaction [5, 6]. In this context, the diagnosis of infection is challenging, because conventional clinical and biological signs may be misleading [7]. Early detection of postoperative pneumonia makes it possible to initiate appropriate therapy more quickly in these patients. Endocan (also called endothelial cell-specific molecule 1 or ESM-1) is a proteoglycan produced and secreted by the lung endothelial cells [8, 9]. Endocan principally circulates in the bloodstream at a level of approximately 1 ng/mL in healthy subjects [10]. Blood endocan increases in the context of sepsis as a result of de novo synthesis and secretion induced by proinflammatory cytokines such as tumor necrosis factor-alpha, interleukins, and polysaccharides [8]. Recent studies have underlined the usefulness of

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endocan as an early predictor of acute lung injury or respiratory failure after major trauma and in septic shock patients [11, 12]. The aim of the present study was to assess whether endocan can be used as a diagnostic marker for postoperative pneumonia in patients undergoing cardiac surgery.

Patients and Methods

The prospective Endocan Predictive Value in Postcardiac Surgery Acute Respiratory Failure (ENDOLUNG) study was conducted in the Department of Cardiac Surgery of Besançon University Hospital between January and July 2016. The study was approved by the Local Ethics Committee (CPP EST II, registered under the number 10/544) and was registered on clinicaltrials.gov (NCT02542423). All participants provided written informed consent. The inclusion criteria were adult patients (aged more than 18 years) scheduled to undergo cardiac surgery and who provided written informed consent. Exclusion criteria were patients aged less than 18 years; emergency surgery; patients with ongoing pulmonary infection, inflammation, or cancer; pregnancy; patient refusal; and adults under legal protection.

Blood samples for endocan measurements were collected in 5 mL ethylenediaminetetraacetic acid tubes at five timepoints, namely, at induction of general anesthesia (baseline), and at 6, 24, 48, and 72 hours after the end of surgery, in accordance with preanalytical recommendations [10]. Blood samples were centrifuged at 3,000 rpm for ±10 minutes at room temperature (18° to 25°C), and plasma was aliquoted in 0.5 mL tubes (Eppendorf, Le Pecq, France) and frozen at −20°C until assayed. Endocan was measured using the Lunginnov ELISA kit (EndoMark H1), which is based on immunoenzymatic assay (Lunginnov SAS, Lille, France). The measurement range is from 0.625 mL 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. Procalcitonin (PCT) and C-reactive protein (CRP) collected at 24 and 72 hours after the end of surgery were measured on Roche Cobas 8000 analyzers (Roche Diagnostics, Meylan, France), using the PCT immunoassay kit (BRAHMS; ThermoFisher Scientific, Asnières-sur-Seine, France) and CRP Gen3 immunoturbidimetric kit (Roche Diagnostics), respectively. The central hospital laboratory where the analyses were performed complied with all recommended quality controls (internal and external quality controls) for the biomarkers tested routinely during the study period.

Definition of Postoperative Pneumonia

The diagnosis of postoperative pneumonia was suspected on the basis of new detection of lung infiltrates on chest radiograph associated with at least two of the following features: fever more than 38.8°C; leukocytosis (>11,000 cells/mm^3) or leucopenia (<3,000 cells/mm^3); or purulent secretion [13]; and confirmed by microbiologic analysis using bronchoalveolar lavage with fiberoptic bronchoscopy.

Data Collection

Data were recorded prospectively. The baseline measurements recorded were age, sex, weight, height, body mass index, and cardiovascular risk factors (diabetes mellitus, dyslipidemia, arterial hypertension, smoking, and family history). The main intraoperative data recorded were the type of surgery and the cross-clamp and extracorporeal circulation times. We postoperatively collected total bleeding, need for transfusion and number of packs transfused, use of inotropes, intubation time, ventilation measurements, need for noninvasive mechanical ventilation, inflammatory/infectious signs on the chest radiograph, length of intensive care unit and hospital stay, and occurrence of complications.

