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Review Article

Acute Respiratory Distress Syndrome in the Perioperative Period of Cardiac Surgery: Predictors, Diagnosis, Prognosis, Management Options, and Future Directions

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Acute respiratory distress syndrome (ARDS) after cardiac surgery is reported with a widely variable incidence (from 0.4%-8.1%). Cardiac surgery patients usually are affected by several comorbidities, and the development of ARDS significantly affects their prognosis. Herein, evidence regarding the current knowledge in the field of ARDS in cardiac surgery is summarized and is followed by a discussion on therapeutic strategies, with consideration of the peculiar aspects of ARDS after cardiac surgery.

Prevention of lung injury during and after cardiac surgery remains pivotal. Blood product transfusions should be limited to minimize the risk, among others, of lung injury. Open lung ventilation strategy (ventilation during cardiopulmonary bypass, recruitment maneuvers, and the use of moderate positive end-expiratory pressure) has not shown clear benefits on clinical outcomes. Clinicians in the intraoperative and postoperative ventilatory settings carefully should consider the effect of mechanical ventilation on cardiac function (in particular the right ventricle). Driving pressure should be kept as low as possible, with low tidal volumes (on predicted body weight) and optimal positive end-expiratory pressure.

Regarding the therapeutic options, management of ARDS after cardiac surgery challenges the common approach. For instance, prone positioning may not be easily applicable after cardiac surgery. In patients who develop ARDS after cardiac surgery, extracorporeal techniques may be a valid choice in experienced hands. The use of neuromuscular blockade and inhaled nitric oxide can be considered on a case-by-case basis, whereas the use of aggressive lung recruitment and oscillatory ventilation should be discouraged.

Key Words: acute lung injury; postoperative pulmonary complications; pneumonia; cardiac anesthesia; critical care; intensive care

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ACUTE respiratory distress syndrome (ARDS) is a cause of high morbidity and mortality. Data from the observational, international, multicenter prospective cohort study LUNG SAFE (Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE)[1] showed a mortality as high as 46% for the severe forms of ARDS. The current Berlin definition of ARDS[2] describes the syndrome in terms of acute onset with bilateral lung opacities not explained by cardiac failure and/or fluid overload (Table 1). However, in patients who develop ARDS after cardiac surgery, it is challenging to exclude a cardiac contribution to the deterioration in gas exchange. It is likely that ARDS after cardiac surgery potentially has a worse prognosis compared with ARDS from other causes because cardiac patients are by definition affected by a significant burden of cardiovascular (and potentially by several other) comorbidities. Moreover, the occurrence of ARDS after cardiac surgery is relatively common, and its management presents a challenge because therapeutic options used for conventional ARDS patients (eg, prone positioning) may not be easily applicable after cardiac surgery. For such reasons, ARDS in cardiac surgery deserves more characterization and clinical studies for clinicians to better understand its peculiar features and to identify the best strategies to improve patient outcomes. This review focuses on the current knowledge in the field of ARDS in cardiac surgery and gaps of knowledge and the available therapeutic options, with consideration of the peculiar aspects of ARDS in the cardiac patient in the postoperative period.

Current Knowledge and Gaps Regarding ARDS in Cardiac Surgery

For the present review, a simplified search on PubMed was conducted on September 19, 2020, using a combination of the following terms: "ARDS" and "cardiac surgery." The search was limited to articles with an abstract that focused on the adult population that were published in English. Fig 1 shows the findings of the simplified search. Although this search was not a proper systematic review (the topic of ARDS overlaps with postoperative pulmonary complications and other important key words), it confirmed the authors' preliminary hypothesis that postoperative ARDS after cardiac surgery has been underinvestigated and deserves more research.

Risk Factors and Incidence for Postoperative ARDS

The current Berlin definition[2] provides a list of 13 risk factors associated with with the diagnosis of ARDS (see Table 1). However, the list does not include high-risk surgical patients, despite the fact that this risk has been well-described in the literature. A secondary analysis of a multicenter cohort study on high-risk surgical patients (1,562 patients, of whom 480 [30.7% of the cohort] underwent cardiac surgery) reported a 7.5% incidence of postoperative ARDS.[3] The authors of that analysis identified the following nine independent predictors of postoperative ARDS: sepsis, high-risk aortic vascular surgery, high-risk cardiac surgery, emergency surgery, cirrhosis, admission from other than home, increased respiratory rate, fraction of inspired oxygen (FIO_2) >35%, and oxygen saturation <95%. It remains challenging to identify which features are correlated with such risk because only a limited number of clinical studies have reported data in this regard.[4-9] It seems that preexisting cardiorespiratory conditions are the main contributors to the risk of postoperative ARDS, together with occurrence of multiple transfusions.[7-9] However, drawing conclusions from these studies is challenging because they included patients with heterogeneous clinical characteristics; reported data on small populations (12-108 patients, average 41) with a widely variable incidence of postoperative ARDS (0.4%-8.1%[4-9]); adopted different diagnostic criteria; and were published over a 20-year period (1996-2016). A recent large retrospective study (3,946 patients, ARDS incidence 1.15%), in which multivariate regression analysis was performed, identified the following predictors of postoperative ARDS: prior and/or emergency and/or complex cardiac surgery (the latter defined as concomitant coronary artery grafting and valve surgery or multiple valve surgery) and transfusion of >three red blood cell (RBC) units.[10] Another recent study reported greater

