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Procalcitonin as a predictor of moderate to severe acute respiratory distress syndrome (ARDS) after cardiac surgery with cardiopulmonary bypass (CPB): a study protocol for a prospective cohort study

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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 object is to validate that whether patients with different serum PCT concentration have different incidence of developing moderate to severe ARDS.

Methods and analysis: The study is a prospective, single center, observational cohort study. All patients admitted to the cardiosurgery department who are programmed for a cardiac surgery with CPB are screened for study eligibility. All eligible patients will receive operation with CPB. Blood samples are obtained for test of white blood cell (WBC) count, N-terminal pro-B-type natriuretic peptide (Nt-pro-BNP), C-reactive protein (CRP) and procalcitonin (PCT). Patients are assigned to PCT elevated cohort or control cohort according to serum PCT concentration on the first postoperative day with a cut-off value of 7.0 ng/ml. Data will be collected daily for seven days, which including baseline data, perioperative data and outcomes. The primary endpoint is incidence of moderate to severe ARDS, which is diagnosed according to the Berlin definition.

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

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

Introduction

Epidemiological studies have shown that cardiac surgery is a known risk factor for acute respiratory distress syndrome (ARDS).[1-3] There are more than 300,000 patients who undergo cardiac surgery every year in the United States, as many as 20% will have ARDS.[4] The risk factors include the type of surgery, cardiopulmonary bypass, ischemia-reperfusion injury, transfusion-related acute lung injury and drug toxicity. The mortality rate associated with ARDS is approximately 40% in the general population, but much higher among post–cardiac surgery patients, which may be as high as 80%.[5 6] Moderate to severe ARDS causes the majority of death cases, and the possible therapeutic choices are different in different severity of ARDS. Mild ARDS patients usually need non-invasive treatments, while moderate to severe ARDS patients are more likely in need of more aggressive interventions such as prone positioning, recruitment maneuver, neuromuscular blockage agents, inhaled nitric oxide, high frequency oscillatory ventilation and even extracorporeal membrane oxygenation. It is meaningful to identify patients with moderate to severe ARDS.

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).[7] The possible causes are the exposure of blood to non-physiological surfaces, ischemia-reperfusion injury due to aortic clamping and extracorporeal circulation,[8] as well as a translocation of endotoxins from gut to the bloodstream after the release of the aortic clamp,[9] which can activate inflammatory cascades similar to those observed in sepsis. Cytokines such as interleukin (IL)-6, IL-8, tumor

necrosis factor (TNF)-alpha as well as C-reactive protein (CRP), lipoprotein-binding protein (LBP) and procalcitonin (PCT) may play an important role in the immune reaction, while PCT liberation is predominantly depended on the use of CPB.[10]

PCT is initially described as an early, sensitive and specific marker for sepsis associated with bacterial infection.[11] However, it is also increased in clinical situations without infections such as major surgery, burns, or trauma.[12] Previous studies suggested that the concentration of serum PCT increased at the end of CPB, reaching its peak on the first day and then declined rapidly.[7 13] It is also suggested that significant elevation of PCT level can be observed when complications presented.[7 14 15] Therefore, we hypothesis that PCT could be a predictor of the development of ARDS, especially moderate to severe ARDS, in patients undergo cardiac surgery with CPB. Our aim is to validate that whether patients with different serum PCT concentration have different incidence of developing moderate to severe ARDS.

Methods and analysis

Study design overview

The present study is a prospective, single center, observational cohort study in patients after elective cardiac surgery.

Study setting and population

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

All patients admitted to the cardiosurgery department who are programmed for a cardiac surgery under CPB are screened for study eligibility.

Inclusion criteria are:

1) Age 18 years and above;
2) Programmed cardiac surgery under CPB;
3) Be free from active preoperative infection or inflammatory disease (meet all of the following criteria at study entry: leukocyte count < $12*10^9$/L, PCT < 0.5 ng/ml, body temperature < 37.5°C);
4) Able to consent.

Exclusion criteria are:

1) History of chronic obstructive pulmonary disease (COPD), asthma or interstitial lung disease (ILD);

2) History of lung surgery;

3) Pregnant or lactating women;

4) Unwillingness of the patient to provide consent;

5) Enrolled in another trial.

