Association between Maturation and Aging and Pulmonary Responses in Animal Models of Lung Injury

A Systematic Review

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ABSTRACT

Background: Advanced age is associated with an increased susceptibility and mortality of the acute respiratory distress syndrome. This may be due to the progressive changes in innate immune responses and intrinsic properties of the lung that occur during the process of aging. Therefore, this study assesses the association between maturation and aging and pulmonary responses to injury in animal models of lung injury.

Methods: A systematic search was conducted in PubMed, EMBASE (up to June 2014) and in the references of relevant articles to identify the studies using *in vivo* models of lung injury caused by an acute pulmonary insult, in which at least two age groups were compared. Because methodological diversity precluded combining these studies in a quantitative meta-analysis, data are presented based on the qualitative comparison with the adult group.

Results: Of the 2,840 identified studies, 51 were included in this review. Most studies showed that, in response to a pulmonary insult, increasing age is associated with more pulmonary inflammation, edema, alveolar damage, and higher mortality. In addition, results indicate the existence of age-dependent changes in key components of the intracellular signaling pathways involved in the inflammatory response.

Conclusions: Increasing age seems to be correlated with exaggerated pulmonary responses to injury, ultimately leading to more severe lung injury. Pulmonary inflammation seems relatively suppressed in infants/juveniles, whereas in the middle aged/elderly, the inflammatory response seems delayed but aggravated. This implies that investigators and clinicians need to use caution about extrapolating results from adolescent or youngadult animals to pediatric or elderly patients in clinical practice.
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EPIDEMIOLOGICAL studies reveal striking differences among children, adults, and elderly in risk factors, susceptibility, course, and outcome of the acute respiratory distress syndrome (ARDS).[1–10] Although ARDS is a major contributor to mortality in all age groups, the incidence, morbidity, and mortality tend to gradually increase with age,[4,5,11] which seems partially independent of comorbidity.[9,12–14] These findings suggest potential age-dependent differences in the pathophysiology of ARDS.

In the acute phase of ARDS, the innate immune response causes inappropriate accumulation and activation of blood leukocytes, excessive production of inflammatory mediators, and uncontrolled coagulation.[15,16] Interestingly, not only the innate immune response but also intrinsic properties of the lung are known to change during the process of maturation and aging.[17–27] Although newborns have a relatively impaired immune response to bacteria,[24,27] elderly have a persistent low-grade innate immune activation generating a constitutive proinflammatory environment (termed inflammaging).[22,28] Aging is also associated with a gradual deterioration of the immune system (termed immunosenescence).[22,28] Although the interplay between these age-dependent immunological and morphological changes correlate with the clinical patterns of disease,[18,23,24,26] the underlying molecular mechanisms are poorly understood.

Of the numerous animal models used to elucidate the pathophysiology and treatment of ARDS,[29,30] most of them used adolescent or young–adult animals. However, it is

What We Already Know about This Topic

- The effects of aging on the lung response to injury is not thought about yet with an increasing aging population, this is an important concern

What This Article Tells Us That Is New

- An investigation of the literature documents that the inflammatory response to injury is exaggerated in aged animals, and there is more edema and alveolar damage and a higher mortality

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Table 1. Stages of Lung Maturation and Aging and Their Time Scale in Various Animals

Process	Stage	Species	Duration	Characteristics
Maturation				
Infants	Late saccular	Human	34–38 wk	Expansion of the airspaces
		Rabbit	E29–E30	
		Mouse	P0–P4	
		Rat	P0–P4	
	Alveolar	Human	36 wk; 1–2 yr	Alveolarization by formation of secondary septa (septation)
		Rabbit	E30–term	
		Mouse	P4–P14	
		Rat	P4–P14	
	Microvascular maturation	Human	0–3 yr	Remodeling and maturation of interalveolar septa and of the capillary bed
		Rabbit	Unknown	
		Mouse	P14–P21	
		Rat	P14–P21	
Juvenile	Normal growth	Human	2 yr to adulthood	Normal growth of the lung
		Rabbit	Birth to adulthood	
		Mouse	4 wk–2 mo	
		Rat	4 wk–3 mo	
Mature				
Young adults		Human	16–35 yr	
		Rabbit	Unknown	
		Mouse	2–10 mo	
		Rat	3–12 mo	
Late mature				
Middle aged		Human	35–60 yr	Early aging
		Rabbit	Unknown	
		Mouse	10–18 mo	
		Rat	12–24 mo	
Aging				
Elderly		Human	>60 yr	Development of senile emphysema
		Rabbit	Unknown	
		Mouse	≥18 mo	
		Rat	≥24 mo	

Reproduced with permission from McGraw-Hill Education, and this table has been partially adapted from table 5-1 by Schittny and Burri, New York, Fishman's, 2008, pp 91–114.[35] In addition, this table is extended with information based on Flurkey *et al*.,[37] Burri,[36] and Andreollo *et al*.[38] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

E = embryonic day; P = postnatal day.

increasingly clear that age impacts the susceptibility for and severity of ARDS.[31]

Accordingly, we hypothesized that maturation and aging affect the pulmonary responses to injury in an age-dependent manner, which is associated with increased lung injury and augmented inflammatory responses with increasing age. This review aims to investigate age-related differences in pulmonary responses to injury in animal models of lung injury, discuss the potential underlying mechanisms, and outline the possible implications for research and clinical management.

Materials and Methods

Search Strategy and Selection Criteria

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[32] A search was conducted in PubMed and EMBASE (up to June 2014) using variants of the following search terms: "lung injury," "maturation or aging," and "animal." The full electronic search strategy is presented in appendix 1.

L.R.S. and R.M.W. independently conducted the literature searches and assessed the eligibility of the identified publications. We included studies using standard *in vivo* animal models of lung injury caused by an acute pulmonary insult,[29,30] which compared at least two age groups. Studies included for data extraction were restricted to original full-text articles published in English. Excluded were studies that did not report at least one of the primary outcomes of interest (as described in the Data Extraction and Risk of Bias Assessment) or focused on surfactant-related infant respiratory distress syndrome.