Statistical Analysis

A previous study showed an average difference between groups of 1.4 ng/mL with a mean standard error of 2 ng/mL [11]. Assuming that 10% of patients would have postoperative pneumonia, a sample size of 160 patients was necessary to show an average difference of 1.5 ng/mL between the two groups with a standard error of 2 ng/ml, with an alpha risk of 0.05 and 80% power.

Quantitative data are expressed as mean ± SD when normally distributed, and as median (interquartile range) otherwise. Qualitative data are described as number (percentage). Preoperative, intraoperative, and postoperative characteristics were compared using the independent-samples Student's t test, Mann-Whitney U test, and χ^2 or Fisher's exact tests, as appropriate.

The threshold values of endocan that could predict early pulmonary infection, and associated sensitivity and specificity were determined using receiver-operating characteristics curve analysis. Independent predictors of postoperative pulmonary complications were identified by logistic regression. Variables with a p value less than 0.20 by univariate analysis were included in the model. A p value less than 0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Between January 1 and May 23, 2016, a total of 255 patients underwent cardiac surgery in our institution, of whom 196 agreed to participate in the study. Among these, 31 patients who underwent off-pump surgery and 10 patients with missing data were excluded. A total of 155 patients was included in the final analysis. The baseline characteristics of the study population are shown in Table 1. Overall, 17 patients had postoperative pneumonia after surgery. There was no significant difference at baseline between patients who had postoperative pneumonia (POP group), and patients who did not (no-POP group), except for body mass index greater than 27 kg/m^2, aortic cross-clamping time, cardiopulmonary bypass time, and length of operation.

Table 2 shows the postoperative complications in both groups. There was a higher overall rate of complications

Table 1. Baseline Characteristics of Study Population

Characteristics	Total (n = 155)	POP Group (n = 17)	No-POP Group (n = 138)	*p* Value
Age, years	69.8 ± 9.2	71.5 ± 7.2	69.6 ± 9.4	0.42
<60	18 (11.6)	0 (0)	18 (13.0)	0.22
60–70	63 (40.6)	9 (52.9)	54 (39.1)	0.30
>70	75 (48.4)	8 (47.1)	67 (48.6)	1
Female	43 (27.7)	6 (35.3)	37 (26.8)	0.57
Hypertension	113 (72.9)	15 (88.2)	98 (71.0)	0.16
Current smoker	26 (16.8)	4 (23.5)	22 (15.9)	0.49
BMI, kg/m^2	27.6 ± 4.7	29.3 ± 3.5	27.4 ± 4.8	0.039
BMI >27 kg/m^2	79 (51.1)	13 (76.5)	66 (47.8)	0.038
Diabetes mellitus	43 (27.7)	3 (17.7)	40 (29.0)	0.40
Dyslipidemia	84 (54.2)	12 (70.6)	72 (52.2)	0.20
eGFR, mL/min	76.8 ± 20.7	70.8 ± 15.8	77.6 ± 21.1	0.15
>85	55 (35.5)	4 (23.5)	51 (37.0)	0.42
50–85	89 (57.4)	11 (64.7)	78 (56.5)	0.61
<50	11 (7.1)	2 (11.8)	9 (6.5)	0.35
Atrial arrhythmia	30 (19.4)	5 (29.4)	25 (18.1)	0.33
Extracardiac arterial disease	61 (39.4)	5 (29.4)	56 (40.6)	0.44
LVEF, %	58.6 ± 12.4	55.4 ± 11.4	58.9 ± 12.0	0.22
>50%	112 (72.3)	14 (82.4)	98 (71.0)	0.40
30–50%	14 (9.0)	1 (5.9)	13 (9.4)	1
<30%	6 (3.9)	1 (5.9)	5 (3.6)	0.51
Pulmonary hypertension	9 (5.8)	1 (5.9)	8 (5.8)	1
sPAP 35–55 mm Hg	8 (5.2)	0 (0)	8 (5.8)	0.59
sPAP >55 mm Hg	1 (0.6)	1 (5.9)	0 (0)	0.11
Hemoglobin, g/dL	13.9 ± 1.6	14.2 ± 1.6	13.9 ± 1.6	0.75
Platelet count	241.7 ± 81.1	247.9 ± 156.4	240.9 ± 78.8	0.66
Leukocytes	7.3 ± 2.4	7.1 ± 2.6	7.3 ± 2.4	0.38
Type of surgery				
Isolated CABG	67 (43.2)	6 (35.3)	61 (44.2)	0.61
Isolated AVR	35 (22.6)	4 (23.5)	31 (22.5)	1
CABG + AVR	34 (21.9)	5 (29.4)	29 (21.0)	0.53
Other	20 (12.9)	2 (11.8)	18 (13.0)	1
Clamp time, minutes	73.3 ± 32.9	90.9 ± 39.6	71.1 ± 31.5	0.047
CPB time, minutes	88.9 ± 40.6	115.4 ± 49.4	85.6 ± 38.3	0.013
Intervention duration, minutes	351.7 ± 100.5	444.2 ± 228.5	340.4 ± 63.8	0.008

