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# POSTOPERATIVE SERUM LEVELS OF ENDOCAN ARE ASSOCIATED WITH THE DURATION OF NOREPINEPHRINE SUPPORT AFTER CORONARY ARTERY BYPASS SURGERY

Adrien Bouglé [a], Pierre-Antoine Allain [a], Séverine Favard [b], Nora Ait Hamou [a], Aude Carillion [a], Pascal Leprince [c d], Benjamin Granger [e], Julien Amour [a d]

a Department of Anaesthesiology and Critical Care Medicine, hôpital Pitié-Salpêtrière, Sorbonne University, UPMC université Paris 06, Assistance publique–Hôpitaux de Paris (AP–HP), 47-83 boulevard de l'Hôpital, 75651 Paris cedex 13, France

b Department of biological endocrinology and oncology hôpital Pitié-Salpêtrière, Assistance publique–Hôpitaux de Paris (AP–HP), 75651 Paris cedex 13, France

c Department of cardiothoracic and vascular surgery, hôpital Pitié-Salpêtrière, Sorbonne University, UPMC université Paris 06, Assistance publique–Hôpitaux de Paris (AP–HP), 75651 Paris cedex 13, France

d UMR INSERM 1166, IHU ICAN, hôpital Pitié-Salpêtrière, Sorbonne University, UPMC université Paris 06, 75651 Paris cedex 13, France

e Department of Clinical Epidemiology and Biostatistics, hôpital Pitié-Salpêtrière, Sorbonne University, UPMC université Paris 06, Assistance publique–Hôpitaux de Paris (AP–HP), 75651 Paris cedex 13, France

## ABSTRACT (word count = 248)

**Background**: Cardiopulmonary bypass (CPB) is associated with a systemic inflammatory response and an endothelial dysfunction, whose qualitative assessment appears to be a major issue. Endocan (ESM-1, endothelial cell specific molecule – 1) is a protein preferentially expressed by the endothelium and previously associated with prognosis of septic shock or acute respiratory distress syndrome. In this pilot study, we investigated the kinetic of endocan in planned coronary artery bypass grafting (CABG) surgery with CPB.

**Patients and methods**: We conducted an observational, prospective, mono center study. All adult patients with left systolic ejection fraction > 50%, undergoing planned on-pump CABG, were screened for inclusion. A written informed consent was obtained.

**Measurements and main results**: Serum endocan concentrations were respectively 2.4 [2.1-3.0] $ng.mL^{-1}$, 10.4 [7.4-13.9] $ng.mL^{-1}$, 5.7 [4.4-8.2] $ng.mL^{-1}$, and 5.4 [4.1-7.5] $ng.mL^{-1}$ at Day 0, Day 1, Day 3 and Day 5. Endocan concentrations increased at Day 1, Day 3, and Day 5 in comparison with preoperative concentration ($p<0.001$). In multivariate analysis, age ($p=0.002$), history of acute coronary syndrome ($p=0.024$) and the catecholamine-free days at Day 28 ($p=0.007$) were associated to the increase of perioperative endocan concentrations.

**Conclusion**: Serum endocan concentration increases after CABG surgery with CPB until Day 1. The norepinephrine support increases the risk of endocan release, suggesting a relationship between the kinetic of endocan and the vasoplegic syndrome. At Day 3, endocan concentration decreases slowly but is not normalized at Day 5. Further studies should investigate the prognostic value of the magnitude of postoperative endocan concentration after cardiac surgery.