Table 1
ARDS Definition Task Force

Berlin Definition of Acute Respiratory Distress Syndrome According to the Task Force			
Diagnostic criteria	1. Onset within 1 wk of a known clinical insult or new/worsening respiratory symptoms 2. Bilateral opacities (on CXR or CT scan) not fully explained by effusions, lobar/lung collapse, or nodules 3. Respiratory failure not fully explained by cardiac failure or fluid overload		
Oxygenation impairment*	Mild	Moderate	Severe
	$200 < PaO_2/FiO_2 \leq 300$	$100 < PaO_2/FiO_2 \leq 200$	$PaO_2/FiO_2 \leq 100$
Common risk factors for ARDS	Pneumonia, non-pulmonary sepsis, aspiration of gastric contents, major trauma, pulmonary contusion, noncardiogenic shock, inhalation injury, severe burns, pancreatitis, drug overdose, multiple transfusions or TRALI, pulmonary vasculitis, drowning		

NOTE. Diagnostic criteria take into account the timing of onset, the imaging, and the origin of pulmonary edema.
Abbreviations: ARDS, acute respiratory distress syndrome; CT, computed tomography; CXR, chest x-ray; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; TRALI, transfusions-related acute lung injury.
* A minimum level of 5 cmH_2O of positive end-expiratory pressure is delivered (continuous positive airway pressure may be applied noninvasively for mild ARDS cases).Adapted from Ferguson et al.[3]