Values are mean ± SD or n (%).

AVR = aortic valve replacement; BMI = body mass index; CABG = coronary artery bypass graft surgery; CPB = cardiopulmonary bypass; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; POP = postoperative pneumonia; sPAP = systolic pulmonary artery pressure.

in the POP group. There were 4 postoperative deaths overall (2.6%): 1 patient in the no-POP group died of heart failure; and 3 patients in the POP group died, 1 of stroke, 1 of heart failure, and 1 of ARDS. In the POP group, there were more reintubations, need for vasopressors, hemofiltration, and a longer duration of hospital stay.

The kinetics of endocan blood levels followed the same pattern in both groups, but with higher values in the POP group (Table 3). The endocan level was significantly higher at induction of general anesthesia and 6 hours after the end of surgery in the POP group as compared with the no-POP group. There was also a significant increase in PCT in the POP group, apparent at 3 days after surgery. The CRP levels were significantly higher in the POP group at each timepoint (preoperative, 24 hours, and 72 hours).

At induction of anesthesia, an endocan cutoff value of 3.7 ng/mL had 65% sensitivity and 72% specificity for the prediction of POP; at 6 hours, the values were, respectively, 71% and 75% at a cutoff value of 12.1 ng/mL (Fig 1).

At induction of anesthesia as well as at 6 hours, multivariate analysis showed that body mass index greater than 27 kg/m^2, duration of the operation, and endocan value above the threshold value were independent predictors of POP (Table 4). The average time to

Table 2. Postoperative Complications

Complications	Total (n = 155)	POP Group (n = 17)	No-POP Group (n = 138)	*p* Value
Transfusion	73 (47.1)	9 (52.9)	64 (46.4)	0.62
Intubation, hours	12.1 ± 24.6	28.4 ± 73.3	10.1 ± 4.5	0.07
Bleeding at 24 hours, mL	481.5 ± 211.5	506.5 ± 226.6	478.4 ± 210.3	0.64
Need for vasopressors	47 (30.3)	9 (52.9)	38 (27.5)	0.048
Chest radiograph	41 (26.5)	9 (52.9)	32 (23.2)	0.017
Condensation	5 (3.2)	3 (17.6)	2 (1.4)	0.010
Pleural effusion	35 (22.6)	6 (35.3)	29 (21.0)	0.22
Atelectasia	14 (9.0)	6 (35.3)	8 (5.8)	0.001
Intensive care unit stay, days	5.1 ± 4.2	9.7 ± 8.2	4.5 ± 3.0	0.002
Hospital stay, days	12.7 ± 8.3	21.7 ± 17.8	11.6 ± 5.5	<0.01
Complications				0.14
Acute kidney failure	23 (14.8)	5 (29.4)	18 (13.0)	0.001
Renal replacement therapy	3 (1.9)	3 (17.6)	0 (0)	0.011
Cardiogenic shock	2 (1.3)	2 (11.8)	0 (0)	0.29
Circulatory assistance	3 (1.9)	1 (5.9)	2 (1.4)	1
Atrial fibrillation	69 (44.5)	8 (47.1)	61 (44.2)	0.21
Stroke	2 (1.3)	1 (5.9)	1 (0.7)	0.17
Reintervention for PE	7 (4.5)	2 (11.8)	5 (3.6)	…
Reintubation	5 (3.2)	4 (23.5)	1 (0.7)	<0.01
Other infections	8 (5.2)	2 (11.8)	6 (4.3)	0.21
Death	4 (2.6)	3 (17.6)	1 (0.7)	0.004

PE = pleural effusion; POP = postoperative pneumonia.

diagnosis of POP was 96 ± 60 hours, and the average time to initiation of antibiotics was 99 ± 65 hours (Fig 2).

