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Incidence of reexpansion pulmonary edema in minimally invasive cardiac surgery

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ABSTRACT

Minimally invasive cardiac surgery requires fewer blood transfusions and mediastinitis is less frequently observed compared to conventional median sternotomy surgical intervention, and it leads to earlier recovery and discharge. However, once reexpansion pulmonary edema occurs, the patient requires long-term management in the intensive care unit. This retrospective study was performed to investigate the incidence of reexpansion pulmonary edema in minimally invasive cardiac surgery. Patients who underwent minimally invasive cardiac valve surgery using cardiopulmonary bypass and port-access by a minimal right lateral thoracic incision between January 2010 and January 2018 were enrolled in this single-center retrospective study, which was approved by the institutional review board of Japanese Red Cross Nagoya Daiichi Hospital (Nagoya, Japan), and the requirement for written informed consent was waived. All data were collected from electronic charts. The primary outcome was the incidence rate of reexpansion pulmonary edema in patients undergoing minimally invasive cardiac surgery. A total of 662 patients underwent minimally invasive cardiac surgery, and we analyzed 651 of these cases. No case of reexpansion pulmonary edema was observed in this study. The statistically-calculated incidence rate of reexpansion pulmonary edema was less than 0.6% (95% confidence interval: 0.0–0.6). The incidence of cerebral infarction was 0.92% (n = 6). Intensive care unit stay days, hospital stay days after surgery, and the death rate after 30 days were 1.5 ± 2.0 days, 9.6 ± 3.9 days, and 0.15%, respectively. Although there was no incidence of clinical reexpansion pulmonary edema in this study, the predicted incidence of reexpansion pulmonary edema by statistical analysis was less than 0.6%.

Keywords: reexpansion pulmonary edema, minimally invasive cardiac surgery, retrospective study, incidence

Abbreviations:
MICS: Minimally invasive cardiac surgery
RPE: reexpansion pulmonary edema
ICU: intensive care unit
CPB: cardiopulmonary bypass
GA: general anesthesia

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INTRODUCTION

Recently, port-accessed cardiac valve surgery using a thoracoscope has assumed a central role in minimally invasive cardiac surgery (MICS) for cardiac valve surgery interventions. MICS is beneficial for patients, as it requires fewer blood transfusions and mediastinitis is less frequently observed compared to conventional median sternotomy surgical intervention, and it leads to earlier recovery and discharge. However, these benefits are negated if there are complications. Cerebral infarction is a well-known serious complication of MICS.[1] Reexpansion pulmonary edema (RPE) is also a severe complication of MICS. Once RPE occurs, the patient is forced to undergo long-term management in the intensive care unit (ICU). Some patients with RPE may require extracorporeal membrane oxygenation.[2-4] Prevention of complications is very important in anesthesia management. RPE remains a rare and potentially harmful complication that occurs when a collapsed lung is reexpanded during treatment of conditions such as hemopneumothorax and large pleural effusion after single lung ventilation.[5,6] We have considered the optimal method to prevent RPE to be hypothermia cardiopulmonary bypass (CPB) since we started performing MICS in our institution, and we have routinely used mild-hypothermic CPB to prevent reperfusion lung injury during MICS. In this retrospective study, we aimed to investigate the incidence of RPE in MICS.

METHODS

Study Population

This single-center retrospective study was approved by the institutional review board of Japanese Red Cross Nagoya Daiichi Hospital (Nagoya, Japan), and the requirement for written informed consent was waived by the institutional review board. Patients who underwent minimally invasive cardiac valve surgery using CPB and port-access by a minimal right lateral thoracic incision between January 2010 and January 2018 were enrolled in the study regardless of whether the surgery was elective or emergent in nature.