Data Extraction and Risk of Bias Assessment

L.R.S. and R.M.W. independently extracted data from all eligible studies. The primary outcome measures included the presence of increased lung permeability (wet-to-dry

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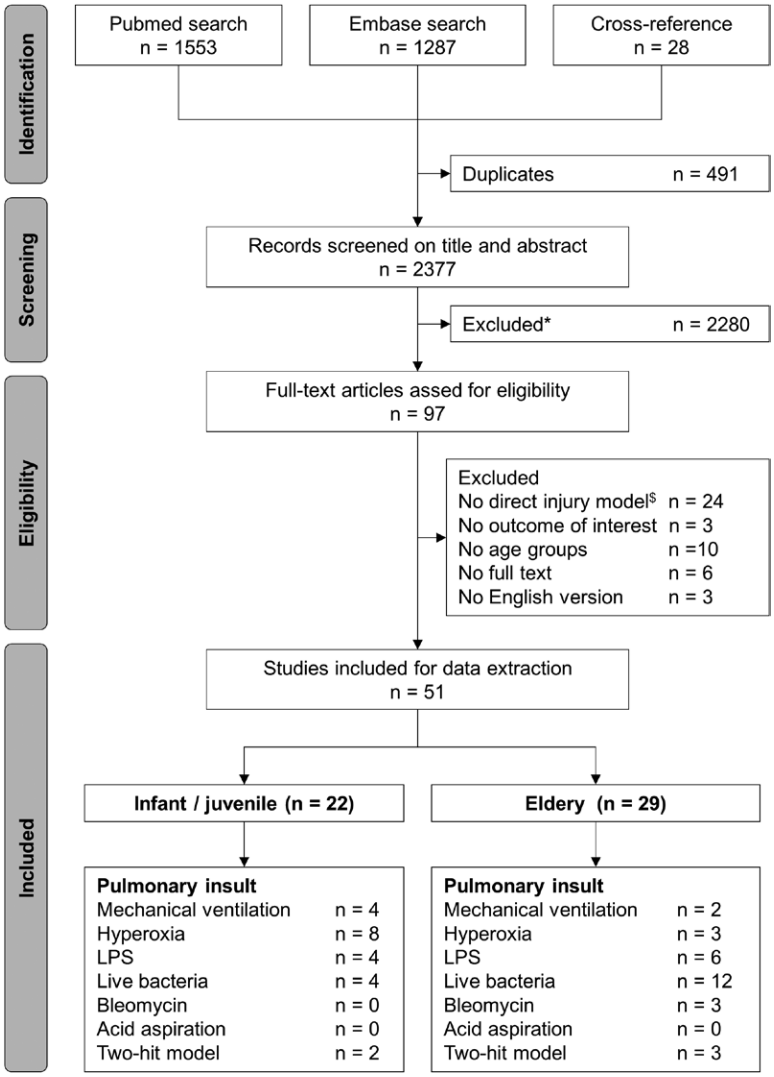

Fig. 1. Literature search strategy. *During screening of title/abstract, studies were excluded for the following reasons: no animal *in vivo* model (n = 389), no model of lung injury caused by an acute pulmonary insult[29,30] (n = 958), no comparison between two age groups (n = 719), no original study (n = 50), conference abstracts (n = 164). $Direct injury model = *in vivo* animal models of lung injury caused by an acute pulmonary insult.[29,30] LPS = lipopolysaccharide.

ratio, protein leakage, or pulmonary capillary filtration coefficient), lung injury (changes in respiratory compliance and lung injury score by histopathology), pulmonary inflammation (cell influx and levels of inflammatory mediators), oxidative stress (levels and activity of oxidants and antioxidants, including myeloperoxidase activity), and mortality. All these outcome measures are key features in the pathophysiology of ARDS.[15,16,29] In addition, information on potential underlying molecular mechanisms was extracted from the included studies.

The included studies were stratified by age groups that correspond to the developmental stages of the human lung (table 1).[35–38] First, mice aged 2 to 10 months and rats aged 3 to 12 months represented the (young-) adult reference group. Second, mice or rats aged 2 months or younger and 3 months were classified as infant/juveniles; this age group included lung developmental stages ranging from early alveolarization to lung growth. Third, mice or rats aged 10 months or older and 12 months were classified as middle aged/elderly.

We used a list of 10 items based on a recent publication evaluating a quality assessment tool for animal studies[39] to identify potential selection bias, performance bias, detection bias, and other bias. Because of the lack of a validated tool for quality assessment of animal studies, this checklist was only used to investigate the risk of bias and not to exclude studies from the data analysis due to poor quality.

Data Analysis

Methodological diversity precluded combining quantitative data from the individual studies in a meta-analysis. Therefore, we present data on the primary outcomes by means of a qualitative comparison with the adult reference group.

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Table 2. Animal Models Evaluating Differences in Lung Injury and Mortality between Infants/Juveniles and Adults

References	Pulmonary Insult	Lung Injury		Mortality
		Edema	Histology	
Adkins *et al.*[42]	VILI	↑	↑	↑
Kornecki *et al.*[43]	VILI	↓	↓*	↔
Copland *et al.*[44]	VILI	↓	↓	↓
Chan *et al.*[45]	VILI	NR	NR	↓
Smith *et al.*[46]	VILI	↑	↔	NR
Cannizzaro *et al.*[47]	VILI + hyperoxia	NR	NR	NR
Yam *et al.*[48]	Hyperoxia	↓	↓	↓
Frank *et al.*[49]†	Hyperoxia	↓	↓	↓
Ischiropoulos *et al.*[50]	Hyperoxia	↓	NR	NR
Laudert *et al.*[51]	Hyperoxia	↓	↓	↓
Keeney *et al.*[52]	Hyperoxia	↓	↓	↓
Johnston *et al.*[53]	Hyperoxia	↓	↓	↓
D'Angio *et al.*[54]	Hyperoxia	NR	↓	↓
Berkelhamer *et al.*[55]	Hyperoxia	NR	NR	↓
Martin *et al.*[56]	LPS	NR	NR	↔
Lee *et al.*[57]	LPS	NR	NR	NR
Franco *et al.*[58]	LPS	↓	↓	NR
Bodas *et al.*[59]	LPS	NR	↓	NR
Smith *et al.*[46]	LPS	↔	↔	NR
Smith *et al.*[46]	LPS + VILI	↓	↓	NR
Martin *et al.*[60]	Pneumonia	NR	NR	↔
Sordelli *et al.*[61]	Pneumonia	NR	NR	NR
Martin *et al.*[62]	Pneumonia	NR	NR	↑
Garvy and Harmsen[63]	Pneumonia	NR	NR	↑

* *Ex vivo* measurement. † Also investigated in rabbits, hamsters, and guinea pigs; data not shown.