Comment

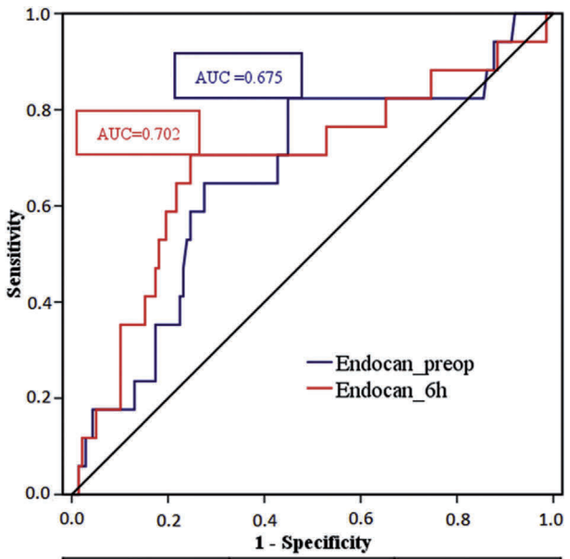
Postoperative pneumonia after cardiac surgery is still a major and common problem. Despite several steps forward in anesthetic skills, and improvements in surgical techniques and equipment, cardiac surgery patients are increasingly older, with numerous comorbidities, and are therefore susceptible to pulmonary complications. Identifying patients at high risk of having pulmonary dysfunction could allow early detection and rapid intervention to minimize morbidity and mortality. This diagnostic dilemma warrants a new and specific biomarker that could help to make the diagnosis of postoperative pneumonia earlier. In recent years, many perioperative biomarkers have been tested and proposed in clinical trials. Procalcitonin has been widely tested in cardiac surgery to detect postoperative infection, but its utility

Table 3. Endocan, Procalcitonin, and C-Reactive Protein Levels in Study Population at Different Measurement Timepoints

Variable	Total	POP Group	No-POP Group	*p* Value
Endocan, ng/mL				
Preoperative	3.9 ± 2.9	5.3 ± 3.6	3.8 ± 2.8	0.030
6 hours	10.5 ± 7.9	14.2 ± 9.4	10.0 ± 7.6	0.013
24 hours	10.9 ± 9.4	14.6 ± 11.7	10.5 ± 9.0	0.065
48 hours	8.2 ± 6.5	10.7 ± 7.8	7.9 ± 6.3	0.083
72 hours	7.1 ± 4.9	8.6 ± 5.9	6.9 ± 4.9	0.154
Procalcitonin, ng/mL				
24 hours	1.1 ± 2.2	1.9 ± 2.3	1.0 ± 2.1	0.078
72 hours	1.0 ± 2.4	1.9 ± 1.8	0.9 ± 2.4	<0.01
C-reactive protein, mg/L				
Preoperative	7.2 ± 13.5	12.7 ± 18.4	6.5 ± 12.7	0.012
24 hours	153.6 ± 52.6	192.3 ± 57.4	148.7 ± 50.1	0.003
72 hours	225.5 ± 68.6	275.1 ± 52.9	220.0 ± 68.2	0.004

Values are mean ± SD. Endocan preoperative (n = 155), 6 hours (n = 155), 24 hours (n = 155), 48 hours (n = 149), 72 hours (n = 141); procalcitonin 24 hours (n = 147), 72 hours (n = 137); C-reactive protein preoperative (n = 149), 24 hours (n = 150), 72 hours (n = 140).

POP = postoperative pneumonia.



