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Review Article

Perioperative "remote" acute lung injury: recent update

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Abstract

Perioperative acute lung injury (ALI) is a syndrome characterised by hypoxia and chest radiograph changes. It is a serious post-operative complication, associated with considerable mortality and morbidity. In addition to mechanical ventilation, remote organ insult could also trigger systemic responses which induce ALI. Currently, there are limited treatment options available beyond conservative respiratory support. However, increasing understanding of the pathophysiology of ALI and the biochemical pathways involved will aid the development of novel treatments and help to improve patient outcome as well as to reduce cost to the health service. In this review we will discuss the epidemiology of peri-operative ALI; the cellular and molecular mechanisms involved on the pathological process; the clinical considerations in preventing and managing perioperative ALI and the potential future treatment options.

Keywords: acute lung injury, intraoperative care/adverse effects, postoperative complications, inflammation, anesthetics, general, fluid therapy

Introduction

The term acute lung injury (ALI) was first introduced in 1994 by the American–European Consensus Conference Committee[1]. It is defined as acute onset hypoxia with PaO_2/FiO_2 between 200-300; presence of bilateral infiltrates on the chest radiograph; in absence of pulmonary hypertension or other cardiac pathologies. The term was coined to identify cases which are not severe enough to fall into the criteria of Acute Respiratory Distress Syndrome (ARDS), for the ease of identification and further research. Since then, ALI has attracted significant attention in both clinical and laboratory research. Interestingly, general abdominal surgery carries similar ALI risk as general thoracic surgeries, and animal studies of remote trauma and non-pulmonary transplant demonstrates features of ALI, suggesting that peri-operative ALI is at least partially attributable to remote injury. In this article, we will discuss the epidemiology of perioperative ALI, as well as the biochemical mechanisms and clinical considerations of perioperative ALI due to remote injury.

Epidemiology

In the general surgical population, the incidence of ARDS is reported to be 0.2%[2]. Indeed, it is thought that patients who undergo elective minor orthopaedic and pelvic surgeries are at minimal risk of developing perioperative ALI[3-4]. Thoracic and abdominal surgeries are associated with higher risks. In patients without significant risk factors, the average ALI incidence in thoracic and abdominal surgery is 1.3-

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4%[5-7], with 1.2%-2.3% incidence of respiratory failure[8-9]. Interestingly, despite the surgical manipulation of the lung, the incidence of perioperative ALI in lobectomy and pneumonectomy is only 2.8%-5%. In cardiac and aortic surgery, the incidence of perioperative ALI is also around 5%; however, this can increase to as high as 28%-35% in high risk procedures[10-11]. Esophagectomy is associated with a high incidence of ALI and reported to be between 16%-41%[12-14]. There is not enough published data to create a comprehensive list of surgeries and associated ALI risks, but recommendations for a surgery related risk stratification system have been proposed by Kor *et al*.[11].

The pre-morbid state of the patient plays a significant role of the development of perioperative ALI. Two cohort studies involving a total of 7,126 patients with pre-operative risk factors for developing ALI reported an incidence of 6.8%-7.5%[11,15]. A number of studies have looked into pre-operative patient parameters and constructed ALI prediction models; however, their application in clinical practice has not been reported. Emergency surgery is the most consistently reported predictor of ALI; other frequently reported predictors of ALI include age, pre-operative renal failure, chronic obstructive pulmonary disease (COPD) and pneumonia, hypoalbuminaemia and alcohol consumption. These four models employed different markers of respiratory distress (desaturation, tachyapnoea, dysapnoea and oxygen requirement), all of which are statistically significant predictors from the literature that are listed in ***Table 1***[3,11,15-18].

Development of perioperative ALI is associated with significantly worse outcomes (See ***Fig. 1*** for summary of ALI clinical outcomes). Patients with ALI are twice as likely to be admitted to intensive care unit (ITU) and require an average of an 8 day stay (which is 4-8 times longer than those without ALI). This includes a relative risk ratio of 2.5 for mechanical ventilation compared to normal ventilation, in which patients spend on average 6 days on mechanical ventilation. This is 6 times longer than the duration of non ALI patients. This prolongs the duration of the hospital stay to an average of 15-20 days, up to 2.5 times longer compared to patients without ALI[7,15]. The prolonged ITU and hospital stay is not without its own risks. The total in-patient mortality rate is between 22 to 24%, which is 5-10 times higher than comparative population without ALI. However, most of this is accounted for by ITU mortality of 20%[15,19-20]. Even when the patient recovers from the episode and is discharged, their long term prognosis is still significantly worse than those without ALI. A two year follow up study reported that survivors of perioperative ALI required on average of 2 episodes of readmission and 6 days of hospital stay per year while another study reported 30 day mortality to be up to 30% and 90 day mortality to be 55%[16,21].