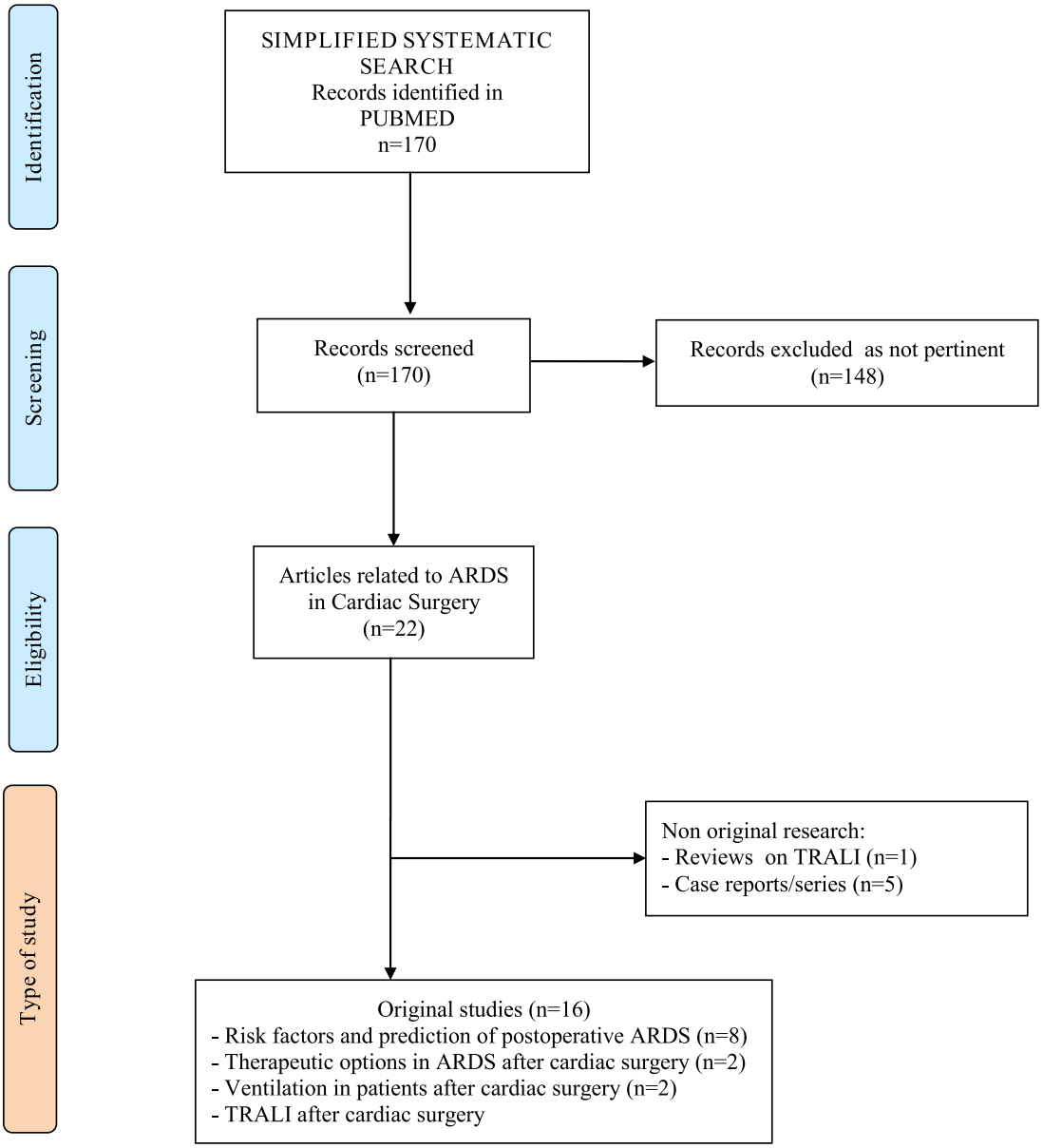

Fig 1. Modified PRISMA flowchart of the simplified systematic search conducted on acute respiratory distress syndrome after cardiac surgery. ARDS, acute respiratory distress syndrome; TRALI, transfusion-related acute lung injury.

postoperative ARDS incidence in patients undergoing type A aortic dissection repair (15.9%), but no preoperative risk factors were identified.[11] More research is needed to characterize the risk factors for ARDS after cardiac surgery and strategies to decrease its incidence.

The Challenge of ARDS Diagnosis in the Context of Cardiac Surgery

For patients who develop ARDS after cardiac surgery, the evaluation of the origin of pulmonary edema becomes extremely challenging because of the presence of preexisting cardiopulmonary comorbidities. In most cardiac patients, the development of ARDS probably is multifactorial from its beginning, and the presence of preexisting cardiac dysfunction theoretically aggravates the degree of pulmonary edema in patients who develop ARDS; thus, it is possible that mild injuries potentially result in moderate/severe forms of ARDS. Of note, the authors of the Berlin definition[2] removed the criteria of pulmonary arterial wedge pressure (PAWP) based on the observation that a nonnegligible number of patients admitted to the general intensive care unit (ICU) with ARDS demonstrated increased PAWP. For example, in a landmark randomized controlled trial (RCT),[12] almost one-third of ARDS patients assigned to management according to the data from the pulmonary artery catheter had PAWP values >18 mmHg. This finding reinforced how challenging it is to determine the extent of cardiac contribution to the pulmonary edema that develops in ARDS cases, even when the diagnosis is made by experienced clinicians under the strict criteria of an RCT. Interestingly, Kogan et al.[10] showed that the introduction of the Berlin definition[2] produced similar figures of ARDS

prevalence after cardiac surgery (1.15%) compared with the previous definition (1.14%). In summary, the postoperative period after cardiac surgery is a time of increased risk for the development of ARDS in a consistent proportion of patients. There are unique challenges in the diagnosis of ARDS after cardiac surgery because, in most patients, the contribution of cardiac dysfunction cannot be ruled out.

Reducing the Incidence of ARDS After Cardiac Surgery in Clinical Practice

Although patients with preoperative pulmonary disease and/or cardiac dysfunction may have a higher risk of developing ARDS, clinicians should keep in mind that these factors are not always modifiable. Pulmonary function is negatively affected by a wide spectrum of left ventricular (LV) comorbidities. Conditions such as left-sided heart valve diseases, low LV ejection fraction, and advanced LV diastolic dysfunction all cause an increase of LV end-diastolic pressures and poor LV compliance, with backwards reflection on the lungs. Conversely, there are modifiable factors in the intraoperative and postoperative periods that can be optimized to help minimize the risk of ARDS development. Direct surgical injury[13] (eg, pleural opening and use of retractors and lung manipulation) and the use of cardiopulmonary bypass (CPB)[14] commonly are encountered as intraoperative factors that trigger inflammation at the pulmonary level. In parallel, both surgical and perfusion strategies to decrease perioperative lung damage have been developed (eg, minimally invasive surgery[15] and use of miniaturized CPB circuits[16]). From the perspectives of cardiac anesthesiologists and intensivists, there are some key aspects that may contribute to the reduction of the incidence of postoperative ARDS after cardiac surgery (Table 2).[17-22] In particular, the following are discussed:

1. Optimization of mechanical ventilation (MV)
2. Limitation of transfusions of blood products
3. The hemodynamic effect of MV (focusing on right ventricular [RV] function)

Table 2
Key Aspects to Limit the Incidence of ARDS After Cardiac Surgery: Perspectives of Cardiac Anesthesiologists and Intensivists

Optimize the MV settings	Prefer low TV (based on PBW) Determine the optimal PEEP Use the lowest possible driving pressure The role of open lung concept remains unclear
Limit transfusions of blood products	Reduce hemodilution Avoid fluid overload Implement bundles for blood product management Use point-of-care tests for coagulopathy and bleeding
Consider hemodynamic impact of MV on right ventricle	Significant strain on right ventricle may be not-well tolerated Avoid hypoxia, hypercarbia, acidosis (effects on PVR) Perform early echocardiography to evaluate RV function Establish timely hemodynamic support if needed

Abbreviations: ARDS, acute respiratory distress syndrome; MV, mechanical ventilation; PBW, predicted body weight; PEEP, positive end-expiratory pressure; PVR, pulmonary vascular resistance; RV, right ventricular; TV, tidal volume.