Anesthesia, CPB and perioperative management

All patients' cardiosurgery undergo with general anesthesia and median sternotomy. Anticoagulation is obtained by using sodium heparin at a dose of 3 mg/kg for CPB patients. After attaining an activating clotting time (ACT) greater than 480 seconds, CPB is initiated by using an occlusive roller pump (jostra, Germany) and a membrane oxygenator (affinity7000, American), followed with moderate hypothermia (28□) and crystalloid cardioplegic cardiac arrest. Pump flow is about 2.0-2.6 l/min/m^2 during CPB and the mean arterial pressure (MAP) is maintained between 60 and 80 mmHg. At the end of surgery, protamine is given at a 1:1 ratio for reversal of the heparin effect (to obtain an ACT < 160s). The ventilator is initially set to deliver a tidal volume around 7-10 ml/kg and a respiratory rate adjusted to maintain an arterial CO_2 pressure ($PaCO_2$) between 35 and 40 mmHg during the surgery. Cephazolin is used as perioperative antibiotic prophylaxis. Patients are monitored postoperatively in the ICU and ventilated until they meet the following criteria:

1) Awake and cooperative;

2) Adequate recovery of muscle strength;

3) Normal tidal volume, normocapnia (end-tidal carbon dioxide 30-45 mmHg),

minimum pulse oxygen saturation (SpO_2) ≥ 95% with fraction of inspiration oxygen (FiO_2) 0.5;

4) Hemodynamic 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.

Patients' endotracheal tube is removed if they meet the criteria. Patients are discharged from ICU after successful extubation. In our clinical practice, blood samples are routinely obtained for test of whole blood routine before and 1 day after operation, respectively. PCT is also tested before and 1 day after operation. N-terminal pro-B-type natriuretic peptide (Nt-pro-BNP) and CRP are tested 1 day after operation. Chest X-ray is routinely obtained before operation, 1 day and 7 days after operation, respectively. Additional chest X-ray examinations are performed if patients represent hypoxia due to suspicious infection, pulmonary atelectasis, pleural effusion or ARDS. Blood gas analysis is tested at least once per day when the patients are in the ICU. After they are transferred to the routine room, blood gas analysis is tested when the physicians considered it is necessary, or when patients' SpO_2 cannot be maintained greater than 95% with a FiO_2 of 0.5.

Follow up and data collection

This is an observational study that no intervention is applied. At study entry, data on demographic, history of smoking, history of past illness characteristics, diagnosis and

the New York Heart Association (NYHA) functional classification [16] are collected. Type of surgery, duration of operation, CPB and aortic clamping and net fluid balance during the operation are recorded. The concentration of serum CRP, Nt-pro-BNP and PCT level on the first postoperative day are also recorded. Patients are assigned to the PCT elevated cohort or control cohort according to serum PCT concentration on the first postoperative day with 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 (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 100 × norepinephrine dose (μg/kg/min) + 15 × milrinone dose (μg/kg/min) + 10000 × vasopressin dose (U/kg/min).[17] Data are collected until the seventh day after operation. ARDS is diagnosed according to the Berlin definition.[18] A checklist (Table 1) is used to assess the development of moderate to severe ARDS. Two physicians make the diagnosis independently. Only the patients who are diagnosed by both two physicians are considered with moderate to severe ARDS. Echocardiography or pulmonary artery catheter (PAC) is applied to exclude hydrostatic edema. Physicians who assess the development of ARDS are unaware of patients' PCT level.

Table 1 Checklist of ARDS

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Timing: Within 1 week of a known clinical insult or new or worsening respiratory symptoms	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Chest imaging: Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Origin of edema: Respiratory failure not fully explained by cardiac failure or fluid overload	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Oxygenation							
Mild: 200 mm Hg $<PaO_2/FiO_2 \leqslant$ 300 mm Hg with PEEP or CPAP$\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Moderate: 100 mm Hg $< PaO_2/FiO_2 \leqslant$ 200 mm Hg with PEEP $\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Severe: $PaO_2/FiO2 \leqslant$ 100 mm Hg with PEEP $\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Does the patient developed ARDS?	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Abbreviations: CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

PCT determination

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

Study endpoints

The primary endpoint is incidence of moderate to severe ARDS.