LPS = lipopolysaccharide; NR = not reported; VILI = ventilator-induced lung injury; ↑ = increased compared with adults; ↔ = equal to adults; ↓ = decreased compared to adults.

Results

Study Selection

The initial search yielded 2,840 publications and cross-referencing identified 28 additional publications; most of these were excluded for the reasons presented in figure 1. Finally, 51 publications were selected for data extraction, *i.e.*, 22 studies on infant/juvenile animals and 29 studies on middle-aged/elderly animals. The models of lung injury that were used included ventilator-induced lung injury (VILI; 6 studies), hyperoxia (11 studies), intratracheal challenge with lipopolysaccharide (LPS; 10 studies), pneumonia models with bacteria (16 studies), and bleomycin (3 studies). In addition, five studies investigated two-hit models, combining LPS with high tidal volume mechanical ventilation, LPS with hyperoxia, or low tidal volume mechanical ventilation with hyperoxia. Of the included studies, two studies used genetically modified animals.[40,41] The effects found in these studies were similar compared with studies with nongenetically modified animals. Details on the included studies are presented in appendix 2. Overall, according to the quality checklist, there was a low risk of performance bias but a high risk of selection and detection bias (appendix 3).

Lung Injury

A clear age-dependent difference in the severity of lung injury was found in the various animal models of lung injury (tables 2 and 3). Independent of the pulmonary challenge, the majority of studies assessing differences between infants/juveniles compared with adults showed less pulmonary edema,[43,44,46,48–53,58] decreased lung tissue damage on histology,[43,44,46,48,49,51–54,58,59] and a lower mortality[44,45,48,49,51–55] (table 2). In contrast, most studies investigating middle-aged/elderly animals showed more pulmonary edema,[40,65–67,73,74,76,80–82,86,88] increased lung tissue damage on histology,[64–67,76,80–82,86,88–90] and a higher mortality compared with their adult reference group[64,65,70,73,80,85–89] (table 3). In addition, eight studies assessing lung compliance showed a more pronounced decrease in compliance with increasing age in VILI models[42–44,47,64,65] or after administration of bleomycin.[89,90] Hyperoxia was the only pulmonary challenge in the middle aged/elderly, which was consistently associated with an increased tolerance.[68–71] However, this tolerance was attenuated in models that combined hyperoxia with a second hit, such as mechanical ventilation or LPS.[66,67,70]

Pulmonary Response to Injury

Several studies assessed the baseline inflammatory status[40,44,58,73,75,82,83,85,88] (data not shown). These latter

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Table 3. Animal Models Evaluating Differences in Lung Injury and Mortality between Middle Aged/Elderly and Adults

References	Pulmonary Insult	Lung Injury		Mortality
		Edema	Histology	
Nin *et al.*[64]	VILI	NR	↑	↑
Setzer *et al.*[65]	VILI	↑	↑	↑
Moitra *et al.*[40]	VILI	↑	NR	NR
Cavassani *et al.*[66]	VILI + hyperoxia	↑	↑	NR
Andrade *et al.*[67]	VILI + hyperoxia	↑	↑	NR
Choi *et al.*[68]	Hyperoxia	↓	NR	↓
Canada *et al.*[69]	Hyperoxia	↔	↔	↓
Otterbein *et al.*[70]	Hyperoxia	↓	↓	↓
Brock and Di Giulio[71]	Hyperoxia	NR	NR	↔
Otterbein *et al.*[70]	Hyperoxia + LPS	NR	NR	↑
Elder *et al.*[72]	LPS	↔	NR	NR
Ito *et al.*[73]	LPS	↑	↔	↑
Ito *et al.*[74]	LPS	↑	NR	↔
Chiu *et al*.[75]	LPS	NR	NR	NR
Moitra *et al.*[40]	LPS	↑	NR	NR
Ren *et al.*[76]	LPS	↑	↑	NR
Esposito and Pennington[77]	Pneumonia	NR	NR	↔
Yokota *et al.*[78]	Pneumonia	NR	NR	↑
Esposito *et al.*[79]	Pneumonia	NR	NR	↔
Antonini *et al.*[80]	Pneumonia	↑	↑	↑
Hinojosa *et al.*[81]	Pneumonia	↑	↑	↑
Mares *et al.*[83]	Pneumonia	NR	↓	↓
Mares *et al.*[82]	Pneumonia	↑	↑	↔
Rottinghaus *et al.*[84]	Pneumonia	NR	NR	NR
Shivshankar *et al.*[85]	Pneumonia	NR	NR	↑
Boyd *et al.*[86]	Pneumonia	↑	↑	↑
Chen *et al.*[87]	Pneumonia	NR	NR	↑
Wen *et al.*[88]	Pneumonia	↑	↑	↑
Xu *et al.*[41]*	Bleomycin	NR	↑	NR
Redente *et al.*[89]†	Bleomycin	↔	↑	↑
Sueblinvong *et al.*[90]	Bleomycin	NR	↑	NR

* Senescence-accelerated prone mice (model of aging) *vs.* senescence-accelerated resistant mice. † In female rats, there were no differences between adults and elderly; data not shown.