Apart from the significant mortality and loss of quality of life from the extended ITU and hospital stay experienced by patients, perioperative ALI is also associated with a significant cost to the health care system. In a study based on American health care expenditure in 2013, it has been estimated that initial hospital management of ALI costs approximately $100,000, with another $35,000 spent on two years of follow up treatment[21].

In summary, perioperative ALI can be a common

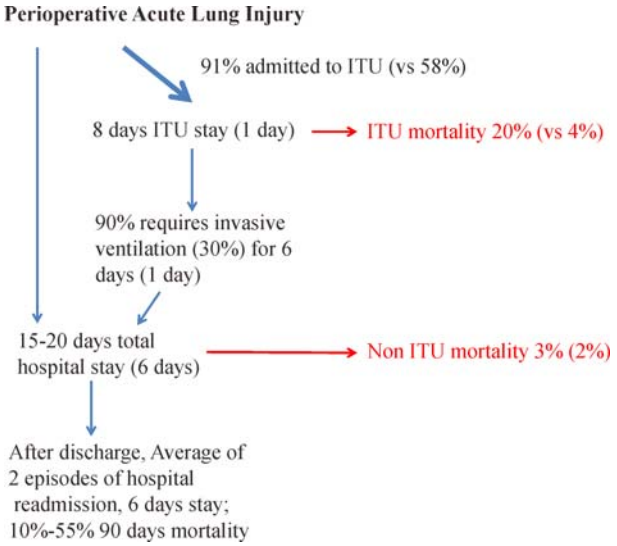

Fig. 1 **"Roadmap" of postoperative acute lung injury (ALI).** Illustrating the higher rate of invasive ventilation, ITU admission; longer length of ITU and hospital stay; re-admission; as well as the much higher ITU and 90 day mortality, non-ALI cohort data presented in brackets for comparison [7,15-16,19-21].

Table 1 **Summary of tested parameters from 6 acute lung injury (ALI) predictive models**

	Tested and reported statistical significance* ($n = 6$)	Tested and reported no statistical significance* ($n = 6$)
General		
Gender	1	1
Age	2	-
Functionally not independent	1	-
Weight loss	1	-
Alcohol	2	-
Smoking	1	2
Admission not from home	1	-
Obesity	1	-
Past medical history, pulmonary		
COPD	2	-
preoperative pneumonia	2	-
preoperative dysapnoea	1	-
preoperative desaturation	1	1
preoperative tachyapnoea	2	-
Aspiration	1	-
FiO_2	1	-
Others		
ASA grade	1	1
preoperative sepsis	1	1
preoperative renal failure	2	-
Cirrhosis	1	-
Albumin	2	-
Shock	1	-
preoperative anaemia	1	-
Advanced cancer	1	-
Periopeartive factors		
Emergency surgery	5	-
Surgery duration	1	-
Fluid infusion	1	-
Blood Transfusion	1	-

Note: *: number of studies which tested the parameter and demonstrated statistical significance. **: number of studies which tested the parameter and reported that there is no statistical significance [3,11,15-18]. COPD: chronic obstructive pulmonary disease.

complication in certain patient groups, and is associated a significantly poor outcome and high treatment cost. Currently, most cases of perioperative ALIs are managed conservatively and, therefore, further investigation into its pathophysiology and treatment is very necessary.

Molecular mechanism of acute lung injury

From the literature reviewed, most of the human studies and an animal model of ALI reported similar presentations of clinical, histological and biochemical changes (***Fig. 2***), despite the varied aetiology of lung injury in the studies. Here, we will attempt to summarise the biochemical pathways found to be involved with the pathogenesis of acute lung injury.

Inflammation

Histologically, ALI is typically associated with increased neutrophil infiltration, increased vascular permeability, and increased tissue oedema, all of which are characteristic features of an inflammatory process. Both human studies and animal models of ALI invariably reported increased production of systemic