Secondary endpoints include:

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 is higher in the PCT elevated group than in the control group. Previous investigations showed the overall morbidity of moderate to severe ARDS was around 0.5%-2% of patients underwent cardiac surgery.[1-3] Our pilot study showed that the incidence could be as high as 15% in the patients with elevated PCT level. Using the Power and Sample Size Calculation program, we will need to investigate 64 exposure subjects and 64 control subjects to be able to reject the null hypothesis. The Type I error probability (α) with testing this null hypothesis is 0.05 and Type II error probability (β) is 0.2.

Statistical analysis

Baseline characteristics will be summarized by univariate analyses. Categorical variables will be presented as numbers and percentages, and analyzed by the χ^2-test. Continuous variables will be checked for normal distribution and presented as mean and standard deviation or median and inter-quartile range as appropriate. Comparison of continuous variables will be performed by using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. All tests of significance will be at the 5% significance level, and two-sided. Analyses are performed by using SPSS 19.0 (IBM Corporation, New York, USA).

Ethical aspects and informed consent

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

After patient's eligibility for the study is confirmed, the study coordinator will be introduced to the family. The surgeon will make sure the family knows the credentials of the study coordinator, and says that this person is going to discuss a research program being conducted, and the patient is qualified to do so. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed, to make sure they understand. The study coordinator will be 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 impact on treatment. Family members will be provided with contact information for the study coordinator, local co-investigator and the local Ethical Committee. Written consent will be obtained in the presence of a witness.

Dissemination plan

Results of the trial will be submitted to international peer reviewed journal. Results will also be presented at national and international conferences relevant to subject fields.

Authors' contributions

HC and RGY participated in the design of the study and drafted the manuscript. ZBC participated in the design of the study. All authors edited the manuscript and read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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2) Adequate recovery of muscle strength;

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Table 1 Checklist of ARDS

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Timing: Within 1 week of a known clinical insult or new or worsening respiratory symptoms	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Chest imaging: Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Origin of edema: Respiratory failure not fully explained by cardiac failure or fluid overload	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Oxygenation							
Mild: 200 mm Hg $<PaO_2/FiO_2 \leqslant$ 300 mm Hg with PEEP or CPAP$\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Moderate: 100 mm Hg $< PaO_2/FiO_2 \leqslant$ 200 mm Hg with PEEP $\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Severe: $PaO_2/FiO2 \leqslant$ 100 mm Hg with PEEP $\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Does the patient developed ARDS?	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Abbreviations: CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

PCT determination

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

Study endpoints

The primary endpoint is incidence of moderate to severe ARDS.

Secondary endpoints include:

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 is higher in the PCT elevated group than in the control group. Previous investigations showed the overall morbidity of moderate to severe ARDS was around 0.5%-2% of patients underwent cardiac surgery.[1-3] Our pilot study showed that the incidence could be as high as 15% in the patients with elevated PCT level. Using the Power and Sample Size Calculation program, we will need to investigate 64 exposure subjects and 64 control subjects to be able to reject the null hypothesis. The Type I error probability (α) with testing this null hypothesis is 0.05 and Type II error probability (β) is 0.2.

Statistical analysis

Baseline characteristics will be summarized by univariate analyses. Categorical variables will be presented as numbers and percentages, and analyzed by the χ^2-test. Continuous variables will be checked for normal distribution and presented as mean and standard deviation or median and inter-quartile range as appropriate. Comparison of continuous variables will be performed by using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. All tests of significance will be at the 5% significance level, and two-sided. Analyses are performed by using SPSS 19.0 (IBM Corporation, New York, USA).

Ethical aspects and informed consent

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

After patient's eligibility for the study is confirmed, the study coordinator will be introduced to the family. The surgeon will make sure the family knows the credentials of the study coordinator, and says that this person is going to discuss a research program being conducted, and the patient is qualified to do so. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed, to make sure they understand. The study coordinator will be 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 impact on treatment. Family members will be provided with contact information for the study coordinator, local co-investigator and the local Ethical Committee. Written consent will be obtained in the presence of a witness.

Dissemination plan

Results of the trial will be submitted to international peer reviewed journal. Results will also be presented at national and international conferences relevant to subject fields.

Authors' contributions

HC and RGY participated in the design of the study and drafted the manuscript. ZBC participated in the design of the study. All authors edited the manuscript and read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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Procalcitonin as a predictor of moderate to severe acute respiratory distress syndrome (ARDS) after cardiac surgery with cardiopulmonary bypass (CPB): a study protocol for a prospective cohort study

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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 object is to validate that whether patients with different serum PCT concentration have different incidence of developing moderate to severe ARDS.

