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

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ABSTRACT

Introduction: Endothelial Specific Molecule-1 or endocan is a novel biomarker associated with the development of acute lung injury (ALI) in response to a systemic inflammatory state such as trauma. Acute Respiratory Distress syndrome (ARDS), a severe form of ALI is a devastating complication that can occur following cardiac surgery due to risk factors such as the use of cardiopulmonary bypass (CPB) during surgery. In this study we examine the kinetics of endocan in the perioperative period in cardiac surgical patients.

Methods: After ethics approval, we obtained informed consent from 21 patients undergoing elective cardiac surgery (3 groups with seven patients in each group: coronary artery bypass grafting (CABG) with the use of CPB, off-pump CABG and complex cardiac surgery). Serial blood samples for endocan levels were taken in the perioperative period (T0: baseline prior to induction, T1: at the time of heparin administration, T2: at the time of protamine, T2, T3, T4 and T5 at 1, 2, 4 and 6 h following protamine administration respectively). Endocan samples were analysed using the enzyme-linked immunosorbent assay (ELISA) method. Statistical analysis incorporated the use of test for normality.

Results: Our results reveal that an initial rise in the levels of serum endocan from baseline in all patients after induction of anaesthesia. Patients undergoing off-pump surgery have lower endocan concentrations in the perioperative period than those undergoing CPB. Endocan levels decrease following separation from CPB, which may be attributed to haemodilution following CPB. Following administration of protamine, endocan concentrations steadily increased in all patients, reaching a steady state between 2 and 6 h. The baseline endocan concentrations were elevated in patients with hypertension and severe coronary artery disease.

Conclusion: Baseline endocan concentrations are higher in hypertensive patients with critical coronary artery stenosis. Endocan concentrations increased after induction of anaesthesia and decreased four hours after separation from CPB. Systemic inflammation may be responsible for the rise in endocan levels following CPB.

1. Introduction

Cardiac surgery is a well-known risk factor for acute respiratory distress syndrome (ARDS) [1]. ARDS is a severe form of lung injury characterized by acute refractory hypoxaemia accompanied by bilateral pulmonary infiltrates resulting from non-cardiogenic pulmonary oedema due to increased permeability of the vascular endothelium [1,2]. Several factors influence the development of ARDS in the context of cardiac surgery, including the use of

Abbreviations: ARDS, acute respiratory distress syndrome; ALI, acute lung injury; ESM-1, endothelial specific molecule-1; ELISA, enzyme-linked immunosorbent assay; TRALI, transfusion-related acute lung injury; LFA-1, leukocyte function-associated antigen-1; ICAM-1, intercellular adhesion molecule-1 (ICAM-1); TNF α, tumour necrosis factor α; VEGF, vascular endothelial growth factor; LPS, lipopolysaccharide; FGF-2, fibroblast growth factor 2; CABG, coronary artery bypass grafting; OPCABG, off-pump coronary artery bypass grafting; CPB, cardiopulmonary bypass; EDTA, ethylenediaminetetraacetic acid.

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cardiopulmonary bypass, type of surgery (eg. complex cardiac surgery requiring long bypass times), ischaemia-reperfusion injury and transfusion-related acute lung injury (TRALI) [3]. ARDS following cardiac surgery is infrequent, with an incidence of 0.4–2.0% [4,5], although a recent report from the United States claims that up to 20% of patients undergoing cardiac surgery may develop ARDS. Development of ARDS may be associated with a mortality rate of up to 80% following cardiac surgery [2–7]. The importance of identifying patients at risk of developing pulmonary dysfunction and ARDS after cardiac surgery lies in the opportunity to tailor patient centred strategies which might not be appropriate for the undifferentiated cardiac surgical population. Examples include modified transfusion thresholds, fluid balance targets and specific lung protective ventilation. Whilst clinical lung injury prediction models exist [8,9] these are based on pre-morbid population based factors and are not accurate enough to inform the clinician managing the individual post-operative patient. Adding a simple, accurate and easily measured biomarker which can be rapidly evaluated post-surgery would be hugely helpful in identifying individual high risk patients in whom pre-emptive strategies might be evaluated and, where appropriate, implemented.