**KEYWORDS**

Cardiopulmonary Bypass

Vasoplegic syndrome

Endothelium

Endocan

**MANUSCRIPT**

## Introduction

Cardiopulmonary bypass (CPB) is complicated with systemic inflammatory response syndrome and endothelium dysfunction, which are associated with an important morbidity and mortality linked to different complications after cardiac surgery [1]. Among these complications, vasoplegic syndrome (VS) occurs in 5-25% of patients and is associated with poor prognosis [2,3]. Because of impaired systemic vascular resistance (SVR), VS causes hemodynamic instability, increases requirements for fluids and vasopressors support in postoperative period, which are well known to increase ICU length of stay, hospital length of stay, and mortality [2,4]. These pathophysiological aspects strongly suggest that biomarkers of endothelial dysfunction may contribute to identify patients at high risk of vasoplegic syndrome leading to hemodynamic instability and postoperative complications. Hence, several biomarkers of endothelial dysfunction were shown to be associated with prognosis after CPB, like endothelin-1 [5] or mitogen-activated protein kinase [6], but are not available in daily clinical practice. Endocan (endothelial cell specific molecule-1) has been recently developed for it use in routine testing. Endocan is a 50 kDa-dermatan sulfate proteoglycan preferentially expressed in the vascular endothelium, but also by different epithelia, such as bronchial and renal epithelia [7]. Endocan expression is enhanced by inflammatory cytokines (IL-1β, TNF-α), but inhibited by INFϒ [8,9]. Endocan was shown to bind the lymphocyte function-associated antigen-1 (LFA-1), inhibiting the LFA-1/ICAM-1 binding [10], involved in the trans-endothelial migration of leukocytes to sites of inflammation, as well as interactions between antigen presenting cells (APC) and T cells (immunological synapse formation).

Increased concentrations of endocan has been shown to be associated with a bad prognosis in patients with severe sepsis [11] or trauma [12]. In cardiac surgery with CPB, the influence of CPB on the kinetic of endocan concentrations is still unknown [13,14], even the preoperative value of endocan was recently shown as an early marker of postoperative pneumonia [15].

In this prospective observational study, we aimed to determine the kinetic of endocan concentrations during intra- and post-operative period in patients undergoing planned CABG surgery with CPB.

## Patients and Methods

*Design*

We conducted an observational, prospective, mono center study in the Cardiology Institute of the Pitié-Salpêtrière University Hospital Center, Assistance Publique – Hôpitaux de Paris (APHP, Paris, France) between October 2015 and February 2016. All adult patients with left systolic ejection fraction > 50%, undergoing planned on-pump coronary artery bypass grafting surgery (CABG), were screened for inclusion. A written informed consent was obtained. Non-inclusion criteria were pregnancy, acute coronary syndrome and emergent surgery.

*Patient's management*

The anesthetic management of patients is standardized in our institution as described previously [16]. Briefly, in the operating room, a standard monitoring was realized comprising an electrocardiogram with ST segment monitoring, pulsed oxygen saturation ($SpO_2$) and invasive blood pressure with a radial arterial catheter before the induction of anesthesia. All patients received target concentration infusion (TCI) of propofol and sufentanil, while depth of anesthesia was monitored with bispectral index for a target maintained between 40 and 60 during all the surgery. A central venous catheter allowing monitoring of central venous pressure and a urinary catheter to monitor urine output and central temperature were placed under general anesthesia. The intraoperative hemodynamic goal was to maintain a mean arterial blood pressure between 65 and 90 mmHg. In case of no response to fluid loading and inefficiency of ephedrine or neosynephrine bolus, an intravenous continuous infusion of norepinephrine was started. In case of left ventricular

dysfunction measured with trans-esophageal echography, dobutamine or adrenaline could be added. Despite transfusion was a decision left to the clinical team, written guidelines are used in our department [16]. Platelet transfusion was administered in case of persistent bleeding without any blood clot formation in operating room and/or when platelet count was less than 80000 $\mu L^{-1}$. No preventive transfusion was given. Adapted from the American recommendations of the Society of Thoracic Surgeons and the Society of Cardiovascular Anaesthesiologists [17] red blood cells transfusion was recommended in our institution in case of hemoglobin less than 7g dL-1, fresh frozen plasma transfusion in case of serious bleeding with prothrombin time less than 50%, and fibrinogen for plasma concentration less than $2g.dL^{-1}$. All patients included in the study were ventilated according to our local guidelines. Before and after CPB, patients were ventilated in a constant flow mode using a tidal volume of 6 mL/kg of predicted body weight, respiratory rate adjusted to maintain end-tidal $CO_2$ between 32 and 36 mmHg, positive end expiratory pressure (PEEP) of 6 $cmH_2O$, inspiratory to expiratory ratio of 1:2. During CPB, patients were ventilated using a tidal volume of 100-120 mL, PEEP of 5 $cmH_2O$ and $FiO_2$ of 30%. Patients were submitted to a lung recruitment maneuver before and after CPB weaning. Briefly, in a pressure-controlled ventilation mode, driving pressure (plateau pressure minus total PEEP) was increased to the recruitment pressure of 30 $cmH_2O$ that was maintained during 30s. Immediately thereafter, baseline ventilation was reinstituted but this time using 5 $cmH_2O$ of PEEP to maintain lung opened. The recruitment maneuver was immediately stopped if there was a change at least 15% of baseline mean arterial pressure.