Optimize Mechanical Ventilation

Cardiac surgery patients often are exposed to risk factors for lung disease. History of smoking is common among these patients,[23] and conditions such as heart valve diseases and/or systolic or diastolic dysfunction may cause pulmonary venous congestion, thereby reducing the efficiency of the alveolar-capillary membrane. The use of small tidal volume (TV) is the "mantra" of ventilation of ARDS patients.[24] A meta-analysis suggested that the use of a lung-protective ventilation strategy with low TV also is associated with improved clinical outcomes among patients without ARDS[25]; however, the PReVENT (PRotective VENTilation in Patients Without ARDS) RCT showed that, in ICU patients without ARDS, a low TV strategy (4-6 mL/kg of predicted body weight) did not change the number of ventilator-free days compared with a high TV strategy (8-10 mL/kg).[26]

The literature regarding the optimal combination of TV and positive end-expiratory pressure (PEEP) in patients undergoing cardiac surgery seems limited. Few good quality studies (six RCTs)[17-22] have investigated the use of different combinations of TV and PEEP in patients undergoing cardiac surgery (see Table 3), but it is difficult to draw conclusions on the best TV and PEEP combination because these studies are relatively outdated, included small populations (25-149 patients, average 61) with variable settings, and mostly were focused on soft indicators (eg, changes in cytokines). Apart from these small and heterogeneous RCTs, a large observational study published in 2012 (3,434 cardiac surgery patients)[27] stratified the population into the following three groups according to the TV: $<$10 mL/kg, 10 to12 mL/kg, and $>$12 mL/kg. The authors found increased organ dysfunction and ICU length of stay in patients receiving greater TVs.

Another unique aspect in the management of MV in patients undergoing cardiac surgery is the use of an open-lung ventilation strategy, including the maintenance of MV during CPB along with recruitment maneuvers, and the use of greater PEEP levels (8 cm H_2O). In this regard, the recent PROVECS (Open Lung Protective Ventilation in Cardiac Surgery) RCT (488 patients) showed that an open-lung strategy does not reduce the incidence of postoperative pulmonary complications compared with usual care.[28] Moreover, in a prespecified subanalysis, the authors showed that although open lung ventilation improved dorsal ventilation in the short term, this benefit was not sustained and was associated with greater plasma biomarkers of epithelial lung injury, suggesting lung

Table 3
Randomized Controlled Studies Addressing the Combination of Tidal Volume and/or Positive End-Expiratory Pressure in Cardiac Surgery Patients

First Author, y	Number of Patients	TV (mL/Kg) + PEEP (cmH_2O)	Advantages of More Protective Ventilation Strategies
Sundar et al.,[17] 2011	149 CABG and/or valve and/or aortic surgery	6 mL/kg +>5 cmH_2O *v* 10 mL/kg +>5 cmH_2O	Higher proportion of patients extubated within 6 h; lower reintubation rate
Zupancich et al.,[18] 2005	40 CABG	8 mL/kg +10 cmH_2O *v* 10-12 mL/kg +2-3 cmH_2O	Lower IL-6 and IL-8 in BAL and serum
Reis Miranda et al.,[19] 2005	62 CABG and/or valve	4-6 mL/kg +10 cmH_2O* *v* 6-8 mL/kg +5 cmH_2O	Serum IL-8 and IL-10 decreased more rapidly
Wrigge et al.,[20] 2005	44 CABG	6 mL/kg + 9 cmH_2O *v* 12 mL/kg +7 cmH_2O	Lower TNF-α in BAL No differences in IL-6 and IL-8 in BAL and serum
Koner et al.,[21] 2004	44 CABG	6 mL/kg + 5 cmH_2O *v* 10 mL/kg + 5 cmH_2O *v* 10 mL/kg + 0 cmH_2O	Lower shunt and improved oxygenation, no differences in proinflammatory cytokine
Chaney et al.,[22] 2000	25 CABG	6 mL/kg + 5 cmH_2O *v* 12 mL/kg + 5 cmH_2O	Less impact on lung compliance and shunt

Abbreviations: BAL, bronchoalveolar lavage; CABG, coronary artery bypass grafting; I/E, Inspiratory-expiratory ratio; IL, interleukin; PEEP, positive end-expiratory pressure; TV, tidal volume.

* The low tidal volume group received ventilation at respiratory frequency of 40 min−1, PEEP of 10 cmH_2O, I/E ratio of 1:1, and lung recruitment maneuvers.

overdistention.[29] It is plausible that an open-lung strategy may cause lung distention under the intraoperative "open-chest" conditions and that alveolar recruitment already was maximized in the control group.

