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Kinetics of endocan in patients undergoing cardiac surgery with and without cardiopulmonary bypass

Pierre-Alain Poinsot[a], Benoit Barrucand[a], Fiona Ecarnot[b,c,*], Philippe Lassalle[d], Guillaume Besch[a,c], Sidney Chocron[c,e], Andréa Perrotti[c,e]

[a] Department of Anesthesiology, University Hospital Jean Minjoz, 25000 Besançon, France
[b] Department of Cardiology, University Hospital Jean Minjoz, 25000 Besançon, France
[c] EA3920, University of Burgundy Franche-Comté, 25000 Besançon, France
[d] Institut Pasteur de Lille, Center for Infection and Immunity of Lille, 59010 Lille, France
[e] Department of Cardiac Surgery, University Hospital Jean Minjoz, 25000 Besançon, France

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ABSTRACT

Background: Endocan plays an important role in the processes of inflammation and infection. The use of cardiopulmonary bypass (CPB) during cardiac surgery can induce an inflammatory response. We aimed to describe the kinetics of endocan in patients undergoing cardiac surgery with and without the use of CPB.

Methods: Single-centre, observational study with retrospective analysis of prospectively collected data, to compare the kinetics of endocan in patients undergoing isolated coronary artery bypass graft (CABG) surgery. Endocan was measured at induction of general anesthesia (baseline), and at 6, 24, 48 and 72 h after the end of surgery. Patients were classified into two groups, namely those undergoing CPB (CPB group) and those without CPB (off-pump group).

Results: In total, 91 patients were included in this analysis: 61 patients in the CPB group and 30 in the off-pump group. There were no major significant differences between groups. Patients with CPB had a significantly higher level of endocan at 6 h (9.7 ± 6.7 ng/ml vs 6.9 ± 3.3 ng/ml, $p = 0.03$), but the difference was no longer statistically significant at subsequent timepoints. Endocan values were not significantly correlated with the duration of CPB ($p = 0.53$).

Conclusion: Endocan levels in patients undergoing isolated CABG surgery with CPB are significantly higher at 6 h than in patients with off-pump surgery, and peaks earlier in those with CPB (6 h) than in those undergoing off-pump surgery (24 h).

1. Introduction

In the context of cardiac surgery, post-operative infections occur in 4.4 to 5.7% of patients [1–3]. The majority are pulmonary complications [1,3,4], and mortality from post-operative infection is reported to be around 35% [2,3]. Numerous risk factors for respiratory complications after cardiac surgery have been identified, and include surgery of the ascending aorta, large transfusion volumes, need for re-intervention, age over 70 years, urgent surgery, longer duration of mechanical ventilation, need for re-intubation, a history of prior cardiac surgery, and the need for peri-operative administration of inotropic agents [1,4]. Diagnosis immediately after surgery is difficult, since the physiological processes inherent to surgery may mask infection. For this reason, a simple and easily measurable biological marker that could confidently predict infection would be extremely useful in this setting, in order to allow early identification of patients likely to go on to develop respiratory infection.

Endocan (also called endothelial cell specific molecule 1 or ESM-1) is a soluble 50 kDa proteoglycan comprising a polypeptide chain of 165 amino acids and a single dermatan sulfate chain covalently attached to serine 137 [5,6]. In vitro, it is mainly found in pulmonary endothelial cells and to a lesser extent in endothelial cells of renal origin [6]. It is upregulated by proinflammatory cytokines, such as TNFα and interleukin (IL)-1β, and downregulated by interferon-γ [6]. In vitro, endocan demonstrates several properties. It regulates extravasation of leukocytes at inflammatory sites by exerting a regulatory effect on the ICAM-1/LFA-1 pathway [5,7], underlining its important role in the processes of inflammation and infection. Endocan is also involved in the development and regeneration of vascular and renal tissue through its interaction with pro-angiogenic factors such as VEGF or HGF-SF [8]. *In*

* Corresponding author at: EA3920, Department of cardiology, University Hospital Jean Minjoz, Boulevard Fleming, 25000 Besancon, France.
E-mail address: Fiona.ecarnot@univ-fcomte.fr (F. Ecarnot).

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Table1
Baseline characteristics of the study population.