LPS = lipopolysaccharide; NR = not reported; VILI = ventilator-induced lung injury; ↑ = increased compared to adults; ↔ = equal to adults; ↓ = decreased compared to adults.

studies reported lower expression of inflammatory mediators and higher levels of antioxidants in infants/juveniles[44,58] and a more activated inflammatory milieu in the middle aged/elderly[73,75,82,83,85,88] when compared with adults. Data on the number of resident alveolar macrophages and neutrophils were conflicting.[40,65,68,75,77,80,82,83]

Given that each model produces different lung injury modifying the molecular mechanisms activated,[29] we present results on the pulmonary response to injury stratified by type of pulmonary insult (tables 4 and 5). In all age groups, cell influx was predominated by neutrophils. Independent of the model used, in most studies, the recruitment of neutrophils into the lung was lower in infants/juveniles[44,46,51,52,54,56–58,60,61] (table 4) and higher in the middle aged/elderly[40,65–67,69,72–74,76–81,86,87,89] (table 5), compared with adults. Some studies reported a delayed recruitment of neutrophils in both extremes of age: infants[52,54,57,58] and elderly.[73,78,82,83,88] In addition, macrophage function in the pneumonia models was impaired in these age groups and associated with a decreased clearance of bacteria (tables 4 and 5).[60–63,77,80,81,85,86,88]

The pulmonary inflammatory mediator response in infants/juveniles was mainly studied in VILI and hyperoxia models, which showed decreased levels compared with adults[43,44,46,53,54] (table 4). Moreover, three hyperoxia models showed that the expression of antioxidants was increased in the infant/juvenile animals, which correlated with increased tolerance to hyperoxia.[48–50] The inflammatory mediator response in middle aged/elderly was dependent on the type of insult (table 5). VILI, LPS, and bleomycin all induced an increased proinflammatory response.[41,65,67,74,76,89,90] In contrast, no clear trend was seen in the pneumonia models[80–83,85–88] (table 5). Also, no correlation was found between the type of bacteria or time point of measurement and the cytochemokine and chemokine response. Although data were limited, an

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Table 4. Inflammatory and Oxidative Stress Response in the Lungs of Infants/Juveniles Compared with Adults

Infants/Juvenile	Decreased	Similar	Increased
VILI			
Inflammatory cells			
Neutrophil influx	44, 46	47	
Cytochemokines			
IL-6	44, 46	47	
TNFα	43, 44, 46		
KC		46	
IL-1β	44, 46		
MIP2		46, 47	44
MCP-1		46	
IL-10	44		
Hyperoxia			
Inflammatory cells			
Neutrophil influx	51, 52,* 54, 58		52*
Cytochemokines			
IL-6	53		
TNFα	53		
IL-1β	53, 54		
MIP2	54		
MCP-1	54		
Oxidative stress			
TBARS	50		
MPO	52		
Antioxidants			
GSH			48
SOD			48–50
GP			48, 49
GR			48
LPS			
Inflammatory cells			
Neutrophil influx	56, 57		
Macrophage function		56	57
Cytochemokines			
IL-6	59		
Pneumonia			
Inflammatory cells			
Neutrophil influx	60, 61	62, 63	
Macrophage function	60, 62		
Bacterial clearance	60–63		
Oxidative stress			
MPO	61		

The reference numbers refer to the main reference list.

* Keeney *et al.* showed difference in compartmental localization of neutrophils, with decreased neutrophils in the parenchyma of infants/juveniles, but increased neutrophils in the alveolar space.

GP = glutathione peroxidase; GR = glutathione reductase; GSH = glutathione; IL = interleukin; KC = keratinocyte chemoattractant; LPS = lipopolysaccharide; MCP = monocyte chemotactic protein; MIP = macrophage inflammatory protein; MPO = myeloperoxidase; SOD = superoxide dismutase; TBARS = thiobarbituric acid reactive substances; TNF = tumor necrosis factor; VILI = ventilator-induced lung injury.

increased oxidative stress response was found in middle aged/elderly[66,67,72,80] when compared with adults.

Molecular Signaling Pathways

Molecular mechanisms underlying the observed age-dependent differences in lung injury were investigated in several studies.[40,41,46,49,50,55,58,59,68,73,76,81,84–86,89,90] An age-dependent increase in susceptibility to lung injury was associated with differences in inflammatory and host defense

Table 5. Inflammatory and Oxidative Stress Response in the Lungs of Middle Aged/Elderly Compared with Adults

Elderly	Decreased	Similar	Increased
VILI			
Inflammatory cells			
Neutrophil influx			65–67
Cytochemokines			
IL-6			65
TNFα			67
IL-1β		65	
MIP2		65	
Oxidative stress			
MDA			66, 67
TBARS			66
MPO	40		
Hyperoxia			
Inflammatory cells			
Neutrophil influx		68	69
Oxidative stress			
MPO	70		
CAT	69		
Antioxidants			
GSH	69	68	
SOD		68, 69	
GP		68	
HO-1			68
LPS			
Inflammatory cells			
Neutrophil influx			72–74, 76
Cytochemokines			
IL-6		72	76
TNFα		72	74, 76
IL-1β		72, 74	76
MIP2			74
Oxidative stress			
MPO		40, 73	
ROS			72
Pneumonia			
Inflammatory cells			
Neutrophil influx	82, 83, 87,* 88		77–81,86,87*
Macrophage function	78, 80		
Bacterial clearance	77, 80, 81, 85, 86, 88		83
Cytochemokines			
IL-6	81, 83, 86		80, 82, 85
TNFα	81, 83	82, 86	80
KC	83		87
IL-1β	86		85
CINC	88		
IL-10	83	82	
IFNγ	82, 83	80	
IL-4	83	80, 82	
Oxidative stress			
MPO	83, 87		
ROS			80

(*Continued*)

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Table 5. Continued

Elderly	Decreased	Similar	Increased
Bleomycin			
Inflammatory cells			
Neutrophil influx			89
Cytochemokines			
TGF-b			41,† 89, 90
KC			89
CXCL12			41
MIP2		89	
IL-17			89

The reference numbers refer to the main reference list.

* Chen *et al*. showed difference in compartmental localization of neutrophils, with increased neutrophils in the parenchyma, but decreased neutrophils in the alveolar space. † Senescence-accelerated prone mice (model of aging) *vs*. senescence-accelerated resistant mice.

