

# BMJ Open Procalcitonin as a predictor of moderate to severe acute respiratory distress syndrome after cardiac surgery with cardiopulmonary bypass: a study protocol for a prospective cohort study

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**To cite:** Chen H, Cheng Z-B, Yu R-G. Procalcitonin as a predictor of moderate to severe acute respiratory distress syndrome after cardiac surgery with cardiopulmonary bypass: a study protocol for a prospective cohort study. *BMJ Open* 2014;**4**:e006344. doi:10.1136/bmjopen-2014-006344

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2014-006344>).

Received 9 August 2014  
Revised 13 October 2014  
Accepted 15 October 2014



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## ABSTRACT

**Introduction:** Procalcitonin (PCT) is activated during cardiopulmonary bypass (CPB) and may be a predictor of acute respiratory distress syndrome (ARDS). The objective of this study is to determine whether patients with different serum PCT concentrations exhibit different rates of developing moderate to severe ARDS.

**Methods and analysis:** This is a prospective, single centre, observational cohort study. All patients admitted to the cardiosurgery department for cardiac surgery with CPB were screened for study eligibility. All eligible patients received a CPB procedure. Blood samples were obtained to determine white cell counts as well as N-terminal pro-B-type natriuretic peptide, C reactive protein and PCT levels. Patients were assigned to the PCT elevated cohort or the control cohort based on serum PCT concentrations on the first postoperative day with a cut-off value of 7.0 ng/mL. Data, including baseline, perioperative and outcome data, were collected daily for 7 days. The primary end point was the incidence of moderate to severe ARDS, which was diagnosed according to the Berlin definition.

**Ethics and dissemination:** The study was approved by the Institutional Review Board of Fujian Provincial Hospital. Study findings are disseminated through peer-reviewed publications and conference presentations.

**Study registration:** Chinese Clinical Trial Registry (ChiCTR-OCH-14005076).

## INTRODUCTION

Epidemiological studies have demonstrated that cardiac surgery is a known risk factor for acute respiratory distress syndrome (ARDS).<sup>1–3</sup> Over 300 000 patients undergo cardiac surgery every year in the USA, and up to 20% will experience ARDS.<sup>4</sup> The risk factors include the type of surgery, cardiopulmonary bypass, ischaemia-reperfusion injury, transfusion-related acute lung injury and drug toxicity. The mortality rate associated with ARDS is approximately 40% in the

general population; however, this rate is considerably higher (up to 80%) among postcardiac surgery patients.<sup>5 6</sup> Moderate-to-severe ARDS causes the majority of deaths associated with this syndrome, and the possible therapeutic choices differ for the varying severities of ARDS. Patients with mild ARDS typically only require non-invasive treatments, whereas patients with moderate to severe ARDS are more likely to require more aggressive interventions, including prone positioning, recruitment manoeuvres, neuromuscular blockage agents, inhaled nitric oxide, high frequency oscillatory ventilation and even extracorporeal membrane oxygenation. Thus, the identification of patients with moderate to severe ARDS is clinically meaningful.

Although cardiac surgery with cardiopulmonary bypass (CPB) is considered a highly sterile type of surgery, it can lead to a systemic inflammatory response syndrome (SIRS).<sup>7</sup> The possible causes of SIRS include the exposure of blood to non-physiological surfaces, ischaemia-reperfusion injury due to aortic clamping and extracorporeal circulation.<sup>8</sup> In addition, the translocation of gut endotoxins to the bloodstream after the release of the aortic clamp is another potential cause<sup>9</sup> that can activate inflammatory cascades similar to those observed in sepsis. Cytokines, such as interleukin (IL)-6, IL-8, tumour necrosis factor- $\alpha$  and C reactive protein (CRP), lipoprotein-binding protein and procalcitonin (PCT) potentially play important roles in immune reactions, whereas PCT liberation is predominantly dependent on the use of CPB.<sup>10</sup>

PCT is initially described as an early, sensitive and specific marker for sepsis associated with bacterial infection.<sup>11</sup> However, PCT

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BMJ Open: first published as 10.1136/bmjopen-2014-006344 on 29 October 2014. Downloaded from <http://bmjopen.bmj.com/> on June 10, 2025 at Agence Bibliographique de l'Enseignement Supérieur (ABES).

levels are also increased in clinical situations not associated with infections, including major surgery, burns or trauma.<sup>12</sup> Previous studies suggested that serum PCT concentrations increase at the end of CPB, peaking on the first day and then rapidly declining.<sup>7 13</sup> Data have suggested that significant increases in PCT levels are observed when complications present.<sup>7 14 15</sup> Therefore, we hypothesise that PCT could serve as a predictor of the development of ARDS, especially moderate to severe ARDS, in patients undergoing cardiac surgery with CPB. Our aim is to determine whether patients with different serum PCT concentrations exhibit different rates of developing moderate to severe ARDS.