Driving pressure (difference between plateau airway pressure and PEEP) represents the most important factor associated with postoperative pulmonary complications after general anesthesia, as shown by a recent meta-analysis[30] and a post hoc propensity score−weighted analysis of the LAS VEGAS (Local Assessment of Ventilatory Management During General Anesthesia for Surgery) study.[31] This finding was not surprising because driving pressure is the best variable in stratifying the risk of mortality in ARDS patients.[32] It is difficult to technically determine what is the optimal driving pressure in cardiac surgery patients and eventually to determine the cutoff for greater risk of complications/mortality, especially during the intraoperative period under open-chest conditions (altered chest wall mechanics). Nonetheless, it seems sensible to keep the driving pressure as low as possible during the intraoperative and postoperative periods, with low TV (based on predicted body weight) and an optimal PEEP level (best profile from cardiopulmonary perspectives). The use of tables (or eventually of other tools, such as a mobile app) to calculate the correct TV should be encouraged. Although one size does not fit all, in the absence of contraindications, it could be reasonable to pursue this strategy perioperatively in all cardiac patients, irrespectively from their risk factors. A separate issue deserving more investigation in the near future is the use of one-lung ventilation (OLV), which is particularly needed during minimally invasive cardiac surgery. OLV represents a new challenge for the cardiac anesthesiologist, and evidence regarding the best intraoperative OLV management during cardiac surgery still is scarce.

Limiting Blood Product Transfusion

During the perioperative period of cardiac surgery, there is a very high prevalence of transfusion of blood products. Risk factors for transfusions can be related to preoperative (eg, preoperative anemia, emergency surgery, treatment with antiplatelets); intraoperative (eg, CPB-related coagulopathy, hypothermia); or postoperative conditions (eg, hemodilution, bleeding). Although some of these risk factors are not modifiable, others can be perioperatively optimized. For instance, management of preoperative anemia reduces RBC transfusion and adverse outcomes after cardiac surgery;[33] and a recent study highlighted the role of preoperative administration of intravenous iron (>600 mg) and/or high doses of epoetin alfa (>80,000 U). With such preoperative management the authors noted a significant increase in hemoglobin and a lower likelihood and number of transfusions.[34]

Transfusion-related acute lung injury (TRALI) is a serious complication of blood component transfusions, accompanied by increased morbidity and mortality. Its onset is usually within six hours from transfusion, and the pathophysiology is characterized by the combination of the following two events: a "first hit" associated with preexisting risk factors (eg, age, inflammation, exposure to foreign materials) and a "second hit" related to the transfused blood component.[35] This "second hit" may result in different degrees of damage depending on the number of transfusions, type of blood component, blood conservation age, use of female plasma donors, and presence of antibodies and active lipids in the plasma.[36] Unfortunately, the use of different definitions and diagnostic criteria for TRALI has led to a 100-fold variability in its reported incidence (from 0.08%-8% per transfused patient).[37,38] Recently, a consensus on TRALI was released[35] with separation into the following two categories: type 1 (occurring without predisposing risk factors) and type 2 (one or more risk factors or overt ARDS of mild degree). A specific role is ascribed to CPB because of contact with foreign materials, which triggers complement activation, release of proinflammatory cytokines, and leukocyte activation.[39] Such an inflammatory state may, in part, contribute to an increased alveolar-capillary membrane permeability. Within such a complex environment, it is

challenging to fully ascribe lung dysfunction after cardiac surgery to a single mechanism only, either TRALI or other forms of permeability edema. The hypothesis that more transfusions lead to worse pulmonary outcomes should be validated because the available results of RCTs conducted on different transfusion triggers do not fully support this hypothesis. Indeed, the TRACS trial[40] found that ARDS occurred in 1% of patients in the liberal transfusion group versus 2% in the restrictive group. Similarly, Koch et al. found a nonsignificant difference in the incidence of pulmonary morbidity in patients receiving RBC at a 28% hematocrit trigger (5.4%) compared with a 24% trigger (6.3%).[41] The TiTRE2 (Transfusion Indication Threshold Reduction) trial[42] observed pulmonary complications in 13% of patients in the restrictive transfusion group versus 12% in the liberal transfusion group. Finally, the TRICS trial[43] did not directly measure pulmonary-related outcomes; however, MV time was somewhat shorter in patients transfused at a liberal threshold ($p = 0.05$). Nonetheless, it must be emphasized that these observations are limited to the effect of RBC transfusions but are not extended to transfusions of other components (plasma and platelets). Maneuvers aimed to reduce the risk of TRALI should be implemented in the setting of cardiac surgery, including preoperative correction of anemia, avoidance of excessive hemodilution and fluid overload, and careful control of perioperative bleeding. Avoidance of CPB or limitation of its duration also has been suggested.[44,45] Among others, the implementation of "transfusion bundles" may help in reducing the transfusion of all blood products. The available evidence suggests the noninferiority of restrictive cutoffs with compared with liberal strategies.[42,43] Similarly, the introduction of algorithms for the management of bleeding after cardiac surgery may be valuable. For instance, one multicenter study (3,839 patients) showed that introduction of an algorithm based on point-of-care analyses (ie, viscoelastic tests) and use of fibrinogen and prothrombin complex concentrate significantly reduced both overall and separate blood products transfusions.[46] Even if it is reasonable to suspect that TRALI is more common and deleterious in the cardiac surgery setting because of greater severity of patients' baseline clinical conditions and the presence of several risk factors, a clear link between transfusions and poor pulmonary outcomes still is lacking.