Methods and analysis: The study is a prospective, single center, observational cohort study. All patients admitted to the cardiosurgery department who are programmed for a cardiac surgery with CPB are screened for study eligibility. All eligible patients will receive operation with CPB. Blood samples are obtained for test of white blood cell (WBC) count, N-terminal pro-B-type natriuretic peptide (Nt-pro-BNP), C-reactive protein (CRP) and procalcitonin (PCT). Patients are assigned to PCT elevated cohort or control cohort according to serum PCT concentration on the first postoperative day with a cut-off value of 7.0 ng/ml. Data will be collected daily for seven days, which including baseline data, perioperative data and outcomes. The primary endpoint is incidence of moderate to severe ARDS, which is diagnosed according to the Berlin definition.

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

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

Introduction

Epidemiological studies have shown that cardiac surgery is a known risk factor for acute respiratory distress syndrome (ARDS).[1-3] There are more than 300,000 patients who undergo cardiac surgery every year in the United States, as many as 20% will have ARDS.[4] The risk factors include the type of surgery, cardiopulmonary bypass, ischemia-reperfusion injury, transfusion-related acute lung injury and drug toxicity. The mortality rate associated with ARDS is approximately 40% in the general population, but much higher among post–cardiac surgery patients, which may be as high as 80%.[5 6] Moderate to severe ARDS causes the majority of death cases, and the possible therapeutic choices are different in different severity of ARDS. Mild ARDS patients usually need non-invasive treatments, while moderate to severe ARDS patients are more likely in need of more aggressive interventions such as prone positioning, recruitment maneuver, neuromuscular blockage agents, inhaled nitric oxide, high frequency oscillatory ventilation and even extracorporeal membrane oxygenation. It is meaningful to identify patients with moderate to severe ARDS.

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).[7] The possible causes are the exposure of blood to non-physiological surfaces, ischemia-reperfusion injury due to aortic clamping and extracorporeal circulation,[8] as well as a translocation of endotoxins from gut to the bloodstream after the release of the aortic clamp,[9] which can activate inflammatory cascades similar to those observed in sepsis. Cytokines such as interleukin (IL)-6, IL-8, tumor

necrosis factor (TNF)-alpha as well as C-reactive protein (CRP), lipoprotein-binding protein (LBP) and procalcitonin (PCT) may play an important role in the immune reaction, while PCT liberation is predominantly depended on the use of CPB.[10]

PCT is initially described as an early, sensitive and specific marker for sepsis associated with bacterial infection.[11] However, it is also increased in clinical situations without infections such as major surgery, burns, or trauma.[12] Previous studies suggested that the concentration of serum PCT increased at the end of CPB, reaching its peak on the first day and then declined rapidly.[7 13] It is also suggested that significant elevation of PCT level can be observed when complications presented.[7 14 15] Therefore, we hypothesis that PCT could be a predictor of the development of ARDS, especially moderate to severe ARDS, in patients undergo cardiac surgery with CPB. Our aim is to validate that whether patients with different serum PCT concentration have different incidence of developing moderate to severe ARDS.

Methods and analysis

Study design overview

The present study is a prospective, single center, observational cohort study in patients after elective cardiac surgery.

Study setting and population

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

All patients admitted to the cardiosurgery department who are programmed for a cardiac surgery under CPB are screened for study eligibility.

Inclusion criteria are:

1) Age 18 years and above;
2) Programmed cardiac surgery under CPB;
3) Be free from active preoperative infection or inflammatory disease (meet all of the following criteria at study entry: leukocyte count < $12*10^9$/L, PCT < 0.5 ng/ml, body temperature < 37.5°C);
4) Able to consent.

Exclusion criteria are:

1) History of chronic obstructive pulmonary disease (COPD), asthma or interstitial lung disease (ILD);

2) History of lung surgery;

3) Pregnant or lactating women;

4) Unwillingness of the patient to provide consent;

5) Enrolled in another trial.