After surgery, patients were transferred to the postoperative intensive care unit. Postoperative care consisted of early extubation in "fast-track" care. Once their clinical condition no longer

required continuous monitoring, patients were transferred to the surgery ward until they leave the institution.

To achieve postoperative kinetics of serum endocan concentration, four blood samples of 5 mL EDTA tube had been made. The first was performed at Day 0, in the operating room before induction of anesthesia. The following samples were taken in the postoperative days at 8:00 in the morning: Day 1 (D1), Day 3 (D3) and Day 5 (D5). The arterial catheter was used to perform the sample if still in place, otherwise the samples were taken from the central venous catheter or during the daily blood tests in order not to add new puncture.

Measurements of serum endocan concentration were performed using enzyme-linked immunosorbent assay (ELISA) (EndoMark H1 kit; Lunginnov HSH, Lille, France) in the Endocrinal and Oncologic Biochemistry Unit, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (APHP), Paris, France. Each sample was analyzed in duplicate and the average value was used as the result, expressed in $ng.mL^{-1}$.

The limit of detection was 0.15 $ng.mL^{-1}$ and the limit of quantification was 0.3 $ng.mL^{-1}$. Based on prior studies of healthy subjects, we defined normal serum endocan levels as less than 1 $ng.mL^{-1}$ [11].

During the postoperative period, the occurrence of complication as vasoplegic syndrome, pneumonia, acute respiratory failure, need for non-invasive ventilation or reintubation was collected. Vasoplegic syndrome was defined as a severe and persistent hypotension (mean arterial pressure less than 70 mm Hg), occurring in the early postoperative period (within the 6 hours after weaning from CPB), with normal or increased cardiac output (cardiac index more than 2.5 $L.min^{-1}.m^{-2}$) or needing pharmacologic support by norepinephrine [2].

*Statistical analysis*

A linear mixed model with subject random intercepts was used to assess the overall time effect on repeated measures of endocan concentrations.

We tested the associations between different covariates and repeated measures of endocan concentration with a classical 2-step analysis plan based on LMM with subject random intercept. We tested the associations between different covariates and repeated measures of various parameters (1 × 1). In the multivariate model, only factors that attained statistical significance ($p < 0.05$) in the univariate analysis were included.

To assess the correlations between repeated measures of the different parameters, first we used the Spearman coefficient to test the correlation between the mean value of the variable for 1 patient level-headed by the number of measures by patients. With this between-subject correlation, it was understood that if a subject had a high value for one variable, the value of the other variable would also tend to be high (static correlation). We also tested the repeated between 2 parameters with a covariance analysis. With this intrasubject correlation, it was understood (in the case of a positive correlation) that if the value of one variable increased in a subject, the value of the other variable would also tend to increase (a dynamic correlation) [18,19].

Data are expressed as median [Q1-Q3] in non - normally distributed variables or number (%).

All p values are two-tailed, and $p< 0.05$ was considered to denote significant differences.

The data analysis was performed with R version 3.3.0 for Windows (The R Foundation for Statistical Computing, http://www.r-project.org/foundation/).

*Ethical considerations*

The Comité de Protection des Personnes « Ile-de- France V » (Hôpital Saint Antoine, 184 rue du Faubourg Saint-Antoine, 75571 Paris, Cedex 12) approved this study on July, 7th 2015.

## Results

*Patient Characteristics*

The endocan concentrations were measured among 33 patients who underwent planned primary CABG with CPB. Three of them were excluded of the analysis because of missing data. Perioperative characteristics of the 30 enrolled patients are shown in Table 1. Age at enrollment was 64 [59.2-70] years, and 93% were male. Only one patient died in the hospital following rhythm disorder with no myocardial ischemia diagnosed.

*Perioperative Endocan Concentrations*

All patients had the four dosages (preoperative, D1, D3, D5). Among these patients, median preoperative endocan concentration was 2.4 [2.1-3.0] $ng.mL^{-1}$. The postoperative medians of endocan at Day 1, Day 3 and Day 5 were respectively 10.4 [7.4-13.9] $ng.mL^{-1}$, 5.7 [4.4-8.2] $ng.mL^{-1}$, 5.4 [4.1-7.5] $ng.mL^{-1}$. The perioperative kinetic of endocan concentrations was confirmed in the linear mixed model ($p<0.0001$). Each postoperative concentration of endocan was significantly different from the preoperative concentration ($p<0.001$). The perioperative kinetic of endocan concentrations are shown in figure 1.