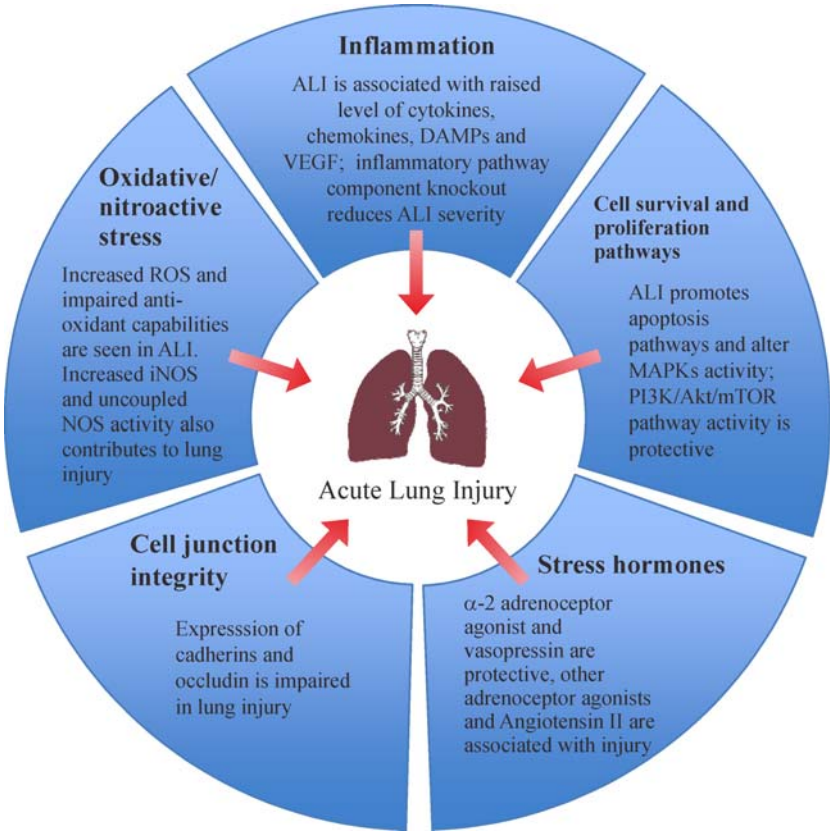

Fig. 2 **Summary of molecular mechanism of acute lung injury (ALI).** ALI is characterized by inflammation, increased oxidative and nitroactive stress, impaired cell junction integrity, release of stress hormones, and altered cell surivial and proliferation pathways. ACE: angiotensin converting enzyme, DAMPs: damage-associated molecular pattern molecules; iNOS: inducible nitric oxide synthase; MCP1: monochemotactic protein 1; MAPK: mitogen-activated protein kinases; MIP1: macrophage inflammatory protein 1; ROS: reactive oxygen species; VEGF: vascular endothelial derived growth factor.

and local cytokines (IL-1β, IL-6, IL-8, IL-10, and TNF-α], chemokines (CXCL1, CINC1, MIP1, and MCP1) and other immune mediators. This occurs without the presence of endotoxin in remote organ injury due to trauma, ischaemia and transplant[22-25]. The inflammatory mediators are thought to play a significant role in the pathogenesis of ALI, as eliminating various parts of the inflammatory cascade alleviates the severity of lung injury[26-30].

Tissue injury, whether of the lung or remote organ, leads directly to cell injury and necrosis. In this process, TNF-α and IL-1β are released[31]. This has several effects. For example, TNF-α increases vascular permeability, which results in an increased recruitment of neutrophils and macrophages. It can inactivate IκB thorough phosphorylation, thereby lifting the inhibition of NF-κB, which further upregulates the expression of IL-1β[32-33]. Increased levels of TNF-α and IL-1β recruit more macrophages and neutrophils, as well as promoting their survival. IL-1β is also able to upregulate the production of acute phase proteins, such as CRP and complement, as well as promote the expression of other cytokines, chemokines and adhesion molecules[34].

Among the cytokines upregulated by TNF-α and IL-1β are IL-6 and IL-8. IL-6, which is produced mainly by endothelial cells, modulates the immune response by altering the expression of neutrophil, macrophage and T cell chemokines (including CXCL1, MIP1, MCP1 and CCL5, all of which are reported to be associated with the pathogenesis of ALI), and also upregulates adhesion molecules such as selectin ICAM-1 and VCAM-1. IL-8, which is a chemoattractant produced by macrophages, induces neutrophil chemotaxis, and upregulates the phagocytic function of neutrophils[35].

Interestingly, although elevation in IL-10 is reported by a number of studies in association with ALI, it is actually an anti-inflammatory cytokine, which inhibits TNF-α, IL-1β, and NF-κB, as well as causing de-adherence of macrophages[36]. It is likely that its role in ALI is more regulatory in nature. This is difficult to prove, however, as most studies to date demonstrate an increased level of IL-10 with ALI mimetics and a reduced level of IL-10 with ALI treatment[37].

Toll like receptors are pattern recognition receptors, which are usually known for their affinity to bacterial endotoxins. However, studies have shown that knockout

of toll like receptor 4 (TLR4), as well as its adaptor protein MyD88 is associated with reduction in ALI severity in apparently aseptic conditions[26-28]. More recent studies have alluded to the possibility that as well as bacterial molecular patterns, TLR4 is also able to identify endogenous ligands associated with tissue injury[38]. TLR-4/MyD88 complex acts through downstream molecule IKK, which phorophorylate and inactivate IκB, thereby lifting inhibition on NF-κB[38-39].