## METHODS AND ANALYSIS

### Study design overview

The present study is a prospective, single centre, observational cohort study involving patients undergoing elective cardiac surgery.

### Study setting and population

The study setting is a cardiosurgical intensive care unit (ICU; 20 beds) and cardiosurgery department (118 beds) at Fujian Provincial Hospital (2500 beds), Fujian Provincial Clinical College of Fujian Medical University, Fuzhou, China.

All patients admitted to the cardiosurgery department for a cardiac surgery involving CPB were screened for study eligibility.

The following inclusion criteria were used:

1. Patients were 18 years of age and older;
2. Patients underwent cardiac surgery involving CPB;
3. Patients were free from active preoperative infection or inflammatory disease (all of the following criteria were achieved at study entry: leucocyte count  $<12 \times 10^9/L$ , PCT  $<0.5$  ng/mL, body temperature  $<37.5^\circ C$ );
4. Patients were capable of providing consent.

The following exclusion criteria were used:

1. History of chronic obstructive pulmonary disease (COPD), asthma or interstitial lung disease;
2. History of lung surgery;
3. Pregnant or lactating women;
4. Unwilling to provide consent;
5. Enrolled in another trial.

### Anaesthesia, CPB and perioperative management

All patients undergo cardiosurgery with general anaesthesia via median sternotomy. Anticoagulation is promoted in CPB patients via the administration of 3 mg/kg sodium heparin. After attaining an activating clotting time (ACT) greater than 480 s, CPB is initiated by using an occlusive roller pump (Jostra, Germany) and a membrane oxygenator (Affinity7000, American) followed by moderate hypothermia ( $28^\circ C$ ) and crystalloid cardioplegic cardiac arrest. The pump flow is approximately  $2.0\text{--}2.6$  L/min/ $m^2$  during CPB. The

mean arterial pressure is maintained at 60–80 mm Hg. At the end of surgery, protamine is administered at a 1:1 ratio to reverse the heparin effect (to obtain an ACT  $<160$  s). The ventilator is initially set to deliver a tidal volume approximately 7–10 mL/kg, and the respiratory rate is adjusted to maintain an arterial  $CO_2$  pressure ( $PaCO_2$ ) of 35–40 mm Hg during the surgery. Cephazolin is administered as perioperative antibiotic prophylaxis. Patients are monitored postoperatively in the ICU and receive ventilation until the following criteria are met:

1. Awake and cooperative;
2. Adequate recovery of muscle strength;
3. Normal tidal volume, normocapnia (end-tidal carbon dioxide 30–45 mm Hg), and minimum pulse oxygen saturation ( $SpO_2$ )  $\geq 95\%$  with a fraction of inspiration oxygen ( $FiO_2$ ) of 0.5;
4. Haemodynamic stability (small dosage of vasopressor support and mean arterial pressure within 10–15% of baseline);
5. No severe arrhythmias;
6. No bleeding or indications of re-exploration.

The patient's endotracheal tube is removed if he/she achieves the criteria. Patients are discharged from the ICU after successful extubation. In our clinical practice, blood samples are routinely obtained for whole blood assessment prior to and 1 day after the operation. PCT is also assessed prior to and 1 day after the operation. N-terminal pro-B-type natriuretic peptide (Nt-pro-BNP) and CRP levels are assessed 1 day after the operation. A chest X-ray is routinely obtained prior to the operation as well as 1 and 7 days after the operation. Additional chest X-ray examinations are performed if patients exhibit hypoxia due to suspicious infection, pulmonary atelectasis, pleural effusion or ARDS. A blood gas analysis is performed at least once daily when the patients are in the ICU. After they are transferred to a normal room, a blood gas analysis is performed when deemed necessary by the physicians or when patients'  $SpO_2$  cannot be maintained at a level greater than 95% with a  $FiO_2$  of 0.5.

### Follow-up and data collection

This is an observational study wherein no intervention is applied. At study entry, data regarding patient demographics, history of smoking, history of past illness patient characteristics, diagnosis and the New York Heart Association (NYHA) functional classification<sup>16</sup> are collected. The type of surgery, duration of operation, CPB and aortic clamping, and net fluid balance during the operation are recorded. Serum CRP, Nt-pro-BNP and PCT concentrations are also recorded on the first postoperative day. Patients are assigned to the PCT elevated cohort or control cohort based on serum PCT concentrations on the first postoperative day using a cut-off value of 7.0 ng/mL. Daily fluid balance and highest vasoactive-inotropic score (VIS) are calculated. VIS is calculated as dopamine dose ( $\mu g/kg/min$ )+dobutamine