CAT = catalase; CINC = cytokine-induced neutrophil chemoattractant; CXCL12 = C-X-C motif chemokine 12; GP = glutathione peroxidase; GSH = glutathione; HO = heme oxygenase; IFN = interferon; IL = interleukin; KC = keratinocyte chemoattractant; LPS = lipopolysaccharide; MDA = malondialdehyde; MIP = macrophage-inflammatory protein; MPO = myeloperoxidase; ROS = reactive oxygen species; SOD = superoxide dismutase; TBARS = thiobarbituric acid reactive substances; TGF = transforming growth factor; TNF = tumor necrosis factor; VILI = ventilator-induced lung injury.

signaling pathways, including altered gene expression,[46] transcription factors,[46,59,68,81] phosphorylation of intracellular signaling molecules,[76,81,84,86] and membrane sensing molecules[46,81,85,86] (table 6). In addition, age-related intrinsic dysregulation of proteostasis (protein homeostasis) induced a proinflammatory state that augmented lung injury.[59] In contrast, infants showed increased expression of genes encoding antioxidants resulting in decreased lung injury when compared with adults.[49,50,55] Finally, age-dependent differences were found in molecular pathways involved in the repair and remodeling phase of ARDS. Aged animals showed a lower expression of components of the vascular endothelial growth factor receptor pathway, known to play a protective role in ARDS.[73] In contrast, high age was associated with increased levels of components of the profibrotic response such as transforming growth factor and metalloproteinases.[41,58,89,90] Figure 2 provides a summary of the differences between infants/juveniles and middle-aged/elderly animals compared with the adult reference group.

Discussion

The main finding of this systematic review is that increased age is associated with exaggerated pulmonary responses to injury. *In vivo* animal models of lung injury consistently show that age is an important independent host factor influencing fundamental pathophysiological mechanisms known to be involved in ARDS. This influence of age seems far more complex than merely a more pronounced proinflammatory or antiinflammatory response; age tends to affect multiple processes of the pulmonary response to injury (fig. 2).

The findings on preclinical studies are in line with epidemiological studies showing that the incidence of ARDS in children is lower than in adults, whereas the incidence and mortality are significantly higher in elderly.[1–10] The data from this review support the clinical findings that increased susceptibility to ARDS in elderly is not only due to comorbidity[9,12–14] but also due to age, which is an important independent determinant associated with severity of lung injury.

Pathophysiology of ARDS in the Context of Maturation and Aging

This review shows that, in different animal models of lung injury, increasing age is associated with increased endothelial–epithelial permeability, altered function of alveolar macrophages, increased influx of neutrophils, an exaggerated inflammatory mediator response, and increased oxidative stress (fig. 2). Studies addressing underlying molecular mechanisms of these age-dependent differences in the pulmonary response to injury are limited. However, they are in line with studies investigating the processes of maturation and aging in general. Prominent aging-associated alterations in the inflammatory response include dysfunctional immune cells, senescent cells that secrete proinflammatory cytokines, and the occurrence of a defective autophagy response.[22] Moreover, recent evidence indicates that neutrophils from humans of advanced age show untargeted tissue migration with increased primary granule release and neutrophil elastase activity leading to more tissue inflammation.[91] This may in part explain the delayed but overwhelming recruitment and extensive alveolar damage found in elderly animals with lung injury. In addition, aging in general is associated with changes in intracellular signaling pathways involved in inflammation and cell integrity.[22] Increasing age is associated with overactivation of the nuclear factor-κB pathway.[22,59,68,81] Taken together, these alterations result in a proinflammatory state, failure to effectively clear pathogens, dysfunctional host cells, and impaired repair mechanisms making elderly prone to exaggerated responses to injury.

In the context of current evidence on maturation and aging, we speculate that age-dependent changes in morphology, cell integrity, and the innate immune response are important determinants of the severity of lung injury after a pulmonary challenge (fig. 3). Together with comorbidity and physiological reserves, these patient-related biological factors may ultimately determine the susceptibility of the patient to develop ARDS.

Limitations

To the best of our knowledge, this is the first review to systematically investigate current knowledge on the effect of age on the pulmonary response to acute injury in preclinical models. Despite the clear association emerging between age and differences in the pulmonary response, some limitations of this study need to be addressed.

Systematic reviews are subject to publication bias of the studies showing no differences.[92] In addition, quality assessment showed a high risk of selection and detection bias in the included studies, which could overrate their conclusions. Only a minority of the studies reported the use of randomization (24%) and blinding (29%). Although in animal experiments, variation between

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Table 6. Molecular Mechanisms Associated with Age-dependent Alterations in Pulmonary Response to Injury

Molecular Mechanism	Pulmonary Insult	Influence of Age	Lung Injury
NF-κB signaling[59,68,81]	Unchallenged	Age-related increase in NF-κB expression associated with increased inflammation	Not applicable
Transcription factors regulating stress-responsive genes[68]	Hyperoxia	Decreased binding activity of regulatory transcription factors (AP1, c-fos, NF-κB, and C/EBP) and delayed mRNA expression in eldery	Decreased
Altered transcriptional landscape[46]	LPS + VILI	Age-dependent differential gene expression in response to injury, predominately by upregulation of host defense genes (*Kras*, *Myc*, *Cdkn1*, *CD14*, *TLR4*, *TIRAP*) in adults and genes involved in cell differentiation and apoptosis (*App*, *Blc2*, *Fn1*, *Stat1*, *SMAD4*) in infants	Increased
TLR signaling pathway[76,81,84,86]	LPS/pneumonia	Age-dependent difference in TLR expression, function, and phosphorylation of downstream signaling molecules (ERK, JNK, pp65, and p38)	Increased
Bacterial cell surface adhesion molecules[85]	Pneumonia	Increased expression of cell surface adhesion molecules, platelet-activating factor receptor, polymeric immunoglobulin receptor, keratin-10 and LR in elderly	Increased
Ubiquitin proteasome system[59]	LPS	Increasing age is associated with proteostasis imbalance that leads to accumulation of ubiquitinated proteins inducing increased NF-κB levels, ER stress, and apoptosis	Increased
Antioxidants[49,50,55]	Hyperoxia	Increased expression of antioxidants including superoxide dismutases, catalase, and glutathione peroxidase in infants	Decreased
VEGF signaling pathway[73]	LPS	Lower expression of VEGF A, B, C and VEGF receptors in elderly	Increased
TGFβ1-SMAD pathway[41,89,90]	Bleomycin	Increased levels of TGF-receptor 1 and TGF-1 mRNA, protein, and activity as determined by increased Smad3 expression, protein phosphorylation, and DNA binding in elderly	Increased
Metalloproteinases[58,90]	Unchallenged/LPS	Profibrotic phenotype characterized by increased mRNA expression of fibronectin extracellular domain A, MMP-2, and MMP-9 with increasing age	Increased
Stromal cell-derived factor[41]	Bleomycin	Increased number of fibroblast progenitor cells/fibrocytes and a decrease in the ability of mesenchymal stem cells to respond to SDF-1 generated by the injured lung with increasing age in SAMP mice	Increased