Primary Outcome

Our primary outcome was the incidence rate of RPE in patients undergoing MICS. The primary outcome was determined from some symptom and the chest radiograph after surgery intervention until leaving the ICU. We did not include asymptomatic or uneventful cases with ambiguous unilateral changes. We examined all chest radiographs after surgical intervention until the patients were discharged from the ICU, a chest radiograph just after surgery intervention, while some chest radiographs were substituted; these were routine chest radiographs acquired every morning. Chest radiographs were independently reviewed by two reviewers (TT, SY). Radiographs were deemed positive or negative for the primary outcome when there was initial agreement between both reviewers. When the reviewers disagreed, the primary outcome was adjudicated by consensus during a second review conducted by three reviewers (TT, SY, SI).

RPE in MICS typically presents soon—min to h—after the surgical intervention, according to some reports.[2-4] The clinical course varies from isolated radiographic changes to complete cardiopulmonary collapse; in addition, most patients present with acute-onset hypoxemia. In addition, when an abnormal unilateral shadow was observed on chest radiography due to pulmonary

atelectasis, it was improved by bronchoscopic aspiration. Therefore, we deduced that pulmonary atelectasis was excluded by improvement with bronchoscopy.

General Anesthesia Procedure

Standard (noninvasive arterial blood pressure, electrocardiography, and pulse oximetry) and bispectral index monitoring were performed. After placement of a radial artery cannula for blood pressure monitoring and sampling, general anesthesia (GA) was induced in all patients. Fentanyl (Janssen Pharmaceutical K.K., Tokyo, Japan) and midazolam (Sandoz K.K., Tokyo, Japan) were administered intravenously to induce GA. Remifentanil (Ultiva; Janssen Pharmaceutical K.K.) and rocuronium (MSD K.K., Tokyo, Japan) were additionally used to facilitate tracheal intubation. A double-lumen tube (Covidien Japan Inc., Tokyo, Japan) or an intubation tube (Japan Medicalnext Co., Ltd., Tokyo, Japan) with a tracheal blocker (Daiken Medical Co., Ltd., Osaka, Japan) was used for intubation. GA maintenance was performed using air, oxygen, remifentanil, and sevoflurane (1.0–1.5%; AbbVie GK, Tokyo, Japan) or propofol (Diprivan; AstraZeneca K.K, Osaka, Japan). After placing the patients in the left-partial lateral position, we began one-lung ventilation. At this time, GA maintenance was performed using air, oxygen, remifentanil 0.1–0.25 μg/kg/min, and propofol 1.0–2.5 μg/ml (TE-371 target-controlled infusion pump; Terumo K.K., Tokyo, Japan) or sevoflurane. After starting CPB, GA maintenance was performed using remifentanil (0.1–0.25 μg/kg/min) and propofol (1.0–2.5 μg/ml) or diazepam (10 mg; Horizon injection; Maruishi K.K., Osaka, Japan). Before ending CPB, GA maintenance was performed using remifentanil (0.1–0.25 μg/kg/min) and propofol. The bispectral index was maintained at the target value of 40–60. Ventilation of both lungs was started before ending CPB. CPB was terminated with inotropic drug support, and the patient was admitted to the ICU with intubation. The following parameters were decided by each anesthesiologist: intraoperative positive end-expiratory pressure for the left lung, infusion volume, blood transfusion (hemoglobin level was maintained above 8 g/mL during surgery), anesthesia method (gas or propofol), choice of vasopressor (dopamine, dobutamine, or noradrenaline), choice of intubation tube (double-tumen tube or normal tube with bronchial blocker), intravascular volume when ending CPB, positive end-expiratory pressure for the right lung during surgery, steroid injection during surgery,[2,7] neutrophil elastase inhibitor injection during surgery (sivelestat sodium hydrate [Elaspol; Ono Pharmaceutical Co., Ltd., Osaka, Japan]),[8] and intermittent bilateral lung inflation during surgery.[3]