Vascular endothelial growth factor (VEGF) is a group of growth factors which promotes angiogenesis and has some chemotactic functions. It has been demonstrated that VEGF expression is upregulated by various inflammatory mediators described above, including IL-1β, IL-6 and TNF-α[40-41]. It has been reported that administration of VEGF increases lung vasculature permeability, and VEGF inhibition alleviates lung injury[42-44]; however, reports of VEGF attenuating lung injury also exist[45-46]. It is possible that the effect of VEGF depends on the timing in relation to the injury.

Oxidative and nitrosative stress

Studies have shown that remote ALI is associated with increased oxidative stress markers, and treatments which reverse ALI are associated with reduced level of oxidative stress, suggesting that oxidative stress may be involved in the pathogenesis of ALI[47]. More directly, anti-oxidant ammonium pyrrolidinedithiocarbamate has been reported to reduce ALI after liver transplant in rats[48]. Most of the endogenous reactive oxygen species (ROS) are produced by NADPH oxidase which is neutralised by a number of anti-oxidant enzymes such as superoxide dismutase, glutathione S transferase, catalase and heme-oxygenase. When the anti-oxidant capability of the cell is exhausted, oxidative damage induces the activation of Bcl-2, which triggers mitochondrial breakdown and apoptosis[49]. In the context of ALI, an increase in ROS production, as well as impaired anti-oxidant capabilities are seen with remote organ ischaemia, haemorrhage, hypoxia and burns/blast trauma[50-53].

Recently, studies have also investigated the role of nitric oxide (NO) and nitric oxidase synthase (NOS) in ALI. NOS is a group of enzymes which catalyses the generation of NO from arginine; there are three isoforms of NOS in human, including neuronal isoform nNOS, endothelial isoform eNOS and inducible isoform iNOS. Whereas eNOS is constitutively expressed and is generally thought to play a protective role, iNOS expression is upregulated by cytokines such as IL-1β and TNF-α, and is thought to contribute to tissue injury[54]. This isoform specific effect has been demonstrated by Sedoris[55]. While NO can act as an anti-oxidant, excessive oxidative stress can cause accumulation of peroxinitrite, a reactive nitrogen species that results in injury through oxidation or nitration[56]. A number of animal models of Lipopolysaccharide (LPS) that induces ALI have reported an increased level of iNOS, while treatment of ALI is associated with reduced level of iNOS[57-59]. Similar findings have also been seen in ALI secondary to high volume ventilation, ischaemia/reperfusion injury and chemical injury[60-62]. The role of eNOS is less clear, while eNOS knockout is associated with reduced lung injury after LPS exposure, reduced eNOS activity worsens lung injury secondary to bowel and brain ischaemic/reperfusion injury[62-64]. This suggests that the role of NO is pathology specific and the effect is likely concentration dependent.

Asymmetric dimethylarginine (ADMA) is a structural analogue of L-arginine, which competitively binds to all isoforms of NOS. The binding causes the uncoupling of NOS, which diminishes NO production and increases ROS production[65]. The process is usually kept in check by dimethylargininase (DDAH) which hydrolyses ADMA[66]. Reduced DDAH activity and excessive ADMA have been reported in association with ALI, while increased DDAH activity reduces the extent of ALI[62,64,67].

Cell survival and proliferation pathways

A number of animal models of ALI secondary to remote organ injury and other conditions have reported an altered activity of the PI3K/Akt/mTOR pathway, a series of signalling molecules which plays a vital role in cell proliferation. General anaesthetic agents exert their cytoprotective effects at least in part by upregulating this pathway. PI3K and mTOR are reported to inhibit the expression of NF-κB; mTOR could regulate downstream molecules like HIF1α[68],which upregulates the expression of antioxidative enzymes, promotes cell survival, and encourages angiogenesis; however, its role can be dual depending on elevated level as it has been reported with both improvement and deterioration of lung injury[68-69]. One of the downstream effects of HIF-1α is to inhibit HMGB1 release from the nucleus. HMGB1 is a chromatin protein, that acts as a damage-associated molecular pattern. It can interact with TLR4/MyD88, which upregulates NF-κB and MAPK; it can also interact with RAGE. HMGB1 is implicated in brain trauma induced acute lung injury; it is reported that RAGE knockdown is protective against ischaemic-reperfusion, and high soluble RAGE is associated with prolonged ventilation and lung transplant failure[70].