Minimizing the Effects of MV and Optimizing Hemodynamics

A limitation to therapeutic strategies for ARDS is often related to their cardiovascular effects, as shown, for instance, with prone positioning (discussed later in more detail). In this context, the effect of MV on RV function is predominant, although this aspect has not received enough attention when discussing the available therapeutic options according to the severity of ARDS.[2] RV protection should be considered for all ARDS patients and may become of utmost importance for those who develop respiratory dysfunction after cardiac surgery. Generally, the right ventricle is highly sensitive not only to preload but also to rapid increases of afterload determined, for example, by hypoxia, acidosis, and/or high intrathoracic pressures. Ability of the right ventricle to compensate for acute changes in afterload is poor, and progressive RV decompensation is followed by the increase of its end-systolic volume. Moreover, the failing right ventricle has a prolonged myocardial wall strain that finally exceeds the duration of LV myofibers strain. As a result, the right ventricle will have higher end-systolic pressures than the left ventricle, causing paradoxical septal motion with reduction in LV filling; ultimately this will cause a decrease in LV stroke volume. Early detection of RV dysfunction with echocardiography may have a clinically significant effect for establishing timely cardiovascular support or adapting the MV settings. The reduction in venous return during MV, especially if high PEEP is used, may lead to an excess of fluid administration. A cornerstone of hemodynamic optimization is that an increase in cardiac index pursued via fluid administration should not be paired with significant decreases in hemoglobin levels and oxygen saturation.[47] Indeed, if the hemoglobin level decreases and oxygenation worsens, even a significant increase in the cardiac index may not result in improved oxygen delivery. This may occur frequently in cardiac surgery because patients often are hemodiluted with the use of CPB. Moreover, it is important to consider that cardiac surgery patients frequently experience alterations at the microcirculatory level. For instance, sublingual microscopy techniques (eg, sidestream dark field) have demonstrated significant impairment at the level of sublingual microcirculation during both on-pump and off-pump cardiac surgery.[48] It seems reasonable that microcirculatory impairment occurs at different territories and involves the lungs. Such microcirculatory changes are the base of the so-called "hemodynamic incoherence," a condition in which resuscitation procedures aimed at correcting systemic hemodynamic variables frequently are ineffective in improving microcirculatory perfusion[49] because of the discordance between macrocirculation and microcirculation. Unfortunately, the loss of hemodynamic coherence is common after cardiac surgery, particularly as a consequence of hemodilution after CPB causes loss of RBC-filled capillaries and an increased diffusion distance between RBCs and the tissues.[50] In addition, stasis of microcirculatory blood flow as a result of increased systemic vascular resistance and/or presence of systemic edema further reduces oxygen delivery. When microcirculatory alterations are severe, the loss of hemodynamic coherence cannot be managed and solved by correcting systemic hemodynamic variables or by improving MV.[51] As such, multidrug and supplementary therapeutic approaches may be considered for further research (eg, inotropic and vasoactive molecules, diuretics, and use of anti-inflammatory strategies as blood purification techniques).[52]

ARDS in Cardiac Surgery Patients: Treatment Options

Several options have been proposed and investigated in large RCTs for the treatment of ARDS patients, but not all of them may be feasible in the perioperative period of cardiac surgery. Because the evidence does not come from studies conducted in patients who developed ARDS after cardiac

surgery, the authors of the present review briefly discuss each treatment option, focusing also on the peculiarities of cardiac patients that may support (or not) the use of these therapeutic alternatives.

Noninvasive Respiratory Support

The role of noninvasive respiratory support in adult patients with ARDS still is debated, and it is possible that mainly patients with mild ARDS may benefit from this intervention.[53] Among the therapeutic options for support in acute respiratory failure, high-flow nasal oxygen (HFNO) represents the least invasive form. It has been clinically introduced with different targets. For instance, in an RCT the use of HFNO decreased the hospital length of stay and the risk of ICU readmission after cardiac surgery.[54] Conversely, the usefulness of HFNO in reducing the risk of reintubation after cardiac surgery is more debatable,[55,56] and larger studies are desirable.

Continuous positive airway pressure and/or noninvasive ventilation (NIV) have been proposed to improve oxygenation in the cardiac surgery ward,[57] to prevent reintubation[58] and for the treatment of postoperative pulmonary complications after cardiac surgery. In a recent meta-analysis, Wu et al. meta-analyzed nine RCTs (830 patients) and demonstrated that prophylactic use of NIV after cardiac surgery can decrease the lengths of hospital and ICU stay with no differences in terms of cardiac and pulmonary complications.[59] However, included studies were heterogeneous; six investigated continuous positive airway pressure only, and three used bilevel positive airway pressure. In addition, values of airway pressures, duration of treatments, and type of interventions largely differed in that analysis. Thus, conclusions should not be regarded as definitive. Of note, the use of NIV also has been proposed in post-ICU care, possibly resulting in better oxygenation in patients with acute respiratory failure after discharge from the ICU.[57] It is reasonable to consider the use of NIV in cardiac surgery patients, especially given the potential positive hemodynamic effects on the left ventricle; however, as for the use of any positive-pressure ventilation, it is advisable to monitor the effects on RV performance.