CPB Procedure

The CPB procedures were the same in all cases; size-adapted bypass circuits and membrane oxygenators were used. The total bypass circuit priming volume was 1,557 mL, including extracorporeal ultrafiltration circuit with dextran, lactated Ringer's solution, mannitol, heparin, and potassium chloride. A 16 Fr vein catheter for CPB was inserted via the femoral vein, an artery cannula was inserted via the ascending aorta, the vent cannula was inserted via the right pulmonary vein, and an antegrade cardioplegia cannula was inserted via the ascending aorta. Porcine heparin 300 U/kg (Heparin Sodium Injection; AY Pharmaceutical Co., Ltd., Tokyo, Japan) was administered before starting cannulation for CPB, and 50 U/kg additional heparin boluses were administered to maintain an activated clotting time of at least 400 s. Mild hypothermic CPB was performed at 32°C with the pump flow rate at 2.2 L/min/m^2 body surface area in all cases. Noninvasive organ saturation monitoring (NIRO-200NX; Hamamatsu Photonics K.K., Hamamatsu, Japan) was performed on the right leg as an index of limb ischemia; if the monitor indicated low saturation, CPB blood temperature was lowered to 30°C. Protamine 3 mg/kg (Protamine Sulfate; Mochida Pharmaceutical Co., Ltd., Tokyo, Japan) was administered to antagonize the heparin effect. We used an intraoperative cell salvage device (Cell Saver 5; Haemonetics, Braintree,

MA) in all cases, and red blood cell concentrates were transfused to maintain hemoglobin over 8 mg/dL during CPB.

Statistical Analysis

All data were collected from electronic charts. To estimate the incidence rate of RPE in patients undergoing MICS, an exact 95% binomial confidence interval (CI) was calculated as "Clopper Person Exact Confidence Interval Formula".[9,10] All data were analyzed using SAS version 9.4 software (SAS Institute Inc., Cary, NC).

RESULTS

Between January 2010 and January 2018, 662 patients underwent MICS. Patients who underwent beating-heart surgery and those who underwent median sternotomy were excluded from the study. We analyzed a total of 651 MICS cases. Patient characteristics, surgical results, and anesthesia results are presented in Table 1. No RPE cases were noted during the study period; hence it was not possible to statistically compare RPE with non-RPE cases. However, we used a statistical method to estimate the incidence rate of RPE; an exact 95% binomial confidence interval was calculated.[9,10] As a result, the statistically calculated incidence rate of RPE was lower than 0.6% (95% confidence interval: 0.0–0.6). The following secondary outcomes were also evaluated (Table 2). The incidence of cerebral infarction was 0.92% (n = 6). The cerebral infarctions were mild, and the patients could be discharged from our hospital after rehabilitation. ICU stay days, hospital stay days after surgery, and the death rate after 30 days were 1.5 ± 2.0 days, 9.6 ± 3.9 days, and 0.15%, respectively.

Table 1 Demographic, Surgical, and Anesthesia Characteristics

Variable (n = 651)	Mean ± SD or %	Median (IQR)
Demographic information		
Age (years)	64.2 ± 16.3	67 (55–77)
Height (cm)	160.6 ± 37.1	158 (150–166)
Body weight (kg)	55.3 ± 12.2	53 (46–62)
Body mass index (kg/m^2)	21.8 ± 4.2	21 (19–24)
Male:female (%)	43:57:00	
Surgical information		
AVR (%)	28.9	—
AVR+MV and/or TV (%)*	3.4	—
AVR+α (%)**	1.4	—
MVR or MVP (%)	42.7	—
MV+TV or + α (%)**	20	—
TV or TV + α (%)**	1.4	—
ASD or VSD (%)	1.5	—
Tumor (%)	0.8	—
CPB information		
Duration of surgery intervention (min)	230.8 ± 66.5	217 (184–267)
Duration of CPB (min)	155.6 ± 50.4	143 (119–182)