A number of studies have also demonstrated the role of apoptotic pathways in ALI. BAX and BAK are pro-

apoptotic members of the Bcl-2 family. This is usually kept in check through binding to other proteins or through sequestering of proteins needed for activation[71]. ALI models are associated with increased levels of BAX and BAK, as well as reduced level of the pro-survival Bcl-2[68,72-73]. One possible mechanism of this is oxidative stress causing the activation of BAX and BAK[49]. Activated BAX and BAK are converted from monomers to oligomers, which form pores on the mitochondrial membranes. This facilitates translocations of cytochrome c, which activates the caspase cascade and causes apoptosis[71]. Increased caspase activity is also seen in patients with ALI, while ALI treatments reduce caspase activities[72-74]. However, the activation of the apoptotic pathway is likely to be a result of existing cellular insult, not the direct cause of ALI.

Changes in MAPKs are also seen in ALI models. MAPKs are a group of serine/threonine kinases which integrate stress signals and phosphorylate downstream signals to promote cell survival or cell death. There are three conventional signalling pathways, p38 MAPK, ERK1/2 and JNK. p38 MAPK has a number of pro-survival and pro-apoptotic functions; JNK has a variety of functions, including induction of cell apoptosis in response to various cellular stresses, including ischaemia/reperfusion and inflammatory cytokines such as TNF-α; whereas ERK1/2 are thought to have mainly pro-survival functions[75]. In addition, it is thought that MAPKs act as downstream signal of TLR to increase the expression of IL- 1, IL-6 and IL-8[76]. Increased level of phosphorylated ERK and JNK are seen in ALI models[77-80]. It is possible that while increased JNK is related to lung injury, ERK1/2 is a protective response against the injury. However, it is not possible to confirm without more studies.

Cell junction integrity

One of the hallmarks of ALI is increased vascular permeability, which leads to oedema, protein extravasation and neutrophil infiltration. A number of molecules have been implicated in the breakdown of intercellular stability. Occludin is a polypeptide vital for the formation of tight junction, and reported to be down-regulated by remote organ ischemia reperfusion injury[81-82]. Cadherins are polypeptides which form adherence junctions and interacts with intracellular actin. It was demonstrated that the expression of cadherin and endothelial barrier function are damaged by direct lung injury[83-84].

Stress hormones

Perioperative state, as well as any preoperative pathologies are frequently associated with increased physiological stress. The relationship between stress hormones and severity of lung injury is not well studied; however, recent studies are beginning to demonstrate their important in ALI pathogenesis.

Adrenaline is the hormone responsible for sympathetic activation, which is associated with a number of systemic disease states, including burn injury, sepsis and ARDS[85-86]. It has been reported that administration of adrenaline worsens lung histology and associated inflammatory response in ALI, whereas β-adrenoceptor antagonist alleviates ALI[22,87-88]. Dexmedetomidine is an α-2 adrenoceptor agonist, and has been found to reduce lung injury secondary to remote ischaemia/reperfusion injury, chest trauma as well as surgical pneumoperitoneum[89-91]. The benefit is partially reversed by α-2 adrenoceptor antagonist atipamezole, which suggests that dexmedetomidine possesses protection at least in part *via* α-2 adrenoceptor aganist ALI.[92]. However, the benefit of α-2 antagonist in sepsis induced ALI suggests that the role of α-2 adrenoceptor is pathology specific[88].

Another stress related hormone vasopressin has been reported to play a protective role in ALI. Administration of vasopressin reduces pulmonary oedema and airway secretion, and improves alveolar fluid clearance[93-95]. In addition, a study of ARDS patients reported that terlipressin administration was associated with significantly better oxygenation[96].

The renin-angiotensin system has also been linked to ALI. Angiotensin II is a peptide hormone, converted from angiotensin I by ACE. It can be further modified into angiotensin 1-7 by ACE2. It has been reported that inhibition of ACE or antagonism of angiotensin II is associated with significantly less lung injury and oedema; as well as reduced cytokine and chemokine expression[77,97]. ACE2 and angiotensin 1-7, however, have been reported to be protective against ALI secondary to LPS, bleomycin administration and acid inhalation[42,77,98]. The possible mechanisms include reversing vascular permeability caused by VEGF and down-regulating the pro-apoptotic mediators[42,72,99].

BNP is a 32 amino acid peptide secreted mainly by cardiomyocytes. It is synthesized from preproBNP, which is converted to proBNP, then enzymatically cleaved into BNP and the inactive fragment NT-proBNP. In addition to modulating vascular tone and sodium homeostasis, BNP has been found to dampen inflammatory reaction and promote survival of cardiomyocytes[100]. Although limited, studies into the role of BNP in ALI show promising results. It has been reported that in patients, ALI is associated with significantly increased level of systemic BNP, which may

represent up-regulated compensatory response[101-102]. In animal models of ALI, administration of recombinant human BNP has been shown to reduce the severity of lung injury, as well as the associated inflammatory response and oxidative stress[103-104]. However, more studies are needed to further validate both the diagnostic and therapeutic value of BNP in humans.