AP1 = activator protein 1; C/EBP = CCAAT-enhancer-binding proteins; ER = endoplasmic reticulum; LPS = lipopolysaccharide; LR = laminin receptor; MMP = metalloproteinase; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; SAMP = senescence-accelerated prone; SDF = stromal cell-derived factor; TGF = transforming growth factor; TLR = toll like receptor; VEGF = vascular endothelial growth factor; VILI = ventilator-induced lung injury.

groups is limited by genetic homogeneity and standardized (pre-) experimental conditions, lack of randomization and blinding can reduce the internal validity of an animal experiment,[93,94] implying that differences found between the experimental groups may not be attributed to the treatment under study.[95] Moreover, none of the included studies showed a power calculation. Sample size calculation is required to reduce the incidence of false-negative or false-positive outcomes between groups and to keep the number of animals used as low as possible in view of legal requirements and ethical/practical considerations.[95] These forms of potential bias have also been found in other reviews assessing the quality of animal models[95–97] and probably contribute to the large gap between preclinical and clinical research.[95–99] Use of recently published guidelines for reporting animal research, such as the ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guidelines[100] and STREAM (Studies of Translation, Ethics and Medicine) checklist,[97] have the potential to improve experimental design and reporting of animal studies, as such preventing these problems. Differential use of animal species, lung injury models, exposure time, doses, and variation in outcome measures makes it difficult to pool the data and may also account for some of the conflicting results.[29,30] Therefore, the current review focused only on the pulmonary processes and limited the search to models of lung injury induced by a pulmonary challenge. On the other hand, the consistent outcome in the various pulmonary insults studied underlines the importance of the influence of age. To summarize the current data, we decided to pool the data into three age groups; however, the delineation of these age groups is debatable. The infant/juvenile group includes many different maturational stages, whereas the elderly group includes studies with late-mature animals, corresponding with middle-aged adults. The heterogeneity in these age groups may have influenced the analysis; however, as we aimed to investigate a trend in increasing lung injury with increasing age, the precise classification of age may be less important. Finally, one could argue that the effects found in most of the studies is because of overdosing with increasing age, because most studies use body weight to titrate their pulmonary challenge. It is known that the ratio between lung volume and body weight in mice and rats declines with increasing age[19,101]; therefore, dosing the pulmonary challenge based on lung weight or lung volume would be more accurate. However, because studies that used lung weight showed similar effects, it is unlikely that the associations found are exclusively because of overdosing or underdosing.

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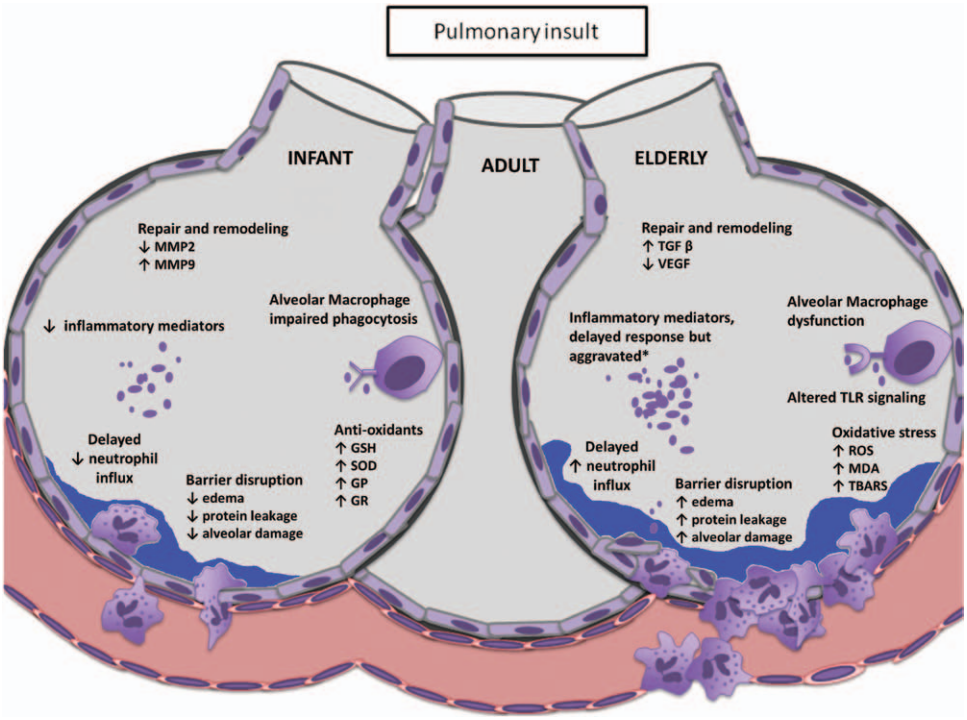

Fig. 2. Summary of the age-dependent differences in pulmonary responses to injury found in the included studies. *The response of inflammatory mediators in elderly was dependent on the type of insult. Ventilation-induced lung injury models and lipopolysaccharide and bleomycin models showed increased levels. In contrast, there was no clear trend in the pneumonia models. GP = glutathione peroxidase; GR = glutathione reductase; GSH = glutathione; MDA = malondialdehyde; MMP = matrix metallopeptidase; ROS = reactive oxygen species; SOD = superoxide dismutase; TBARS = thiobarbituric acid reactive substances; TGF = transforming growth factor; TLR = toll-like receptor; VEGF = vascular endothelial growth factor.