Neuromuscular Blockade

A landmark RCT found that 48 hours of therapy with the neuromuscular blocking agent (NMBA) cisatracurium in patients with moderate-to-severe ARDS (partial pressure of oxygen [PaO_2]/FIO_2 <150) improved the adjusted 90-day survival and decreased the time on the ventilator without increasing muscle weakness.[60] However, it remained debated whether such benefits were influenced by different dosage of sedatives administered to the two groups. Therefore, the ROSE (Reevaluation Of Systemic Early Neuromuscular Blockade) RCT was conducted and compared patients deeply sedated and paralyzed with cisatracurium with a control group treated with lighter sedation targets and no paralysis. The study found almost identical hospital mortality between groups, and results also were similar at three-, six-, and 12-month follow-up. Moreover, during their hospitalization, patients in the NMBA group were less physically active and reported more adverse cardiovascular events compared with patients in the control group.[61] Therefore, the more recent evidence does not support the use of NMBAs in ARDS patients, especially if lighter sedation targets may be pursued. Unfortunately, there is no randomized evidence on the use of NMBAs in patients who develop ARDS after cardiac surgery. The evidence on the potential benefits and harms of NMBAs in this setting is rather indirect. Therefore, in the absence of a strong rationale, it seems reasonable to limit the use of NMBAs to moderate-to-severe ARDS patients requiring deeper sedation, possibly using early paralysis and limiting it to brief periods.

Prone Positioning

The landmark PROSEVA trial showed that prone positioning maintained for roughly 16 h/day improved the outcome of patients with moderate-to-severe ARDS (PaO_2/FIO_2 <150).[62] The trial showed a halved 28-day mortality in the prone group (16.0% *v* 33% in the supine group). Similarly, unadjusted 90-day mortality was 24% in the prone group versus 41.0% in the supine group. Of note, reduction in mortality did not seem to be driven by respiratory improvements, as shown in a post hoc analysis[63] in which the authors showed no differences in survival according to quintiles of changes of $PaCO_2$ and/or the PaO_2/FIO_2 ratio. Conversely, prone positioning led to an ameliorated cardiovascular performance with a significant increase in days free from cardiovascular dysfunction until day 28 in the prone group (12 *v* ten in the control group) and halved the incidence of cardiac arrest (6.8% *v* 13.5%, respectively). This is not surprising because prone positioning has shown positive unloading effects on the right ventricle in patients with ARDS,[64] reducing significantly the RV-to-LV end-diastolic area ratio and the incidence of tricuspid regurgitation. This unloading was followed by greater LV end-diastolic volume and improved cardiac index despite a reduction in heart rate. Despite the encouraging effects of proning on cardiovascular performance in patients with moderate-to-severe ARDS, such an option may be an issue in cardiac surgery patients because of the recent sternotomy. Nevertheless, prone positioning has been described in patients with ARDS after cardiac surgery. One retrospective study included patients who were proned at 3 threedays (median) after cardiac surgery, with an average PaO_2/FIO_2 ratio of 87. At the end of proning, the PaO_2/FIO_2 ratio improved to 194, then slightly decreased (146) one hour after supine repositioning and then increased again (184) after 24 hours from proning.[65] Another retrospective study reported the experience of proning in 127 patients three-to-four days after cardiac surgery for acute respiratory failure (not only ARDS), with a PaO_2/FIO_2 ratio around 140.[66] Although these studies did not report severe complications associated with proning, their retrospective design did not allow for firm conclusions to be drawn about the safety of performing proning after cardiac surgery. In summary,

proning after cardiac surgery may be feasible, but it should be done carefully and by well-prepared teams with adequate human resources and training.

High-Frequency Oscillatory Ventilation

High-frequency oscillatory volume (HFOV) has not shown benefits in ARDS, as demonstrated by two RCTs[67,68] (OSCAR - High-Frequency Oscillation for Acute Respiratory Distress Syndrome, and OSCILLATE- Oscillation for Acute Respiratory Distress Syndrome Treated Early), although a patient level meta-analysis showed a possibility of improved survival when HFOV is introduced in patients with low PaO_2/FIO_2 (<64).[69] However, the OSCILLATE RCT used higher HFOV targets and found a higher use of vasopressors and greater mortality in the intervention group.[67] Guervilly et al. demonstrated that moving from conventional ventilation to HFOV with increments of 5, 10, and 15 cmH_2O of mean airway pressure significantly increased the number of patients with RV dysfunction and/or failure,[70] and these changes were reversed by returning to conventional ventilation. Because there is no evidence supporting the use of HFOV in ARDS patients and considering the negative effects from the cardiovascular perspective, the authors of the present review do not believe it should be implemented after cardiac surgery.