*Correlation between postoperative outcomes and endocan concentrations kinetic*

The median duration of the surgical procedure and of the CPB was respectively 218.5 [205.5-246] min and 71.5 [55-85] min. The median length of stay in ICU and hospital was respectively 4.5 days [2.0-7.0] and 14.0 days [10.0-19.5]. The postoperative rate of infection was 20%, most of these infections being pneumonia (83%). A vasoplegic syndrome was observed in 30% (n=9) of patients. None of these patients developed an Acute Respiratory

Distress Syndrome (ARDS). The median mechanical ventilation free-days and catecholamine free-days at day 28 were respectively 28.0 [27.0-28.0] and 27.5 [27.0-28.0].

No correlation whether the within subject correlation (WSC) or the between subject correlation (BSC) was observed between the perioperative kinetic of endocan concentrations and the kinetics of troponin, procalcitonin and serum creatinin. The results of the correlation test are shown in Table 2. In contrast, with the bivariate and multivariate analysis, the perioperative kinetic of endocan concentrations was associated with age (p=0.001) and with a history of myocardial infarction (p=0.022) (Table 3). During the postoperative period, the kinetic of endocan concentrations was associated with the number of catecholamine-free days at Day 28 (p=0.008), as illustrated on figure 2. In contrast, there was no correlation between preoperative hypertension and the kinetic of endocan concentrations even though 8 (89%) patients treated with norepinephrine support after CPB had preoperative hypertension.

## Discussion

In this study, in planned CABG surgery with CPB, we describe the early postoperative increase of the serum endocan concentration followed by a progressive decrease of the biomarker level until the postoperative fifth day after surgery. In addition, we show that the perioperative kinetic of endocan was correlated to duration of vasoplegic syndrome measured by the number of catecholamine-free days at Day 28.

In this work, we investigated the impact of CPB on the kinetic of endocan concentrations. We therefore selected inclusion criteria to obtain a homogeneous population with low perioperative risk of complications, as illustrated with Euroscore 2 less than 1.0%. In preoperative period of CABG surgery, the baseline endocan concentration was 4 fold increased in comparison to concentrations usually assessed in healthy volunteers in previous studies [10,11]. This difference may be explained because all patients included in this study had severe coronary stenosis. Endocan is a well-known biomarker of the endothelial dysfunction involved in the physiologic mechanism of atherosclerosis [20]. In the specific case of cardio-vascular surgery, 3 studies investigated already the kinetic of endocan concentrations. The first, performed by Stoppelkamp et al., investigated the kinetic of biomarkers, including endocan, in sterile SIRS conditions after cardio-vascular surgery [13]. Endocan was measured at admission, before and in the postoperative period until Day 8. Baseline values of endocan were measured at 2 to 5 $ng.mL^{-1}$. Postoperative endocan concentrations trend to increase in the group without SIRS, but the small sample size (n=10) and the high variability of the concentrations limited the interpretation of results. In a second study, Perrotti et al. conducted a prospective study about the usefulness of endocan to diagnose postoperative pneumonia after cardiac surgery [15]. While endocan baseline values

were measured at 3.9 ± 2.9 $ng.mL^{-1}$, authors reported that endocan level up to 3.7 $ng.mL^{-1}$ before induction of anesthesia was an independent predictor of postoperative pneumonia. At Day 1, endocan concentration increases 3 fold, at 10.9 ± 9.4 $ng.mL^{-1}$. In this study, authors investigated only the first 3 days while our findings show that the endocan concentration did not come back at baseline value before Day 5. In a third study performed in cardiac surgery, Madhivathanan et al. included 21 patients with heterogeneous types of surgery, with or without CPB, CABG or combined surgery [14]. They performed several measurements during surgery and postoperative period, until the postoperative 6-hour. Then, authors measured only the early effect of cardiac surgery on endocan levels. In contrast with the two others and our own results, baseline endocan concentration was 8.0 ± 9.7 $ng.mL^{-1}$, twice the values found in the other two studies. Authors tried to explain this surprisingly high baseline value by the proportion of acute coronary syndrome and hypertension. Nevertheless, endocan concentrations are known to be correlated with the presence and the severity of coronary artery disease in patients with hypertension [21] but the medical management of patients with essential hypertension is associated with decrease of serum endocan concentration [22]. Whatever, in our study, multivariate analysis showed a significant association of endocan kinetic with age and history of coronary disease. History of STEMI was associated with lower serum levels of endocan, which suggests the beneficial effect of medical management of STEMI.