Duration of aortic clamp (min)	109.1 ± 41.8	103 (81–134)
Anesthesia information		
Duration of anesthesia (min)***	332.8 ± 65.2	321 (287–370)
Duration of one-lung ventilation (min)	201.1 ± 62.1	189 (156–235)
PEEP during CPB (%)	35.1	—
PEEP for right lung (%)	0	—
PEEP for left lung (%)	35.1	—
PEEP pressure (mmHg)	7–10†	—
Non-PEEP during CPB (%)	64.9	—
Intermittent bilateral lung inflation during CPB (%)	0	—
Both lungs ventilation on leaving CPB (%)	100	—
Ventilation tidal volume in bi-lung (mL/kg)	6–10†	—
Ventilation tidal volume in one-lung (mL/kg)	5–8†	—
Only TIVA (%)	63.4	—
Inhalation + TIVA (%)	36.6	—
Double-lumen tube (%)	38.4	—
Single tube with bronchial blocker (%)	61.6	—
Total fluid balance (mL)	1836.1 ± 1252.7	1863 (1183–2561)
Total CPB balance (mL)	1069.3 ± 1219.7	1080 (500–1700)
Cell Saver balance (mL)	453.4 ± 326.4	400 (200–650)
Prophylaxis		
Carperitide (%)	6.4	—
Nitroglycerin (%)	8.9	—
Steroid (%)	0	—
Sivelestat sodium hydrate (%)	0	—
Additional perioperative data		
RBC in OR (U)	1.09 ± 2.04	—
FFP in OR (U)	0.44 ±1.86	—
PC in OR (U)	0.37 ± 2.58	—
RBC in ICU (U)	0.31 ± 1.18	—
FFP in ICU (U)	0.34 ± 1.51	—
PC in ICU (U)	0.28 ± 2.34	—
ICU stay days	1.5 ± 2.0	—
Hospital days after surgery	9.6 ± 3.9	8 (7–10)

Data are expressed as means ± SDs or percent (n = 651) and as medians and 25th–75th percentiles (IQR).

*MV includes MVR and MVP, and TV includes TVR and TVP.

**The α includes including maze surgery and/or left atrial appendectomy.

***Time from the initiation of oxygenation to leaving the OR.

†setting range.

ASD: atrial septal defect; AVR: aortic valve replacement; CPB: cardiopulmonary bypass; FFP: fresh frozen plasma; ICU: intensive care unit; IQR: interquartile range; MV: mitral valve; MVP: mitral valve plasty; MVR: mitral valve replacement; OR: operating room; PC: platelet concentrates; PEEP: positive end-expiratory pressure; RBC: red blood cell; SD: standard deviation; TIVA: total intravenous anesthesia; TV: tricuspid valve; TVP: tricuspid valve plasty; TVR: tricuspid valve replacement; U: unit; VSD: ventricular septal defect.

Table 2 Complications

Variable (n = 651)	%	Median (IQR)
Prolonged ventilation > 72 h	0.15	—
Extubation impossibility due to hypoxemia	0	—
Noninvasive positive pressure ventilation	0.46*	—
Reintubation after extubation	0	—
Cerebral infarction	0.92	—
Reoperation for bleeding	1.08	—
Renal failure	0	—
Perioperative myocardial infarction	0	—
Heart block	0	—
Pulmonary embolism	0	—
Thirty-day death rate	0.15	—
In-hospital death rate	0.15	—

*butterfly shadow due to cardiac failure; all were urgent, non-controlled cardiac failure and infective endocarditis cases.
IQR: interquartile range; RPE: reexpansion pulmonary edema

DISCUSSION

MICS offers considerable benefits for patients. However, these benefits often disappear when complications occur. RPE is not a frequent complication during the perioperative period,[2,11] but it can sometimes lead to severe breathing management problems. Hence, RPE has a significant impact on postoperative management. Recently, Keyl et al reported that among 484 patients, 1.5% developed clinical symptoms.[7] Yamashiro et al also reported an incidence of 5.0%.[8] Tutschka et al reported that RPE after MICS is common with an incidence higher than 25%.[11] Our current retrospective study showed that the incidence rate of RPE was lower than that previously reported. In addition, postoperative data such as ICU stay days were also better compared to those reported by previous studies.