ALI secondary to remote organ injury and transplant

While undesirable, surgical manipulation invariably leads to tissue injury, and it has been observed that even in pathologies where lungs are not directly damaged, acute lung injury can ensue from remote organ injury. Perhaps the most well described aetiology of remote organ injury that induces ALI is traumatic brain injury. In TBI cases, acute lung injury is among the most common non-neuronal organ dysfunction, with an incidence of 9%[70,105]. Severe trauma in general is also associated with a high risk of ALI[106]. In addition, high incidence of ALI has also been reported in liver transplant and renal transplant[107-109]. More indirectly, ALI could be reliably reproduced in animals through organ transplant and remote organ ischaemia[24,110]. The severity of ALI correlates to the length of remote organ insult[48,111]. These findings all support the role of lung-remote organs crosstalk in perioperative acute lung injury.

ALI causing remote organ injury has been shown to cause systemic inflammation. Animal studies of transplant related ALI consistently reported increased serum level of cytokines such as IL-1β and TNF-α; these cytokines are also found to be increased lung tissue[28,53,112]. Studies have also shown that disabling part of the inflammatory pathway such as TLR knock-out, NF-κB inhibition and preventing leucocyte adhesion can reduce the extent of lung injury and the level of cytokines in the lungs[28,113]. This suggests that cytokines released from remote organ injury could spread to the lungs *via* the blood supply, where it activates pro-inflammatory pathways in the lungs and leads to ALI. In addition to circulating cytokines, remote organ injury can also cause the release of proinflammatory damage associated molecular pattern such as HMGB1 into the circulation, which can also activate the proinflammatory pathways in the lungs[70].

In addition to inflammation, a number of studies have reported increased oxidative stress in animal models of ALI secondary to remote injury. Limb trauma reduces SOD activity and Glutathione, while increases the levels of hydrogen peroxide and MDA. This pattern is seen systemically in the serum as well as lung tissue. Similar pattern is also seen with transplant[23,50] and haemorrhagic shock[104]. In addition, there is some evidence that oxidative stress is alleviated through over-expression of SOD and through glutathione administration[114-115]. This suggests that oxidative stress may directly contribute towards the pathogenesis of ALI.

While not well studied, dexmedetomidine has demonstrated protective effect in myocardial and renal ischaemia/reperfusion injury[89,92]. This suggests that abnormality in sympathetic activation may play a role in ALI secondary to remote organ injury.

Interestingly, despite the wealth of animal studies showing that intestinal ischaemic-reperfusion injury causes acute lung injury, there is no literature of similar condition in humans. Indeed, the incidence of perioperative ALI is not well presented in the literature outside the topic of thoracic surgery, and may pose an area for future study.

Clinical considerations

Protective ventilation

It is now widely accepted that protective ventilation, a combination of low tidal volume, use of PEEP and recruitment manoeuvre is significantly associated with incidence of perioperative ALI. The PROtective Ventilation group (PROVE) has organised a number of larger scale randomised control trials (RCT). The IMPROVE trial, published in 2013, reported that the incidence of perioperative ALI in abdominal surgery is 0.5% when patients receive protective ventilation compared with 3% of those who received conventional ventilation[116]. Similar results were also found in a meta-analysis which looked into thoracic and neurosurgery[117]. However, protective ventilation does not seem to modify the mortality rate[118-120].

Studies have also looked into the benefits of individual components of protective ventilation. The PROVHILO trial looked into the benefit of PEEP and recruitment manoeuvre with fixed tidal volume. It was found that high PEEP and alveolar recruitment itself did not lead to improvement in oxygenation. On the contrary, PEEP was associated with higher incidence of intra-operative hypotension[121]. This also echoes the findings in non-surgical patients[122]. When low tidal volume ventilation on its own, the results were also somewhat conflicting. While two meta-analyses of 4700 cases reported significantly lower rate of ALI with low tidal volume alone, they did not standardise the protocol for PEEP and recruitment manoeuvre. When controlled for PEEP and recruitment manoeuvre, low tidal volume did not reduce the rate of ALI[6,122-123]. However, studies report that use of protective ventilation does not seem to modify the overall mortality rate[124-125].

One lung ventilation is a special ventilation technique used in thoracic surgery, which is associated with significantly higher rate of perioperative ALI. This could also be reduced by the use of protective ventilation, low tidal volume of 6-8 mL/kg with PEEP and recruitment manoeuvre was associated with significantly lower rate of ALI[126-127]. Other parameters of ventilator setting may also affect the incidence of ALI. A study by Hu *et al.* reported that pressure controlled volume guaranteed ventilation that resulted in better maintenance of lung compliance and blunts increase in inflammatory markers[128].