Our work is the first to assess the kinetic of endocan level for 5 postoperative days in parallel to the period of SIRS in a homogenous sample of patients, all undergoing an homogenous planned on-pump CABG surgery. In this study, we showed that CPB impacted the endocan concentration from Day 1 as shown by the 5-fold increase of endocan

concentration while baseline value was similar to the two others studies performed by Stoppelkamp and Perrotti. In addition, we showed that the endocan concentration progressively decreased until Day-5 with a delayed return to the baseline value. We made the decision to stop the measurement at Day-5 based on the kinetic of procalcitonin, another inflammation biomarker investigated in cardiac surgery [23]. Unfortunately, for endocan, this timing appears to be too early for coming back to the baseline value.

Another important finding coming from this study is the significant association between the increase of endocan concentration and the duration of norepinephrine support, suggesting a correlation between the duration of VS after CPB and the magnitude of postoperative endocan release. However, this study was not designed to demonstrate an association between occurrence of VS and perioperative serum endocan levels. Our findings suggest only that endocan may be a marker of the intensity of VS. Of course, further study has to investigate endocan thresholds.

Because diagnosis of postoperative pneumonia is difficult, some authors as Perrotti et al., tried to find a correlation between biomarkers such endocan and postoperative pneumonia diagnosis [23]. In our study, 5 (17%) patients developed postoperative pneumonia. If the incidence is high, the number of events is still low, limiting the statistical analysis interpretation in this subgroup. In comparison with Perrotti's study, the kinetic of the endocan in patients with postoperative pneumonia was close, respectively at 3.3 ± 1.8 $ng.mL^{-1}$ vs. 5.3 ± 3.6 $ng.mL^{-1}$ at the Day 0, 16.4 ± 10.8 $ng.mL^{-1}$ vs. 14.6 ± 11.7 $ng.mL^{-1}$ at Day 1 and 6.5 ± 4.0 $ng.mL^{-1}$ vs. 8.6 ± 5.9 $ng.mL^{-1}$ at Day 3. In pneumonia subgroup, only 1 patient had endocan concentration up to 3.7 $ng.mL^{-1}$, the cutoff value described by Perrotti et al. as being

the threshold associated to postoperative pneumonia. Unfortunately, we cannot confirm these results in our study.

Of course, our study has several limitations. First, we decided to study a low-risk surgical population. Thus, our results cannot be extrapolated to another surgical procedure than planned CABG with CPB. None of the patients included in our study exhibited pre-existing left ventricular failure, and urgent or complex surgical procedures were excluded. Thus, the selection of our population and the single-center nature of this study greatly limit its external validity. In addition, we included only 30 patients in this study. In view of the considerable variability in serum endocan concentration observed in our cohort, as in previously published studies [13,14], the small size of our cohort obviously limits the relevance and interpretation of our results. Nevertheless, this is the most important sample size in comparison to others studies, with kinetic measurement of endocan concentrations until postoperative Day-5.

Second, we made the choice to standardize the time of postoperative blood collection at 8 AM, whatever was the end time of CPB, to be closer of the “real life”. This choice may induce a measurement bias.

Third, the secondary endpoint of the study was the occurrence of infectious, hemodynamic and respiratory complications. The aim of this study was to observe the kinetics of endocan after cardiac surgery with CPB in a low-risk perioperative population. While our findings suggest an association between the need of vasopressor, indirect marker of VS and serum endocan level, this pilot study was not conclusive as to the association between peri-operative serum endocan levels and morbidity or mortality. Due to the selection of population at low risk of complications, the number of events was hopefully low. Thus, this

study lacked power to be able to demonstrate an association between endocan concentrations and postoperative complications or mortality, especially postoperative pneumonia. It would be interesting to conduct a new study in a larger cohort of unselected cardiac surgery patients and therefore with a higher risk of postoperative complications to investigate the correlation of these events with the kinetic of endocan concentration.

Finally, we observed a reintubation rate at 13%, that is unexpectedly high for a low preoperative risk population, in the range of the reintubation rate observed in a study about hypoxemic patients conducted by Stephan et al. [24]. Patients included in our study presented an elevated rate of pulmonary comorbidities (23%) that could contribute to this high rate of reintubation.