We considered that symptomatic RPE occurring after MICS is relatively rare. The pathophysiologic mechanism of RPE is unknown and considered to involve ischemia-reperfusion injury.[12] Funakoshi and colleagues reported that only inflammatory cytokine levels increase in the short period after lung collapse.[13] Alterations in pulmonary capillary permeability and pro-inflammatory cytokine gene expression have been observed in isolated rabbit lungs.[12] Madershahian and colleagues reported that RPE led to alveolar membrane damage and cytokine production at the time of ischemic-reperfusion injury.[5] In addition, some reports have indicated that the causes of RPE also include mechanical stress disorder, microvascular endothelial dysfunction, vascular hyperpermeability, and the production of the free radicals due to reperfusion.[14-18]

There are no proven methods for preventing RPE; however, some precautionary methods have been attempted, based on suspected mechanisms. The length of CPB and surgery duration are related to vascular hyperpermeability. Therefore, shortening the duration of CPB and of the surgery may constitute necessary precautions to avoid RPE. Hypothermia reduces free radical reactions, stabilizes the cell membrane, and decreases inflammatory reactions.[19-21] Therefore, mild hypothermia during CPB suppresses immune responses leading to RPE, including reperfusion disorder and free radical production. Shortening the duration of one-lung ventilation to the greatest

possible extent is also important, and it can be achieved by shortening the duration of surgery and using our anesthesia procedure.

Some precautionary measures include steroid bolus injection before CPB,[2] continuous injection of sivelestat sodium hydrate,[8] administration of diuretic drugs during CPB (unreported precaution), and positive end-expiratory pressure for the right lung (unreported precaution). Some case reports have suggested that excessive volume may cause RPE, so use of diuretic drugs and application of fluid therapy may affect the results. In addition, use of positive end-expiratory pressure for the right lung during CPB and shortening the duration of one-lung ventilation may have also played a role in RPE prevention. In our cases, neither steroid bolus injection before CPB nor continuous injection of sivelestat sodium were routinely employed. Furthermore, diuretic drug administration and positive end-expiratory pressure for the right lung during CPB were not routinely employed. Considering all reported potential factors in RPE development and our current retrospective study, we consider that effective precautionary measures may be related to the prevention of RPE: mild hypothermic CPB and shortening the duration of surgical intervention. GA procedures such as type of anesthesia drugs and of the intubation tube appear to be unrelated to RPE.

Table 3 Suggestions for effective precautionary measures to prevent RPE

(a) Mild hypothermic CPB
Mild hypothermic CPB (32°C) is always used for MICS.
(b) Shortening the duration of surgical intervention
Including shortening one-lung ventilation time, aorta clumping time, and CPB time.

CPB: cardiopulmonary bypass; MICS: minimally invasive cardiac surgery; RPE: reexpansion pulmonary edema

This study has some limitations that should be addressed. First, it was a single-center retrospective analysis. Second, as no RPE cases were noted during the study period, we could not statistically compare RPE and non-RPE cases. Our GA and surgical techniques may include precautionary procedures, and mild RPE cases without postoperative hypoxemia may not have been included in this study. However, this study can be used as a reference for the low incidence rate of RPE and the possible unnecessary use of conventional drug-based precautionary procedures. In addition, both the length of surgery and the appropriate volume of fluid therapy observed in this study should be noted. However, we were unable to study the influence of high-volume fluid therapy, including massive blood transfusions, because blood transfusions were not routinely used. Further studies are necessary to evaluate different surgical procedures and GA methods and to explore factors contributing to prevention or occurrence of RPE.

In conclusion, this study found no occurrence of RPE following MICS among the 651 investigated cases. Inclusion of mild hypothermic CPB and short surgical intervention times without prophylactic drugs in MICS procedures may prevent the occurrence of RPE.

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DISCLOSURE STATEMENT

None of the authors has any conflicts of interest to declare in relation to this work.

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