	Endocan Preop	Endocan 6H
AUC	0.675	0.702
Sensitivity	65%	71%
Specificity	72%	75%
Cut off	3.7 ng/mL	12.1 ng/mL

Fig 1. Receiver-operating characteristic curves at preoperative (Preop) induction of anesthesia (blue line) and 6 hours (6H) after surgery (red line). (AUC = area under the curve.)

remains controversial. Indeed, cardiopulmonary bypass and cardiac surgery may affect serum levels of several biomarkers, such as PCT and endocan, among others [14–17]. Some researchers clearly describe a relationship between PCT and onset of postoperative infection [18] and also ventilator-associated pneumonia [15], but underline that the diagnostic properties of PCT may not be clearly evident during the first 2 days after surgery [18]. In contrast, endocan appears to be an early marker that

Table 4. Multivariate Analysis of Predictors of Acute Lung Injury Before Surgery and at 6 Hours

Variables	*p* Value	OR (95% CI)
Preoperative		
Body mass index >27 kg/m^2	0.06	3.34 (0.96–11.65)
Intervention duration, minutes	0.03	1.01 (1.00–1.02)
Preoperative endocan >3.67 ng/mL	0.01	4.38 (1.35–14.25)
At 6 hours after surgery		
Body mass index >27 kg/m^2	0.02	4.91 (1.32–18.33)
Intervention duration, minutes	0.048	1.01 (1.00–1.02)
Endocan at 6 hours >12.1 ng/mL	0.001	7.36 (2.16–25.07)

CI = confidence interval; OR = odds ratio.

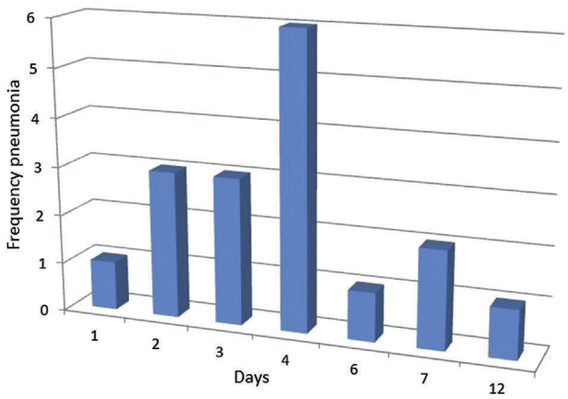


Fig 2. Time to initiation of antibiotic therapy for postoperative pneumonia patients (n = 17).

carries prognostic value in the early hours after surgery. Furthermore, Heredia-Rodríguez and colleagues [19] showed that the predictive value of PCT may be affected by acute kidney injury [19], and endocan has similarly been shown to be correlated to decreasing kidney function [20]. Other authors, such as Chakravarthy and associates [21] found no significant difference in serum PCT levels between patients with or without bacterial infection after cardiac surgery. C-reactive protein is reportedly less specific, and peaks later than PCT [22, 23].

Contrary to PCT or CRP, endocan seems to be specific to pulmonary failure. Mikkelsen and associates [11] showed that in major trauma, low endocan blood levels at hospital admission were associated with subsequent acute lung injury. They hypothesized that the association between lower serum endocan levels and the development of acute lung injury in patients after major blunt trauma reflects dysregulation in leukocyte recruitment. Tang and colleagues [24], in a cohort of 42 ARDS patients, showed that high endocan concentrations predict mortality. Furthermore, they also showed that in ARDS patients, baseline endocan levels are able to predict shock, renal failure, and coagulopathy. They also found a significant link between endocan levels and PCT, but no significant correlation between endocan and CRP levels [24]. In a study including 20 patients, Palud and colleagues [12] found a relationship between low endocan blood levels at hospital admission in septic shock patients and the onset of pulmonary failure at day 3, suggesting that endocan makes it possible to differentiate, among septic patients, those who will go on to have subsequent lung injury. More recently, Ioakeimidou and associates [25] confirmed in a series of 175 septic patients that those who subsequently had ARDS had low endocan levels at admission. Based on these literature data, we decided to conduct a prospective study to test endocan as a diagnostic marker for pneumonia after cardiac surgery.