**Conclusion**

Postoperative serum levels of endocan, a marker of endothelial dysfunction, are increased after on-pump CABG surgery, and are associated with the duration of norepinephrine support, suggesting a relationship between the kinetic of endocan and the vasoplegic syndrome. At Day 3, serum endocan concentration decreases slowly but has not returned to baseline at Day 5. This pilot study assesses the kinetic of endocan in a cohort of low-risk patients, and paves the way for larger studies on the prognostic value of endocan kinetic after cardiac surgery.

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## TABLES

### Table 1: Patients characteristics (n=30)

| Variables | |
|---|---|
| **Preoperative medical characteristics** | |
| Age (years) | 64 [59.2-70] |
| Gender (M/F) | 28/2 |
| Weight (kg) | 82 [73.2-90.2] |
| BMI (Kg/m$^2$) | 27.7 [26.9-30.7] |
| EuroSCORE 2 | 0.9 [0.6-1.2] |
| Pulmonary comorbidity | 7 (23) |
| COPD | 4 (13) |
| Asthma | 1 (3) |
| Obstructive sleep apnea | 3 (10) |
| Diabetes on insulin | 5 (17) |
| Non-insulin-dependent diabetes | 8 (27) |
| Chronic renal failure | 1 (3) |
| Preoperative serum creatinin (µmol.L$^{-1}$) | 89.5 [76.2-103.7] |
| Left ventricular ejection fraction (%) | 60 [58.2-60] |
| History of myocardial infarction | 10 (33) |
| Recent myocardial infarction | 5 (17) |
| Coronary angioplasty | 5 (17) |
| **Characteristics of the surgical procedure** | |
| Surgery time (min) | 218.5 [205.5-246] |
| CPB time (min) | 71.5 [55-85] |
| Aortic cross clamp time (min) | 58.5 [49.2-71] |
| Blood transfusion (%) | 1 (3) |
| Norepinephrine infusion (%) | 11 (37) |
| Dobutamine infusion (%) | 1 (3) |
| Epinephrine infusion(%) | 0 (0) |

| | |
|---|---|
| **Characteristic of the hospital stay** | |
| Length of ICU stay (days) | 4.5 [2.0-7.0] |
| Length of hospital stay (days) | 14.0 [10.0-19.5] |
| SOFA Day 1 | 2.0 [0.2-4.0] |
| Vasoplegic syndrome | 9 (30) |
| Septic shock | 1 (3) |
| Infection: | 6 (20) |
| *Pneumonia* | 5 (17) |
| *Urinary tract* | 1 (3) |
| *Mediastinitis* | 0 (0) |
| Pulmonary embolism | 1 (3) |
| Acute respiratory failure | 8 (27) |
| Noninvasive ventilation | 10 (33) |
| Tracheal reintubation | 4 (13) |
| Acute Respiratory Distress Syndrome | 0 (0) |
| Acute Renal Failure | 1 (3) |
| Renal Replacement Therapy | 0 (0) |
| Catecholamine free-days at Day 28 | 27.5 [27.0-28.0] |
| Mechanical ventilation free-days at Day 28 | 28.0 [27.0-28.0] |
| Death in hospital | 1 (3) |

Data are expressed as median [Q1-Q3] or N (%).

**Table 2: Correlation test between Endocan and others biomarkers**

| Variables | Within subject | Between subject | |
|---|---|---|---|
| | | rho | p |
| Endocan – Procalcitonin | 0.13 | 0.52 | 0.602 |
| Endocan – Troponin | 0.65 | -0.2 | 1.155 |

| | | | |
|---|---|---|---|
| Endocan – Creatinin | -0.11 | 0.13 | 0.894 |

**Table 3: Bivariate and multivariate analysis: variables associated with perioperative kinetic of endocan concentration**