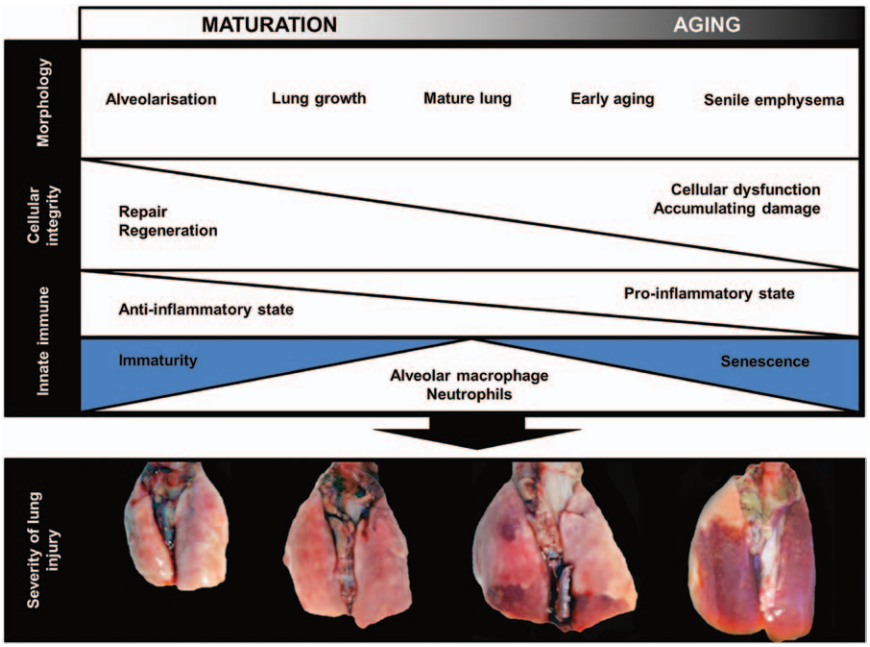

Fig. 3. Influence of maturation and aging on the severity of lung injury. On the basis of the evidence from the included animal studies of acute respiratory distress syndrome in this systematic review, in the context of the current knowledge on maturation and aging, we speculate that the interaction among age-dependent changes in morphology, cell integrity, and the immune response is an important determinant of the severity of lung injury after a pulmonary challenge. The macroscopic pictures of the lungs are preliminary data of a two-hit animal model of lung injury, in which infant, juvenile, adult, and elderly rats were exposed to an identical challenge of lipopolysaccharide combined with mechanical ventilation.

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Conclusions and Recommendations for Future Studies

Our findings imply that results from animal models conducted in adolescent or young adult animals cannot be directly translated to patient populations of different age. To develop effective translational animal models of lung injury, appropriate age groups corresponding with the clinical patient population of interest should be used. In addition, unraveling the underlying mechanisms of age-dependent differences in ARDS could lead to more appropriate design of clinical trials for both children and elderly and may have potential therapeutic implications in the development of age-specific therapeutic targets. However, because the process of maturation and aging is continuous and dynamic, age groups do not necessarily have strict boundaries. Close collaboration between pediatric and adult intensive care physicians is important to further optimize treatment for the individual patient.

In conclusion, this systematic review shows that the pulmonary response to injury varies with age, which may have potential therapeutic implications. Although age-dependent changes in the innate immune response play an important role, the underlying molecular mechanisms are not well understood. In the future, well-designed animal and clinical studies, using appropriate age groups, could unravel these mechanisms and may provide new age-directed therapeutic targets for ARDS.

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Competing Interests

The authors declare no competing interests.

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Appendix 1. Full Electronic Search Strategy for PubMed and EMBASE