Anaesthetic agents

In recent years, a number of published studies looked into the effect of anaesthetic agents on the progression of ALI, with some interesting results.

Sevoflurane, isoflurane and propofol have all been demonstrated to exhibit anti-inflammatory and cytoprotective effects in animal models of ALI, and the benefit is shown consistently in experiments involving LPS exposure, transplant and remote organ injury models, and ventilator induced lung injury models[37,79,81].

Sevoflurane is used in the majority of anaesthetic agent studies. While there are very little available data on the effect of sevoflurane administration on the mortality rate or recovery time in ALI models, an *in-vivo* animal model consistently demonstrated that administration of sevoflurane in ALI model is associated with reduced histological change, reduced wet: dry ratio and improved ventilation parameters (higher pO_2 and lower pCO_2)[51,129-130]. Sevoflurane administration is also associated with significantly lower neutrophil infiltration in the pulmonary tissue of the ALI models[131]. In addition to the histological and blood gas parameter changes, sevoflurane administration is also associated with lower levels of proinflammatory cytokines, most notably Il-1a, Il-6, TNF-α, and lower level of chemokines[80,132]. Sevoflurane administration is also associated with significantly lower NF-kb expression[130].

Sevoflurane administration has also been shown to reduce the activity of cyclo-oxygenase, lipo-oxygenase and cytosolic phospholipase A_2 activities, thereby reducing the production of leukotriene and thromboxane levels[133-134]. Sevoflurane administration is also associated with reduced expression of TLR4[135].

Similar findings are also seen with isoflurane, with promising *in-vivo* survival data. In an experimental model of AKI using zymosan, a fungal surface glucan, isoflurane administration has been demonstrated to increase the survival rate 3-5 folds[73,136]. This is associated with less histological damage, less protein exudate and pulmonary oedema, and reduction in proinflammatory cytokines similar to that of sevoflurane. The studies also looked into pathways related to cell survival, and found that isoflurane administration is associated with significantly reduced caspase activities, downregulation of NF-kb through reduced expression and upregulated i-kb expression, and affects a number of apoptosis related mediators including BAX and Bcl-2. These are likely to account for the cytoprotective effect of isoflurane[73,81,136-137].

Both isoflurane and sevoflurane are thought to play a role in maintaining the integrity of tight junction between airway epithelial cells. Breakdown of the tight junction with increased permeability is noted in both ventilation-induced lung injury and LPS models of ALI. Both volatile agents are noted to upregulate cell junction proteins zona occludens 1 and occludin expression, with normalisation of epithelial permeability[81-82].

There are several explanations to the anti-inflammatory and cytoprotective effects of volatile agent. It was found that in human and rat cell lines, triflurinated carbon molecule significantly reduces the expression of inflammatory cytokines Il-1, Il-6, and Il-8 and chemokines MIP-1 and CINC-1, which is associated with reduced neutrophil chemotaxis. In addition, triflurinated carbon also seems to downregulate the caspase activity[74]. Fortis *et al.* found that GABA administration also significantly reduces the expression of cytokines and chemokines, and this is negated by the co-administration of picrotoxin, a GABA receptor antagonist[37]. Further study into the protective mechanism of inhalational agents is needed as this could lead to the development of better ALI treatments.

Propofol has demonstrated protective effect in ALI models. Zhao *et al.* demonstrated that propofol administration is associated with 2-fold increase in survival in a LPS model of ALI. Findings of reduced histological damage, pulmonary oedema and reduced pro-inflammatory cytokine profile were noted, similar to that of sevoflurane and isoflurane administration. Propofol has also been noted to have anti-oxidative properties, administration is associated with increased SOD and Nrf-2 activities, which reduces tissue hydrogen peroxide and MDA[50,138].

Comparative studies of sevoflurane and propofol found that sevoflurane administration was associated with less neutrophil infiltration and lower cytokine expression[131,139]. In terms of human study, there are four studies with a total of 130 participants, comparing the outcome of propofol and sevoflurane in perioperative ALI; overall, there were no significant differences in the incidence of ARDS and the reported biochemical

difference is conflicting between the studies[25,140-142].

Xenon is a novel general anaesthetic agent, which has previously demonstrated neuroprotective effects. It also has antinflammatory and anti-apoptotic properties in ALI secondary to remote renal injury[68].

In summary, there is now a growing body of evidence that general anaesthetic agents have significant protective effect against ALI, and have a role to play in the prevention and treatment of ALI. Given that most operations possess a high risk of developing perioperative ALI are done under general anaesthesia, the only clinical relevance would be the choice of anaesthetics, however, there is currently no conclusive human study to prove either is superior, although animal studies points towards inhalational agents.