Anesthesia, CPB and perioperative management

All patients' cardiosurgery undergo with general anesthesia and median sternotomy. Anticoagulation is obtained by using sodium heparin at a dose of 3 mg/kg for CPB patients. After attaining an activating clotting time (ACT) greater than 480 seconds, CPB is initiated by using an occlusive roller pump (jostra, Germany) and a membrane oxygenator (affinity7000, American), followed with moderate hypothermia (28□) and crystalloid cardioplegic cardiac arrest. Pump flow is about 2.0-2.6 l/min/m^2 during CPB and the mean arterial pressure (MAP) is maintained between 60 and 80 mmHg. At the end of surgery, protamine is given at a 1:1 ratio for reversal of the heparin effect (to obtain an ACT < 160s). The ventilator is initially set to deliver a tidal volume around 7-10 ml/kg and a respiratory rate adjusted to maintain an arterial CO_2 pressure ($PaCO_2$) between 35 and 40 mmHg during the surgery. Cephazolin is used as perioperative antibiotic prophylaxis. Patients are monitored postoperatively in the ICU and ventilated until they meet the following criteria:

1) Awake and cooperative;

2) Adequate recovery of muscle strength;

3) Normal tidal volume, normocapnia (end-tidal carbon dioxide 30-45 mmHg),

minimum pulse oxygen saturation (SpO_2) ≥ 95% with fraction of inspiration oxygen (FiO_2) 0.5;

4) Hemodynamic 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.

Patients' endotracheal tube is removed if they meet the criteria. Patients are discharged from ICU after successful extubation. In our clinical practice, blood samples are routinely obtained for test of whole blood routine before and 1 day after operation, respectively. PCT is also tested before and 1 day after operation. N-terminal pro-B-type natriuretic peptide (Nt-pro-BNP) and CRP are tested 1 day after operation. Chest X-ray is routinely obtained before operation, 1 day and 7 days after operation, respectively. Additional chest X-ray examinations are performed if patients represent hypoxia due to suspicious infection, pulmonary atelectasis, pleural effusion or ARDS. Blood gas analysis is tested at least once per day when the patients are in the ICU. After they are transferred to the routine room, blood gas analysis is tested when the physicians considered it is necessary, or when patients' SpO_2 cannot be maintained greater than 95% with a FiO_2 of 0.5.

Follow up and data collection

This is an observational study that no intervention is applied. At study entry, data on demographic, history of smoking, history of past illness characteristics, diagnosis and

the New York Heart Association (NYHA) functional classification [16] are collected. Type of surgery, duration of operation, CPB and aortic clamping and net fluid balance during the operation are recorded. The concentration of serum CRP, Nt-pro-BNP and PCT level on the first postoperative day are also recorded. Patients are assigned to the PCT elevated cohort or control cohort according to serum PCT concentration on the first postoperative day with 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 (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 100 × norepinephrine dose (μg/kg/min) + 15 × milrinone dose (μg/kg/min) + 10000 × vasopressin dose (U/kg/min).[17] Data are collected until the seventh day after operation. ARDS is diagnosed according to the Berlin definition.[18] A checklist (Table 1) is used to assess the development of moderate to severe ARDS. Two physicians make the diagnosis independently. Only the patients who are diagnosed by both two physicians are considered with moderate to severe ARDS. Echocardiography or pulmonary artery catheter (PAC) is applied to exclude hydrostatic edema. Physicians who assess the development of ARDS are unaware of patients' PCT level.

Table 1 Checklist of ARDS

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Timing: Within 1 week of a known clinical insult or new or worsening respiratory symptoms	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Chest imaging: Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Origin of edema: Respiratory failure not fully explained by cardiac failure or fluid overload	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Oxygenation							
Mild: 200 mm Hg $<PaO_2/FiO_2 \leqslant$ 300 mm Hg with PEEP or CPAP$\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Moderate: 100 mm Hg $< PaO_2/FiO_2 \leqslant$ 200 mm Hg with PEEP $\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Severe: $PaO_2/FiO2 \leqslant$ 100 mm Hg with PEEP $\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Does the patient developed ARDS?	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Abbreviations: CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

PCT determination

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

Study endpoints

The primary endpoint is incidence of moderate to severe ARDS.

Secondary endpoints include:

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 is higher in the PCT elevated group than in the control group. Previous investigations showed the overall morbidity of moderate to severe ARDS was around 0.5%-2% of patients underwent cardiac surgery.[1-3] Our pilot study showed that the incidence could be as high as 15% in the patients with elevated PCT level. Using the Power and Sample Size Calculation program, we will need to investigate 64 exposure subjects and 64 control subjects to be able to reject the null hypothesis. The Type I error probability (α) with testing this null hypothesis is 0.05 and Type II error probability (β) is 0.2.