Patients with off-pump surgery were excluded from this analysis to ensure a more homogenous population. Apart from there being no cardiopulmonary bypass in

off-pump surgery, another difference between on-pump and off-pump surgery relates to management of ventilation during surgery. During on-pump surgery, ventilation is ongoing, whereas in our institution we completely stop ventilation during cardiopulmonary bypass. This difference could perturb the results. Indeed, endocan is released progressively into the blood flow during maintained ventilation, whereas it accumulates in the lung during the time that ventilation is stopped, with a washout once ventilation is resumed, causing a difference in release kinetics that is unrelated to potential lung damage.

Our study showed that endocan levels were significantly elevated in patients with postoperative pneumonia even before induction of anesthesia, and also 6 hours after surgery. Patients with high blood levels of endocan preoperatively (cutoff 3.7 ng/mL) and 6 hours postoperatively (cutoff 12.1 ng/mL) had postoperative pneumonia as often as seven times more frequently than patients with levels below the cutoff values. The kinetics of endocan had a similar profile in both groups, but with consistently higher values in the postoperative pneumonia group. Endocan levels after cardiac surgery, even in patients with uneventful outcome, probably increase because of a proinflammatory systemic response to surgery and subsequent pulmonary dysregulation. Independent predictive factors of subsequent postoperative pneumonia were the same preoperatively and at hour 6, namely, obesity (body mass index greater than 27 kg/m^2), length of operation, and endocan levels above the cutoff value. Many studies agree that the duration of surgery has an impact on incidence of postoperative pneumonia [1, 26]. Obesity is also known to be an important risk factor for respiratory complications [27]. Postoperative respiratory failure is increased in obese patients by their supine position during prolonged surgery, a greater propensity to alveolar collapse and obstructive sleep apnea syndrome, and greater sensitivity to the respiratory depressive effect of sedating drugs and opiates [28].

Endocan is produced mainly by the pulmonary endothelial cells in response to various bacterial components or proinflammatory cytokines. Endocan exhibits antiinflammation specifically by inhibiting leukocyte extravasation [29–31]. Endocan can be viewed as a negative feedback of the inflammation cascade. Depending on the clinical context, an increase in endocan indicates an early pulmonary response to injury. Conversely, absence of an increase, or even a decrease in endocan could indicate insufficient lung protection against injury. According to the findings of Palud and colleagues [12], Mikkelsen and colleagues [11], and Ioakeimidou and associates [25], low blood endocan in intensive care unit patients is linked to subsequent lung disease. Indeed, in these studies, blood samples were collected in the context of ongoing disease (septic shock and major trauma, respectively) whereas in our study, blood samples were collected from the start of aggression (cardiac surgery). In the former cases, the endocan plasma level increases in response to surgery, but the increase is greater when the lung starts to undergo injury by infectious or inflammatory factors, where pulmonary endothelial cells respond by de novo synthesis and release of endocan. In the studies by Palud and colleagues [12], Mikkelsen and colleagues [11], and Ioakeimidou and associates [25], the low blood endocan may be due to either a failure to maintain the pulmonary response or to accelerated degradation by neutrophil proteases. Indeed, endocan can be cleaved by neutrophil-derived cathepsin G to generate a peptide fragment named p14, which is not detected by the immunoenzymatic assay [30].

Our findings have clinical implications. Although the moderate sensitivity and specificity of endocan preclude starting antibiotic treatment on the basis of endocan results alone, patients with high endocan levels preoperatively or at 6 hours may benefit from aspiration of subglottic secretions, introduction of inclinometers to enhance semirecumbent position, and reinforcement of oral care with chlorhexidine, which have all been shown to prevent postoperative pneumonia [32]. Moreover, these patients could be strictly monitored to detect signs of pulmonary infection earlier, enabling earlier initiation of antibiotic therapy. In routine practice [33], as in our patients, the average time to formal diagnosis of pneumonia after cardiac surgery is 4.6 $\pm$ 3.7 days. Early treatments are known to reduce postoperative complications and public health care costs [34].

In conclusion, we found that higher serum endocan levels were associated with the subsequent development of postoperative pneumonia after cardiac surgery. The rise in endocan starts as early as induction of anesthesia. The fair sensitivity and specificity of endocan precludes initiation of antibiotic treatment on this basis alone, but enables screening of patients at risk.

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