	All patients (N = 91)	CPB (n = 61)	Off-pump (n = 30)	p-value
Age (years)	68.5 ± 8.4	68.6 ± 7.9	68.2 ± 9.5	0.84
Female sex	12 (13.2)	10 (16.4)	2 (6.7)	0.32
Hemoglobin (g/L)	14.1 ± 1.7	14.1 ± 1.6	14.0 ± 2.0	0.62
Hematocrit (%)	42.1 ± 0.5	42.3 ± 0.1	41.9 ± 0.1	0.38
Platelets (E9/L)	243.7 ± 71.9	240.3 ± 67.9	234.7 ± 89.8	0.93
Creatinine (μmol/L)	89.7 ± 53.8	91.0 ± 61.8	94.1 ± 48.7	0.65
Diabetes	42 (44.2)	26 (42.6)	16 (53.3)	0.38
Hypertension	72 (79.1)	45 (73.8)	27 (90.0)	0.10
Dyslipidemia	51 (56.0)	35 (57.4)	16 (53.3)	0.82
Smoker	59 (65.6)	39 (65.0)	20 (66.7)	1
Body mass index				
[18–25]	29 (31.9)	19 (31.1)	10 (33.3)	0.49
[25–30]	40 (43.9)	25 (41.0)	15 (50.0)	
[30–42]	22 (24.2)	17 (27.9)	5 (16.7)	
Non-cardiac arterial disease	43 (47.3)	32 (52.5)	11 (36.7)	0.18
Carotid ultrasound	12 (14.0)	11 (18.0)	2 (6.7)	0.21
Chronic lung disease	8 (9.3)	4 (6.6)	4 (13.3)	0.43
Ejection fraction (%)				
< 30	6 (6.6)	4 (6.6)	2 (6.7)	0.93
[31–50]	31 (34.1)	20 (32.8)	11 (36.7)	
> 50	54 (59.3)	37 (60.7)	17 (56.7)	
Grace score	89.4 ± 17.1	89.3 ± 14.8	89.5 ± 20.1	0.95
Euroscore 2	1.9 ± 2.9	2.1 ± 3.4	1.5 ± 0.9	0.76
Anastomoses, n	3.2 ± 1.0	3.3 ± 0.8	2.8 ± 1.4	0.03
Prolonged use of amines agents (> 12 h)	16 (17.5)	13 (21.3)	3 (10.0)	0.25
Transfusion	34 (37.4)	23 (37.7)	11 (36.7)	1
Syntax score	43.8 ± 11.6	44.4 ± 10.6	42.4 ± 13.5	0.66
Aortic cross-clamping time	61.1 ± 20.4	61.1 ± 20.4	–	–
CPB time	72.3 ± 23.4	72.3 ± 23.4	–	–
Length of operation (min)	344.9 ± 53.7	358.9 ± 45.8	312.0 ± 59.2	< 0.01
Blood loss 12 h (mL)	333.4 ± 165.3	328.8 ± 104.4	341.7 ± 239.1	0.51
ICU stay (days)	3.7 ± 1.7	3.9 ± 1.7	3.9 ± 2.6	0.39
Intubation time (h)	12.9 ± 29.3	17.9 ± 51.1	10.4 ± 3.4	0.04
In hospital stay (days)	10.8 ± 5.3	11.3 ± 6.1	9.9 ± 4.6	0.07

vivo, several studies have described the utility of endocan as an endothelial marker in the context of sepsis [9–13].

Cardiac surgery is unique among the surgical specialities, insofar as it is the only surgical discipline that uses extracorporeal circulation by means of complete cardiopulmonary bypass (CPB). It is well established that the use of CPB during cardiac surgery can induce an inflammatory response [14], and the duration of CPB as well as the clamping time both seem to be related to the generation of cardiovascular and respiratory lesions [15].

The aim of our study was thus to describe the kinetics of endocan in patients undergoing cardiac surgery with and without the use of CPB.

2. Methods

We performed a single-centre, observational study with retrospective analysis of prospectively collected data, to compare the kinetics of endocan in patients undergoing isolated coronary artery bypass graft (CABG) surgery in the Endolung study. The prospective Endolung study, registered on ClinicalTrials.gov under the number NCT02542423, was conducted in the Department of Cardiac Surgery of Besançon University Hospital between January and July 2016. The details of the study have previously been described elsewhere [16]. Briefly, we included adult patients (aged > 18 years) scheduled to undergo cardiac surgery and who provided written informed consent. Exclusion criteria were: patients aged < 18 years, emergency surgery, patients with ongoing pulmonary infection or who developed post-operative pneumonia, inflammation or cancer, pregnancy, patient refusal, and adults under legal protection. The primary objective was to assess the utility of endocan as a diagnostic marker for postoperative pneumonia in patients undergoing cardiac surgery. From 1 January to 23 May 2016, a total of 255 patients were prospectively included.

The following variables were recorded prior to surgery: age; sex; haemoglobin; platelet count; creatinine level; history of diabetes, hypertension, dyslipidemia or non-cardiac arterial disease; history of carotid stenosis; history of chronic respiratory disease; body mass index (BMI); smoking status; left ventricular ejection fraction (LVEF); SYNTAX score and EuroScore. During surgery, we recorded the duration of intubation; the number of anastomoses; total volume of blood loss; need for transfusion; duration of aortic clamping; duration of CPB; total duration of surgery. Post-surgery, we recorded the following: need for prolonged amines (> 12 h); length of stay in intensive care and in-hospital. Blood samples for endocan measurements were collected in 5 mL EDTA tubes at 5 time points, namely: at induction of general anaesthesia (baseline), and at 6, 24, 48 and 72 h after the end of surgery. Samples were centrifuged between 1500 and 2000*g* for 10 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 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 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.

For the purposes of this analysis, patients were classified into two groups, namely those undergoing CPB (CPB group) and those without CPB (off-pump group). The primary objective was to compare the kinetics of endocan in CPB vs off-pump groups, and the primary endpoint was thus endocan level in both groups at each time point. Secondary endpoints were endocan levels according to the duration of CPB.

Quantitative variables are presented as mean ± standard deviation, and qualitative variables as number (percentage). Quantitative variables were compared using the Student t or Mann Whitney *U* test as appropriate and qualitative variables using the chi square or Fisher's