Statistical analysis

Baseline characteristics will be summarized by univariate analyses. Categorical variables will be presented as numbers and percentages, and analyzed by the χ^2-test. Continuous variables will be checked for normal distribution and presented as mean and standard deviation or median and inter-quartile range as appropriate. Comparison of continuous variables will be performed by using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. All tests of significance will be at the 5% significance level, and two-sided. Analyses are performed by using SPSS 19.0 (IBM Corporation, New York, USA).

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Results of the trial will be submitted to international peer reviewed journal. Results will also be presented at national and international conferences relevant to subject fields.

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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 blood cell (WBC) counts as well as N-terminal pro-B-type natriuretic peptide (Nt-pro-BNP), C-reactive protein (CRP) and procalcitonin (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 seven days. The primary endpoint 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).[1-3] Over 300,000 patients undergo cardiac surgery every year in the United States, and up to 20% will experience ARDS.[4] The risk factors include the type of surgery, cardiopulmonary bypass, ischemia-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 post–cardiac surgery patients. [5 6] 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. Mild ARDS patients typically only require non-invasive treatments, whereas moderate to severe ARDS patients 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).[7] The possible causes of SIRS include the exposure of blood to non-physiological surfaces, ischemia-reperfusion injury due to aortic clamping and extracorporeal circulation.[8] In addition, the translocation of gut endotoxins to the bloodstream after the release of the aortic clamp is another potential cause[9] that can

activate inflammatory cascades similar to those observed in sepsis. Cytokines, such as interleukin (IL)-6, IL-8, tumour necrosis factor (TNF)-alpha, and C-reactive protein (CRP), lipoprotein-binding protein (LBP) and procalcitonin (PCT) potentially play important roles in immune reactions, whereas PCT liberation is predominantly dependent upon the use of CPB.[10]

PCT is initially described as an early, sensitive and specific marker for sepsis associated with bacterial infection.[11] However, PCT levels are also increased in clinical situations not associated with infections, including major surgery, burns, or trauma.[12] Previous studies suggested that serum PCT concentrations increase at the end of CPB, peaking on the first day and then rapidly declining.[7 13] Data have suggested that significant increases in PCT levels are observed when complications present.[7 14 15] Therefore, we hypothesis 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 are 18 years of age and older;
2) Patients underwent cardiac surgery involving CPB;
3) Patients are free from active preoperative infection or inflammatory disease (all of the following criteria were achieved at study entry: leukocyte count < $12*10^9$/L, PCT < 0.5 ng/ml, body temperature < 37.5°C);
4) Patients are capable of providing consent.

The following exclusion criteria were used:

1) History of chronic obstructive pulmonary disease (COPD), asthma or interstitial lung disease (ILD);

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 of3 mg/kg sodium heparin. After attaining an activating clotting time (ACT) greater than 480 seconds, CPB is initiated by using an occlusive roller pump (Jostra, Germany) and a membrane oxygenator (Affinity7000, American) followed by moderate hypothermia (28℃) and crystalloid cardioplegic cardiac arrest. The pump flow is approximately 2.0-2.6 l/min/m^2 during CPB. The mean arterial pressure (MAP) is maintained at 60-80 mmHg. 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 mmHg 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 mmHg), and minimum pulse oxygen saturation (SpO_2) ≥ 95% with a fraction of inspiration oxygen (FiO_2) of 0.5;

4) Hemodynamic 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 [16] 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 (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 100 × norepinephrine dose (μg/kg/min) + 15 × milrinone dose (μg/kg/min) + 10000 × vasopressin dose (U/kg/min).[17] Data are collected until the seventh day after the operation. ARDS is diagnosed according to the Berlin definition. [18] 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.

Table 1 ARDS Checklist

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Timing: Within 1 week of a known clinical insult or new or worsening respiratory symptoms	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Chest imaging: Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Origin of oedema: Respiratory failure not fully explained by cardiac failure or fluid overload	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Oxygenation							
Mild: 200 mm Hg $<PaO_2/FiO_2 \leqslant$ 300 mm Hg with PEEP or CPAP$\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Moderate: 100 mm Hg $< PaO_2/FiO_2 \leqslant$ 200 mm Hg with PEEP $\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Severe: $PaO_2/FiO2 \leqslant$ 100 mm Hg with PEEP $\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Has the patient developed ARDS?	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Abbreviations: CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

PCT determination

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

Study endpoints

The primary endpoint is the incidence of moderate to severe ARDS.