Extracorporeal CO_2 Removal and Extracorporeal Membrane Oxygenation

Regarding extracorporeal carbon dioxide removal ($ECCO_2R$), the SUPERNOVA trial showed that patients with moderate ARDS safely can undergo $ECCO_2R$ and, consequently, receive reductions in the TV and driving pressure applied. The authors did not report any adverse event, and the mortality was 27%, which was less than expected. Extracorporeal membrane oxygenation (ECMO) remains controversial for the treatment of ARDS patients. The results of the CESAR trial were encouraging, but the subsequent EOLIA trial was somehow disappointing.[71] The latter RCT was stopped prematurely despite signs of better outcome for the ECMO group, and it was highly criticized for the high crossover rate to ECMO in the control group (28% of the patients). Considering the high level of experience with extracorporeal circuits in the cardiac surgery setting and the readily available presence of dedicated personnel (perfusionists), $ECCO_2R$ and ECMO may represent reasonable options for patients with moderate and severe ARDS, respectively, but more data are needed. Of note, several ECMO strategies may be used under the expertise typical of cardiac centers (venovenous or venoarterial; percutaneous or central cannulation), and this should be considered in relation to the clinical conditions, including the presence of RV dysfunction. However, these strategies expose patients to the risks of cannulation and systemic anticoagulation,[72] and the higher risk of bleeding and transfusions when systemic anticoagulation is started in the perioperative period of cardiac surgery should be considered.

Lung Recruitment and PEEP Uptitration

Another treatment strategy largely investigated for ARDS is the adoption of lung recruitment and PEEP uptitration. The recent ART trial showed that lung recruitment and PEEP titration increased 28-day mortality compared with low PEEP. The need for commencement/escalation for vasopressors or the episodes of hypotension within one hour were significantly greater in the intervention group (35% *v* 28% in control patients). Of note, recent meta-analyses have questioned the role of routine use of higher PEEP and/or recruitment maneuvers in unselected patients with ARDS.[73,74] No studies using lung recruitment on cardiac patients with postoperative ARDS were found for the present review. A study conducted in elective cardiac surgery non-ARDS patients showed that two brief vital capacity maneuvers performed at CPB separation and at ICU arrival improved oxygenation and decreased atelectasis. The effect lasted until ICU discharge.[75] However, these patients were not experiencing ARDS and had stable hemodynamic conditions. Therefore, because the most recent data do not support lung recruitment and aggressive PEEP uptitration, clinicians in the setting of cardiac surgery should be very careful with such approaches in patients with cardiac dysfunctions, especially in those experiencing RV dysfunction. Indeed, the increase in lung volumes and the PEEP uptitration may improve gas exchanges but at the expense of increasing RV afterload. Importantly, recruitment maneuvers may result in profound cardiovascular consequences, even under conditions of normovolemia or hypervolemia, a concept elegantly shown by Nielsen et al. in a study on lung-injured pigs.[76] Of note, the PEEP uptitration commonly is performed without recruitment maneuvers as a clinical response to a worsening PaO_2/FIO_2 ratio. The authors of the present review advise that when increasing PEEP levels, clinicians should investigate for the presence of a significant interatrial shunt as a result of patency of the foramen ovale (PFO) if the PaO_2/FIO_2 fails to improve. Mekontso Dessap et al. showed a prevalence of around 20% of moderate-to-severe PFO shunt, and these patients were not responsive in terms of the PaO_2/FIO_2 ratio to the increase of PEEP from 5-to-10 and to 15 cmH_2O compared with patients with no PFO.[77]

Inhaled Nitric Oxide

The use of inhaled nitric oxide (iNO) currently is not supported in ARDS patients. A meta-analysis showed that despite a transient improvement in oxygenation, iNO was not associated with differences in ventilator-free days, duration of MV, resolution of multiorgan failure, quality of life, length of ICU or hospital stay, or costbenefits.[78] Moreover, there was an increased risk of renal impairment with iNO.[79] Inhaled epoprostenol (prostacyclin) can improve the oxygenation in a proportion of ARDS patients,[80] and it can be an alternative. Furthermore, its use is associated with reduced costs compared with iNO.[81] As for the use of extracorporeal strategies, cardiac anesthesiologists and ICU clinicians usually are confident with iNO. Despite the lack of data, it is not unreasonable to consider

iNO in patients with postoperative ARDS and associated RV dysfunction/failure in order to reduce the shunt. However, clinicians should keep in mind that cardiac patients are at a higher baseline risk of renal injury, and iNO may contribute further to deterioration in renal function.

Conclusions

More research in the setting of ARDS after cardiac surgery is needed at multiple levels (risk factors, diagnosis, treatment options). Prevention of lung injury appears to be of the utmost importance, and a better characterization of the risk factors is needed. Avoiding excessive perioperative transfusions and the optimization of ventilation and hemodynamics seem to be the most modifiable risk factors. In patients who develop ARDS after cardiac surgery, extracorporeal techniques may represent a valid choice in experienced hands. The use of NMBAs, prone positioning, and iNO can be considered on a case-by-case basis, whereas aggressive lung recruitment and oscillatory ventilation probably should be avoided.

Conflict of Interest

All the authors declare no conflict of interest.

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