**Table 1** ARDS checklist

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
<i>Timing:</i> Within 1 week of a known clinical insult or new or worsening respiratory symptoms	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
<i>Chest imaging:</i> Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
<i>Origin of oedema:</i> Respiratory failure not fully explained by cardiac failure or fluid overload	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
<i>Oxygenation</i>							
<i>Mild:</i> 200 mm Hg $<PaO_2/FiO_2 \leq 300$ mm Hg with PEEP or CPAP $\geq 5$ cm H <sub>2</sub> O	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>
<i>Moderate:</i> 100 mm Hg $<PaO_2/FiO_2 \leq 200$ mm Hg with PEEP $\geq 5$ cm H <sub>2</sub> O	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>
<i>Severe:</i> $PaO_2/FiO_2 \leq 100$ mm Hg with PEEP $\geq 5$ cm H <sub>2</sub> O	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>	Yes <input type="checkbox"/>
Has the patient developed ARDS?	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>

ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure;  $FiO_2$ , fraction of inspired oxygen;  $PaO_2$ , partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

dose ( $\mu\text{g/kg/min}$ )+100 $\times$ epinephrine dose ( $\mu\text{g/kg/min}$ )+100 $\times$ norepinephrine dose ( $\mu\text{g/kg/min}$ )+15 $\times$ milrinone dose ( $\mu\text{g/kg/min}$ )+10 000 $\times$ vasopressin dose (U/kg/min).<sup>17</sup> Data are collected until the seventh day after the operation. ARDS is diagnosed according to the Berlin definition.<sup>18</sup> A checklist (table 1) is used to assess the development of moderate to severe ARDS. Two physicians make the diagnosis independently. Only patients diagnosed with moderate to severe ARDS by both physicians are considered. Echocardiography or pulmonary artery catheter (PAC) is applied to exclude hydrostatic oedema. Physicians who assess the development of ARDS are unaware of the patient's PCT level.

### PCT determination

Serum PCT levels were measured using a highly sensitive and specific commercially available immunoluminometric assay kit (Vidasbrahms PCT, mini VIDIS, Italy) according to the manufacturer's recommendation. Quantitative measurement allowed the determination of PCT concentrations ranging from 0.05 to 200 ng/mL.

### Study end points

The primary end point is the incidence of moderate to severe ARDS.

The secondary end points include the following:

1. The duration of mechanical ventilation;
2. The length of ICU stay;
3. Complications after surgery.

### Sample size

Primarily, we expect the incidence of moderate to severe ARDS to be increased in the PCT elevated group compared with the control group. Previous investigations indicate the overall morbidity of moderate to severe ARDS was approximately 0.5–2% of patients undergoing

cardiac surgery.<sup>1–3</sup> Our pilot study revealed that the incidence could be as high as 15% in patients with elevated PCT levels. Using the Power and Sample Size Calculation program, 64 exposure participants and 64 control participants must be investigated to be able to reject the null hypothesis. The type I error probability ( $\alpha$ ) for testing our null hypothesis is 0.05, and the type II error probability ( $\beta$ ) is 0.2.

### Statistical analysis

Baseline characteristics were summarised using univariate analyses. Categorical variables are presented as numbers and percentages, and analysed using the  $\chi^2$  test. Continuous variables are assessed for normal distribution and presented as means and SDs or medians and IQR as appropriate. Continuous variables are compared using the Student's t test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. All tests of significance were two sided and conducted at the 5% significance level. Subgroup analysis was performed to illustrate the effects of different types of surgery. Analyses are performed using SPSS 19.0 (IBM Corporation, New York, USA).

### Ethical aspects and informed consent

The study protocol and consent forms were approved on 7 August 2014 by the Institutional Review Board of Fujian Provincial Hospital. The study was registered on 8 August 2014 at ClinicalTrials.org (ChiCTR-OCH-14005076).

After patient eligibility for the study is confirmed, the study coordinator is introduced to the family. The surgeon ensures that the family is aware of the study coordinator's credentials and indicates that this individual will discuss the research programme being

conducted and that the patient is qualified to participate. Every relevant aspect of the project is described. The study coordinator frequently pauses to ask if there are any questions and requests that the family repeat the topic being discussed in their own words to ensure that they understand. The study coordinator is especially careful to assure the family that they are free to decline consent without consequences and that they can withdraw consent at any time without impacting treatment. Family members are provided contact information for the study coordinator, local coinvestigator and the local Ethical Committee. Written consent is obtained in the presence of a witness.

### Dissemination plan

The study results will be submitted to an international peer reviewed journal. Results will also be presented at national and international conferences relevant to the subject fields. We will also consider disseminating the results to the participants.

**Contributors** HC and R-GY participated in the study design and drafted the manuscript. Z-BC participated in the study design. All authors edited the manuscript, read and approved the final manuscript.

**Funding** This work was supported by grants from the National Clinical Key Specialty (2011170)..

**Competing interests** None.

**Ethics approval** The study was approved by the Institutional Review Board of Fujian Provincial Hospital.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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