The secondary endpoints 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.[1-3] 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 subjects and 64 control subjects must be investigated to be able to reject the null hypothesis. The type I error probability (α) for testing our null hypothesis is 0.05, and the type II error probability (β) is 0.2.

Statistical analysis

Baseline characteristics were summarised using univariate analyses. Categorical variables are presented as numbers and percentages and analysed using the χ^2-test. Continuous variables are assessed for normal distribution and presented as means and standard deviations or medians and inter-quartile ranges 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 August 7th, 2014 by the Institutional Review Board of Fujian Provincial Hospital. The study was registered on August 8th, 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 program 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 is 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 co-investigator 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.

Authors' contributions

HC and RGY participated in the study design and drafted the manuscript. ZBC participated in the study design. All authors edited the manuscript and read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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Procalcitonin as a predictor of moderate to severe acute respiratory distress syndrome ~~(ARDS)~~ after cardiac surgery with cardiopulmonary bypass ~~(CPB)~~: a study protocol for a prospective cohort study

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Word count: ~~1800~~1797

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 ~~validate that~~determine whether patients with different serum PCT concentrations~~have~~ exhibit different ~~incidence~~ rates of developing moderate to severe ARDS.

Methods and analysis: ~~The study~~This is a prospective, single ~~center~~centre, observational cohort study. All patients admitted to the cardiosurgery department ~~who are programmed~~ for ~~a~~ cardiac surgery with CPB ~~are~~ were screened for study eligibility. All eligible patients ~~will receive operation with~~received a CPB procedure. Blood samples ~~are~~ were obtained ~~for test of~~to determine white blood cell (WBC) counts as well as ~~,~~N-terminal pro-B-type natriuretic peptide (Nt-pro-BNP), C-reactive protein (CRP) and procalcitonin (PCT) levels. Patients ~~are~~ were assigned to the PCT elevated cohort or the control cohort ~~according to~~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, ~~will be~~were collected daily for seven days~~, which including baseline data, perioperative data and outcomes~~. The primary endpoint ~~is~~ was the incidence of moderate to severe ARDS, which ~~is~~ was diagnosed according to the Berlin definition.

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

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3) ~~Be~~ Patients are free from active preoperative infection or inflammatory disease (~~meet~~ all of the following criteria were achieved at study entry: leukocyte count < $12*10^9$/L, PCT < 0.5 ng/ml, body temperature < 37.5°C);
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1) History of chronic obstructive pulmonary disease (COPD), asthma or interstitial lung disease (ILD);

2) History of lung surgery;

3) Pregnant or lactating women;

4) ~~Unwillingness of the patient~~ Unwilling to provide consent;

5) Enrolled in another trial.

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All patients~~' cardiosurgery~~ undergo cardiosurgery with general ~~anesthesia~~anaesthesia~~and~~ via median sternotomy. Anticoagulation is ~~obtained by using~~promoted in CPB patients via the administration of~~sodium heparin at a dose of~~ 3 mg/kg sodium heparin~~for CPB patients~~. After attaining an activating clotting time (ACT) greater than 480 seconds, CPB is initiated by using an occlusive roller pump (~~jostra~~Jostra, Germany) and a membrane oxygenator (~~affinity7000~~Affinity7000, American)~~,~~ followed ~~with~~ by moderate hypothermia (28□) and crystalloid cardioplegic cardiac arrest. ~~Pump~~ The pump flow is ~~about 2~~approximately 2.0-2.6 l/min/m^2 during CPB~~, and the~~The mean arterial pressure (MAP) is maintained ~~between~~ at 60~~ and~~ 80 mmHg. At the end of surgery, protamine is ~~given~~ administered at a 1:1 ratio ~~for reversal of~~to reverse the heparin effect (to obtain an ACT <~~160s~~ 160 s). The ventilator is initially set to deliver a tidal volume ~~around 7~~approximately 7-10 ml/kg, and ~~a~~ the respiratory rate is adjusted to maintain an arterial CO_2 pressure ($PaCO_2$) ~~between~~ of 35~~ and~~ 40 mmHg during the surgery. Cephazolin is ~~used~~ administered as perioperative antibiotic prophylaxis. Patients are monitored postoperatively in the ICU and ~~ventilated~~ receive ventilation until ~~they meet~~ the following criteria are met:

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Table 1 ~~Checklist of~~ ARDSChecklist

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Timing: Within 1 week of a known clinical insult or new or worsening respiratory symptoms	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Chest imaging: Bilateral opacities not fully explained by effusions, lobar/lung collapse~~,~~ or nodules	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Origin of oedema: Respiratory failure not fully explained by cardiac failure or fluid overload	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Oxygenation							
Mild: 200 mm Hg $<PaO_2/FiO_2 \leqslant$ 300 mm Hg with PEEP or CPAP$\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Moderate: 100 mm Hg < $PaO_2/FiO_2 \leqslant$ 200 mm Hg with PEEP $\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
Severe: $PaO_2/FiO2 \leqslant$ 100 mm Hg with PEEP $\geqslant$5 cm H_2O	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
~~Does~~ Has the patient developed ARDS?	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Abbreviations: CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

PCT determination

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

Study endpoints

The primary endpoint is the incidence of moderate to severe ARDS.

~~Secondary~~ The secondary endpoints 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 ~~is higher~~to be increased in the PCT elevated group ~~than in~~compared with the control group. Previous investigations ~~showed~~ indicate the overall morbidity of moderate to severe ARDS was ~~around 0~~approximately 0.5%-2% of patients ~~underwent~~ undergoing cardiac surgery.[1-3] Our pilot study ~~showed~~ revealed that the incidence could be as high as 15% in ~~the~~ patients with elevated PCT levels. Using the Power and Sample Size Calculation program, ~~we will need to investigate~~ 64 exposure subjects and 64

control subjects must be investigated to be able to reject the null hypothesis. The ~~Type~~ type I error probability (α) ~~with~~ for testing ~~this~~ our null hypothesis is 0.05, and ~~Type~~ the type II error probability (β) is 0.2.

Statistical analysis

Baseline characteristics ~~will be~~were~~summarized~~ summarised ~~by~~ using univariate analyses. Categorical variables ~~will be~~are presented as numbers and percentages~~,~~ and ~~analyzed~~analysed~~by~~ using the χ^2-test. Continuous variables ~~will be checked~~are assessed for normal distribution and presented as means and standard deviations or medians and inter-quartile ranges as appropriate. ~~Comparison of c~~Continuous variables ~~will be performed by~~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 ~~will be~~were two sided and conducted at the 5% significance level~~, and two sided~~. Subgroup analysis ~~will be~~was performed to illustrate the ~~affection~~ effects of different types of surgery. Analyses are performed ~~by~~ using SPSS 19.0 (IBM Corporation, New York, USA).

Ethical aspects and informed consent

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

After patient~~'s~~eligibility for the study is confirmed, the study coordinator ~~will be~~is introduced to the family. The surgeon ~~will make sure~~ensures that the family ~~knows the credentials of~~ is aware of the study coordinator's credentials~~,~~ and ~~says~~ indicates that this ~~person~~ individual ~~is going to~~will discuss ~~a~~ the research program being conducted~~,~~ and that the patient is qualified to ~~do so~~participate. Every relevant aspect of the project ~~will be~~is described. The study coordinator ~~will stop~~ frequently~~,~~ pauses to ask if there are any questions~~,~~ and requests that the family repeat ~~back in their own words what is~~is the topic being discussed in their own words~~,~~ to ~~make sure~~ensure that they understand. The study coordinator ~~will be~~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 ~~impact on~~impacting treatment. Family members ~~will be~~are provided ~~with~~ contact information for the study coordinator, local co-investigator and the local Ethical Committee. Written consent ~~will be~~is obtained in the presence of a witness.

Dissemination plan

~~Results of the~~The study results will be submitted to an international peer reviewed journal. Results will also be presented at national and international conferences

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relevant to the subject fields. We will also consider ~~disseminate~~ disseminating the results to the participants.

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Authors' contributions

HC and RGY participated in the ~~design of the~~ study design and drafted the manuscript. ZBC participated in the ~~design of the~~ study design. All authors edited the manuscript and read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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