| Variables | *P value* | |
|---|---|---|
| | **Bivariate analysis** | **Multivariate analysis** |
| **Preoperative medical characteristics** | | |
| Gender | 0.6608 | |
| Age | 0.0062 | 0.0021 |
| BMI | 0.3707 | |
| Myocardial infarction | 0.0099 | 0.0242 |
| Recent myocardial infarction | 0.9471 | |
| Coronary angioplasty | 0.2448 | |
| Left ventricular ejection fraction | 0.6734 | |
| Pulmonary morbidity | 0.274 | |
| Obstructive sleep apnea | 0.6263 | |
| Diabetes on insulin | 0.9508 | |
| Non-insulin-dependent diabetes | 0.6665 | |
| IGS II | 0.0257 | 0.6352 |
| EuroSCORE | 0.5357 | |
| **Characteristics of the surgical procedure** | | |
| Surgery time | 0.6407 | |
| Cardiopulmonary bypass time | 0.6182 | |
| Aortic cross-clamp time | 0.6163 | |

| | | |
|---|---|---|
| Norepinephrine infusion | 0.7108 | |
| Blood transfusion | 0.6961 | |
| **Characteristics of the hospital stay** | | |
| Vasoplegic syndrome | 0.7469 | |
| Pneumonia | 0.0208 | 0.2536 |
| Acute respiratory failure | 0.8448 | |
| Noninvasive ventilation | 0.4457 | |
| Tracheal reintubation | 0.5071 | |
| Length of intensive care unit stay | 0.0008 | 0.5745 |
| Length of hospital stay | 0.7525 | |
| Catecholamine-free days at Day 28 | 0,0002 | 0.0077 |
| Mechanical ventilation free days at Day 28 | 0.0093 | 0.1383 |
| Hospital Death | 0.1015 | |

## FIGURES

**Figure 1: Perioperative kinetic of endocan concentrations**

Plasma concentrations of endocan (ng.mL$^{-1}$) are represented as boxplots.

**Figure 2: Perioperative kinetic of endocan concentrations in patients with or without vasoplegic syndrome**

Plasma concentrations of endocan (ng.mL$^{-1}$) are represented as medians [Q1-Q3]. The red box plots represent endocan concentrations in patients without vasoplegic syndrome (defined as catecholamine free-days at Day 28 > 27.5 days, N=15), when the blue box plots represent endocan concentrations in patients with vasoplegic syndrome (defined as catecholamine free-days at Day 28 ≤ 27.5 days, N=15).

## REFERENCES


[1] Ruel M, Khan TA, Voisine P, Bianchi C, Sellke FW. Vasomotor dysfunction after cardiac surgery. European Journal of Cardio-Thoracic Surgery 2004;26:1002–14. doi: 10.1016/j.ejcts.2004.07.040.

[2] Mekontso-Dessap A, Houël R, Soustelle C, Kirsch M, Thébert D, Loisance DY. Risk factors for post-cardiopulmonary bypass vasoplegia in patients with preserved left ventricular function. Ats 2001;71:1428–32.

[3] Levin MA, Lin H-M, Castillo JG, Adams DH, Reich DL, Fischer GW. Early on-cardiopulmonary bypass hypotension and other factors associated with vasoplegic syndrome. Circulation 2009;120:1664–71. doi:10.1161/CIRCULATIONAHA. 108.814533.

[4] Fischer GW, Levin MA. Vasoplegia during cardiac surgery: current concepts and management. Seminars in Thoracic and Cardiovascular Surgery 2010;22:140–4. doi: 10.1053/j.semtcvs.2010.09.007.

[5] Feng J, Chu LM, Robich MP, Clements RT, Khabbaz KR, Hagberg R, et al. Effects of cardiopulmonary bypass on endothelin-1-induced contraction and signaling in human skeletal muscle microcirculation. Circulation 2010;122:S150–5. doi:10.1161/ CIRCULATIONAHA.109.928226.

[6] Khan TA, Bianchi C, Ruel M, Voisine P, Li J, Liddicoat JR, et al. Mitogen-activated protein kinase inhibition and cardioplegia-cardiopulmonary bypass reduce coronary myogenic tone. Circulation 2003;108 Suppl 1:II348–53. doi:10.1161/01.cir. 0000087652.93751.0e.

[7] Zhang SM, Zuo L, Zhou Q, Gui SY, Shi R, Wu Q, et al. Expression and distribution of endocan in human tissues. Biotech Histochem 2012;87:172–8. doi: 10.3109/10520295.2011.577754.

[8] Lassalle P, Molet S, Janin A, Heyden JV, Tavernier J, Fiers W, et al. ESM-1 is a novel human endothelial cell-specific molecule expressed in lung and regulated by cytokines. J Biol Chem 1996;271:20458–64.