Endocan or endothelial cell specific molecule-1 (ESM-1) is a soluble proteoglycan secreted by the pulmonary and renal vascular endothelium [10–12]. Endocan plays a role in modulating leukocyte migration from the blood to the tissues [13]. It binds to the Leukocyte Function- associated Antigen-1 (LFA-1) on the surface of the leukocytes and blocks the interaction between LFA-1 and intercellular adhesion molecule–1 (ICAM-1), inhibiting the recruitment of leukocytes into lungs [13]. The production of endocan itself is regulated by pro-inflammatory cytokines such as tumour necrosis factor α (TNF–α) and lipopolysaccharide (LPS) and pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF-2) [10]. Endocan has been shown to be a marker of endothelial dysfunction, which plays a pivotal role in the pathogenesis of syndromes such as sepsis and ARDS. Blood endocan levels have been correlated with sepsis severity and prognosis [14,15]. Recently, endocan has shown to predict the development of acute lung injury in trauma patients [16] and has shown some correlation with the severity of ARDS and survival in patients with ARDS [17].

The potential of endocan to predict ARDS in the context of cardiac surgery has not yet been evaluated and the kinetics of endocan during and after cardiac surgery are also unknown. The primary objective of this study was to investigate the kinetics of endocan in patients undergoing elective cardiac surgery with and without the use of cardiopulmonary bypass. We hypothesized that endocan levels would increase following cardiac surgery and patients undergoing cardiopulmonary bypass may have higher postoperative endocan levels than those undergoing cardiac surgery without the use of cardiopulmonary bypass.

2. Materials and methods

2.1. Setting and patient population

This was a single-center, prospective observational study conducted at St. George's Hospital, London, UK. Following ethical approval (Research and Ethics Committee Reference: 14/LO/0459), we obtained written informed consent from 21 adult patients undergoing elective cardiac surgery between February and August 2014. Patients were classified into three specific groups: group 1 - patients undergoing coronary artery bypass grafting (CABG) without the use of CPB or off pump CABG (OPCABG), group 2 - patients undergoing coronary artery bypass grafting with the use of CPB and group 3 - patients undergoing complex cardiac surgery with the use of CPB. We defined complex cardiac surgery as follows: redo cardiac surgery, repair/replacement of two or more cardiac valves and major aortic surgery involving the use of deep hypothermic circulatory arrest. We excluded patients less than 18 years of age, pregnant patients, undergoing emergency surgery, and patients with history of active cancer, recent chest infection, renal impairment and severe respiratory disease prior to surgery.

2.2. Data collection

Data were recorded prospectively from the patient's medical record using a predefined case report form. The following data were collected: demographic data including the patient's age, sex, weight and height; comorbid conditions; preoperative laboratory investigations; type of surgery; duration of cardiopulmonary bypass and cross clamp time, blood product transfusion during surgery and details of endocan sampling. Management of mechanical ventilation and fluid administration during the perioperative period followed standard institutional protocols and the discretion of the cardiac anaesthetist and intensivist involved. Whole blood samples (5 ml for each sample) for endocan were collected in EDTA anticoagulated tubes (Beckton-Dickenson, Plymouth UK) at specific time points (T0: baseline prior to induction of anaesthesia, T1: at the time of heparin administration, T2: after administration of protamine, T3, T4, T5 and T6 at 1, 2, 4 and 6 h following protamine administration respectively).

2.3. Plasma endocan assay

The whole blood samples were transferred to the department of chemical pathology on the same day of collection. Samples were centrifuged at 3000 rpm for 10 min. The plasma was aliquoted and stored at −70 °C. A commercially available, sandwich-based enzyme-linked immunosorbent assay (ELISA; LUNGINNOV® Systems, Lille, France) was used to determine endocan concentrations. The limit of detection was 0.15 ng/mL and the limit of quantification was 0.3 ng/mL. Total assay total imprecision was 2.4–17.0% in the range 0.82–4.94 ng/mL.

2.4. Statistical analysis

Baseline characteristics including patient demographics and other perioperative data are summarised using univariate analyses. We tested continuous data for normal distribution with the Wilkinson single rank test. The variables are presented as mean values and standard deviations if normally distributed, and otherwise, as medians. We performed the statistical analysis using the SPSS statistics package (SPSS version 21.0).

3. Results

We studied 21 patients, with seven patients in each of the three groups viz., OPCABG, CABG with the use of CPB and complex cardiac surgery. The demographic and perioperative data of the patients are depicted in Table 1.

Table 2 shows the perioperative plasma endocan concentrations (mean + SD) in all patients (see Figs. 1 and 3).

Fig. 2 shows the median values of plasma endocan concentrations in all the three groups at various time points. In patients undergoing off pump CABG we noted that the endocan concentrations steadily increased from baseline with peak levels at four hours post protamine. This was in contrast to the values observed patients undergoing cardiac surgery with the use of CPB, where there was a fall in plasma endocan concentrations after separation