Fluid administration and transfusion

In most operations, intravenous fluid is routinely administered, with blood component transfusion sometimes in case of high blood loss. However, a number of observation studies have reported that during the perioperative period, high volume of fluid administration is associated with significantly higher incidence of ALI[143-145]. It has been demonstrated in RCTs of perioperative ALI cases that conservative fluid management is associated with better oxygenation and shorter intubation time[146-147]. In a large RCT of medical and surgical patients with ALI, it was found that conservative fluid administration is associated with significantly better oxygenation, lung compliance, and 60 day survival[148].

Nevertheless, it gets more complex in trauma. In animal studies, haemorrhage is associated with significantly decreased oxygenation, increased pulmonary vascular permeability and cell infiltration[104,149]. However, in trauma patients, fluid administration is still linked with incidence of ALI. Two observational studies with a total of more than 2300 patients identified that the rate of ALI/ARDS is significantly higher in patients administered with larger volume of IV fluid[20,150]. However, it is not known if this is an association or a causation, as larger fluid administration could be associated with severity of the trauma.

Like fluid administration, blood product transfusion has also been associated with the development of ALI[20,151]. It is noted that the incidence of ALI associated with perioperative transfusion is significantly higher than the incidence in the general population[152], and that the incidence of perioperative transfusion associated acute lung injury (TRALI) is significantly higher with larger volume of transfusion[4]. A number of specific blood components are suggested as the cause of transfusion-related ALI, including erythrocyte derived micro-particles and serum antibodies and platelet released VEGF[43,153-154]. However, the exact mechanism is likely to be complex and multi-factorial.

Conclusion and way forward

In summary, perioperative ALI is a complex pathology which involves the activation of inflammatory pathways, increased endovascular permeability, increased oxidative stress and change in stress hormones. It occurs as a result of the interaction between surgical and anaesthetic factors, and patient's pre-operative condition. This is best described by the multi-causal model such as the one proposed by Middlegurg *et al*.[155].

In certain patient cohorts, perioperative ALI could be a frequent and devastating complication, associated with long periods of invasive monitoring and treatment, longer stay in hospital, more long term complications and increased mortality. This is also associated with significant cost to the health system.

In addition to protective ventilation, use of inhalational anaesthetic agent and conservative fluid administration, a number of potential prophylaxis and treatment for perioperative ALI have been identified and investigated in recent years. In animal studies, suppression of various parts of inflammatory cascade consistently reduced the severity of lung injury. One method to supress inflammation in humans is with corticosteroids. Indeed, administration of corticosteroid is associated with significantly milder histological and mechanical lung changes, and significantly lower cytokine level compared to the control group[156-157]. It is, however, worth noting that the role of corticosteroids in paediatric patients with is less clear, with conflicting data regarding its benefits[158].

Neutrophil elastase is a proteinase secreted by neutrophils and macrophages during inflammation, and knockout studies suggest that it plays a role in leucocyte recruitment, inflammatory mediator release and phagocytosis[159]. In patients with ARDS secondary to sepsis, selective neutrophil elastase inhibitor sivelestat has been reported to improve oxygenation, reduce lung injury and shorten the length of ICT stay[160-161]. In the context of postoperative ALI without sepsis, while it improves inflammatory mediator levels, the benefit on prognosis is unclear[162-164].

Other treatments which have shown potential benefit in human studies include therapeutic ventilation hypercapnia and terlipressin administration which have been shown to improve oxygenation and reduce lung injury[96,165].

A wide range of interventions have shown benefit in animal studies, some using substances which are already licenced for use in humans. Hypertonic saline has shown benefits in animal studies, studies reported significantly lower lung injury and oedema associated with hypertonic saline administration, which is also associated with lower rate of mortality[166-167]. TNF-α inhibition has shown promising results in animal model of ALI, which may warrant further human studies with existing anti-TNF therapy[168-169].

As discussed above, manipulation of the renin-angiotensin-aldosterone system has shown promise as treatments for ALI. ACE inhibition, ARB blockade and upregulation of ACE II have all been shown to reduce the severity of ALI in animal models[42,77,98]. Mineralocorticoid antagonist spironolactone administration has also been associated with reduced ALI in an ischaemic-reperfusion model[170]. Similarly, α-2 adrenoceptor agonist dexmedetomidine and vasopressin have also shown therapeutic benefits in animal models[92,94,96] whereas studies suggests that use of adrenaline in ALI should be avoided[87].

Despite the limited conservative management options available for perioperative ALI, more potential treatment modalities are emerging which have shown promising results. However, larger scale human studies are needed to validate those findings, and potentially contribute towards a much lower mortality and morbidity rate associated with perioperative ALI.

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