[9] Bechard D, Meignin V, Scherpereel A, Oudin S, Kervoaze G, Bertheau P, et al. Characterization of the secreted form of endothelial-cell-specific molecule 1 by specific monoclonal antibodies. J Vasc Res 2000;37:417–25.

[10] Bechard D, Scherpereel A, Hammad H, Gentina T, Tsicopoulos A, Aumercier M, et al. Human endothelial-cell specific molecule-1 binds directly to the integrin CD11a/ CD18 (LFA-1) and blocks binding to intercellular adhesion molecule-1. J Immunol 2001;167:3099–106.

[11] Scherpereel A, Depontieu F, Grigoriu B, Cavestri B, Tsicopoulos A, Gentina T, et al. Endocan, a new endothelial marker in human sepsis. Crit Care Med 2006;34:532–7. doi:10.1097/01.CCM.0000198525.82124.74.

[12] Mikkelsen ME, Shah CV, Scherpereel A, Lanken PN, Lassalle P, Bellamy SL, et al. Lower serum endocan levels are associated with the development of acute lung injury after major trauma. Journal of Critical Care 2012;27:522.e11–7. doi:10.1016/j.jcrc. 2011.07.077.

[13] Stoppelkamp S, Veseli K, Stang K, Schlensak C, Wendel HP, Walker T. Identification of Predictive Early Biomarkers for Sterile-SIRS after Cardiovascular Surgery. PLoS One 2015;10:e0135527. doi:10.1371/journal.pone.0135527.

[14] Madhivathanan PR, Fletcher N, Gaze D, Thomson R, Chandrasekaran V, Al-Subaie N, et al. Perioperative kinetics of endocan in patients undergoing cardiac surgery with and without cardiopulmonary bypass. Cytokine 2016;83:8–12. doi:10.1016/j.cyto.2016.03.006.

[15] Perrotti A, Chenevier-Gobeaux C, Ecarnot F, Bardonnet K, Barrucand B, Flicoteaux G, et al. Is Endocan a Diagnostic Marker for Pneumonia After Cardiac Surgery? The ENDOLUNG Study. Ann Thorac Surg 2017. doi:10.1016/j.athoracsur.2017.07.031.

[16] Amour J, Garnier M, Szymezak J, Le Manach Y, Helley D, Bertil S, et al. Prospective observational study of the effect of dual antiplatelet therapy with tranexamic acid treatment on platelet function and bleeding after cardiac surgery. Br J Anaesth 2016;117:749–57. doi:10.1093/bja/aew357.

[17] Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, Hessel EA, Haan CK, et al. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. Ann Thorac Surg 2007;83:S27–86. doi:10.1016/j.athoracsur.2007.02.099.

[18] Bland JM, Altman DG. Calculating correlation coefficients with repeated observations: Part 1--Correlation within subjects. Bmj 1995;310:446.

[19] Bland JM, Altman DG. Calculating correlation coefficients with repeated observations: Part 2--Correlation between subjects. Bmj 1995;310:633.

[20] Çimen T, Efe TH, Akyel A, Sunman H, Algül E, Şahan HF, et al. Human Endothelial Cell-Specific Molecule-1 (Endocan) and Coronary Artery Disease and Microvascular Angina. Angiology 2016;67:846–53. doi:10.1177/0003319715625827.

[21] Wang X-S, Yang W, Luo T, Wang J-M, Jing Y-Y. Serum endocan levels are correlated with the presence and severity of coronary artery disease in patients with hypertension. Genet Test Mol Biomarkers 2015;19:124–7. doi:10.1089/gtmb.2014.0274.

[22] Celık T, Balta S, Karaman M, Ahmet Ay S, Demırkol S, Ozturk C, et al. Endocan, a novel marker of endothelial dysfunction in patients with essential hypertension: comparative effects of amlodipine and valsartan. Blood Press 2015;24:55–60. doi:10.3109/08037051.2014.972816.

[23] Aouifi A, Piriou V, Blanc P, Bouvier H, Bastien O, Chiari P, et al. Effect of cardiopulmonary bypass on serum procalcitonin and C-reactive protein concentrations. Br J Anaesth 1999;83:602–7.

[24] Stéphan F, Barrucand B, Petit P, Rézaiguia-Delclaux S, Médard A, Delannoy B, et al. High-Flow Nasal Oxygen vs Noninvasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery: A Randomized Clinical Trial. Jama 2015;313:2331–9. doi:10.1001/jama.2015.5213.