PubMed	
Lung	("lung injury" [MeSH] OR "acute lung injury" [MeSH] OR "Respiratory Distress Syndrome, Adult" [MeSH] OR "Ventilator-Induced Lung Injury" [MeSH] OR "acute lung injury" [Tiab] OR "ARDS" [Tiab] OR "acute respiratory distress syndrome" [Tiab] OR "acute respiratory distress" [Tiab] OR "lung injury" [Tiab] OR "lung inflammation" [Tiab] OR "lung damage" [Tiab] OR "pulmonary inflammation" [Tiab] OR "pulmonary damage" [Tiab] OR "Ventilator-Induced Lung Injury" [Tiab] OR "pulmonary clearance" [Tiab] OR "pulmonary infiltration" [Tiab])
Model	("Respiration, Artificial" [MeSH] OR "Lipopolysaccharides" [MeSH] OR "Oleic Acid" [MeSH] OR "Respiratory Aspiration" [MeSH] OR "Bleomycin" [MeSH] OR "Acids" [MeSH] OR "Bacteria" [MeSH] "Hyperoxia" [MeSH] OR "pneumonia" [MeSH] OR "mechanical ventilation" [Tiab] OR "Lipopolysaccharid*" [Tiab] OR "tidal volume" [Tiab] OR "barotrauma" [Tiab] OR "volutrauma" [Tiab] OR "Oleic Acid" [Tiab] OR "Acid aspiration" [Tiab] OR "Bleomycin*" [Tiab] OR "Acid*" [Tiab] OR "Bacteria" [Tiab] OR "Hyperoxia" [Tiab] OR "pneumonia" [Tiab] OR "Saline lavage" [Tiab] OR "aspiration*" [Tiab] OR "LPS" [Tiab] OR "ventilation" [Tiab])
Aging	("Aging" [MeSH] OR "Growth and Development" [MeSH] OR "Aged" [MeSH] OR "aging" [Tiab] OR "ageing" [Tiab] OR "aged" [Tiab] OR "age" [Tiab] OR "lung development" [Tiab] OR "maturation" [Tiab] OR "Elderly*" [Tiab] OR "pediatric*" [Tiab] OR Neonatal* [Tiab] OR "paediatric*" [Tiab] OR "infant*" [Tiab] OR "juvenile*" [Tiab])
Animals	Laboratory animal search filter[33] ("animal experimentation" [MeSH] OR "models, animal" [MeSH] OR "Animals" [MeSH:noexp] OR "animal population groups" [MeSH] OR "chordata" [MeSH:noexp] OR "chordata, nonvertebrate" [MeSH] OR "vertebrates" [MeSH:noexp] OR "mammals" [MeSH:noexp] OR "primates" [MeSH:noexp] OR "rodentia" [MeSH] OR ((animals[tiab] OR animal [Tiab] OR mice [Tiab] OR mouse [Tiab] OR murine [Tiab] OR woodmouse [tiab] OR rats [Tiab] OR rat [Tiab] OR murinae [Tiab] OR muridae [Tiab] OR cottonrat [Tiab] OR cottonrats [Tiab] OR hamster [Tiab] OR hamsters [Tiab] OR rodentia [Tiab] OR rodent [Tiab] OR rodents [Tiab] OR pigs [Tiab] OR pig [Tiab] OR swine [Tiab] OR swines [Tiab] OR piglets [Tiab] OR piglet [Tiab] OR boar [Tiab] OR boars [Tiab] OR "guinea pigs" [Tiab] OR "guinea pig" [Tiab] OR cavia [Tiab] OR rabbits [Tiab] OR rabbit [Tiab] OR dogs [Tiab] OR dog [Tiab] OR sheep [Tiab] OR sheeps [Tiab] OR ovis [Tiab] OR goats [Tiab] OR goat [Tiab] OR monkey [Tiab] OR monkeys [Tiab] OR ape [Tiab] OR apes [Tiab] OR chimpanzee [Tiab] OR chimpanzees [Tiab] OR gorilla [Tiab] OR gorillas [Tiab] OR orangutans [Tiab] OR horse [Tiab] OR horses [Tiab] OR wistar [Tiab] OR "sprague dawley" [Tiab] OR C57BL6 [Tiab] OR BALB [Tiab] OR F-344 [Tiab] OR ICR [Tiab] OR "New Zealand White" [Tiab]) NOT medline[sb]))
EMBASE	
Lung injury	Exp *lung injury/ OR Exp acute lung injury/ OR Exp Respiratory Distress Syndrome/ or *respiratory distress syndrome/ OR Exp *adult respiratory distress syndrome/ or Exp *ventilator induced lung injury/ OR (acute lung injury or ARDS OR acute respiratory distress syndrome OR lung injury OR lung inflammation OR lung damage OR pulmonary inflammation OR pulmonary damage).ti,ab.
Model	Exp tidal volume/ OR Exp artificial ventilation/ OR Exp mechanical ventilation/ OR Exp Respiration, Artificial/ OR Exp Lipopolysaccharide/ OR Exp Oleic Acid/ OR Exp artificial ventilation / OR Exp Respiratory Aspiration/ OR Exp Bleomycin/ OR Exp Acids/ OR Exp Bacteria/ OR Exp pneumonia/ OR Exp Hyperoxia/ OR (mechanical ventilation OR Lipopolysaccharide OR Oleic Acid OR Acid aspiration OR Bleomycin OR Acids OR Bacteria OR pneumonia OR Hyperoxia OR Saline lavage OR aspiration).ti,ab.
Aging	Exp *aging/ OR Exp *"growth, development and aging"/ OR Exp Aging/ OR Exp lung development/ OR Exp Aged/ OR (aging OR aeging OR aged OR "lung development" OR maturation OR elderly OR pediatric OR juvenil OR paediatric OR neonatal OR infant OR senescent).ti,ab.
Animals	*Laboratory animal search filter*[34] *experimental animal/ OR Exp *experimental cat/ OR Exp *experimental dog/ OR Exp *experimental guinea pig/ OR Exp *experimental host/ OR Exp *experimental monkey/ OR Exp *experimental mouse/ OR Exp *experimental pig/ OR Exp *experimental rabbit/ OR Exp *experimental rat/ OR Exp *germfree animal/ OR Exp *spinal animal/ OR (animal OR animals OR dog OR dogs OR pig OR pigs OR swine OR swines OR hog OR hogs OR boar OR boars OR porcine OR piglet OR piglets OR sheep OR sheeps OR lamb OR lambs OR goat OR goats OR rabbit OR rabbits OR rodentia OR rodent OR rodents OR murinae OR mouse OR mice OR mus OR musculus OR murine OR woodmouse OR apodemus OR rat OR rats OR rattus OR guinea pig OR guinea pigs OR cavia OR porcellus OR hamster OR hamsters OR marmot OR marmots OR cottonrat OR cottonrats OR primate OR primates OR monkey OR monkeys OR ape OR apes OR wistar OR F-344 OR C57BL6 OR BALB).ti,ab.

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Appendix 2. Study Characteristics of the Included Studies

References	Species	Strain	Gender	Lung Development Stage	Age of the Study Group	Age of the Reference Group
Adkins *et al.*[42]	Rabbits	NZW	NR	Growth	4–6 wk	2.1–3.0 kg; age not reported
Kornecki *et al.*[43]	Rats	SD	M	Microvascular maturation	17 d	75 d
Copland *et al.*[44]	Rats	SD	M	Alveolar stage	5–8 d	3–4 mo
Chan *et al.*[45]	Rats	SD	M	Alveolar stage	5 d	300 g; age NR
Smith *et al.*[46]	Mice	C57BL6	M	Microvascular maturation	3 wk	16 wk
Cannizzaro *et al.*[47]	Mice	BALB/c	F	Alveolar stage	2 wk	8 wk
Yam *et al.*[48]	Rats	SD	M/F	Alveolar stage	4–7 d	80 d
Frank *et al.*[49]	Guinea pig; hamster;mice; rabbit; rats	SD; NR	NR	Alveolar stage	2–10 d	Adults; age NR
Ischiropoulos *et al.*[50]	Rats	SD	M	Microvascular maturation	20–23 d	3.5 mo
Laudert *et al.*[51]	Rats	SD	NR	Late saccular; microvascular maturation; growth	1, 27, 44 d	96 d
Keeney *et al.*[52]	Rats	SD	M	Late saccular	0 d	60–75 d
Johnston *et al.*[53]	Mice	C57BL/6	M	Late saccular	2 d	8 wk
D'Angio *et al.*[54]	Mice	C57BL6	M	Late saccular stage	1, 5 d	8 wk
Berkelhamer *et al.*[55]	Mice	C57BL/6	F	Alveolar stage; microvascular maturation	7–21 d	8 wk
Martin *et al.*[56]	Rats	SD	M	Late saccular; alveolar stage; microvascular maturation; growth	0, 3, 7, 15, 28 d	150–200 g; age, NR
Lee *et al.*[57]	Rats	PVG	NR	Late saccular; alveolar stage	1, 7 d	9–11 wk
Franco *et al.*[58]	Rats	SD	M	Alveolar stage	6 d	250 g; age, NR
Bodas *et al.*[59]	Mice	C57BL/6	M	Microvascular maturation	3 wk	6 mo
Martin *et al.*[60]	Rats	SD	M	Late saccular	12, 24, 36 h	150 g, 6 wk
Sordelli *et al.*[61]	Mice	Swiss	NR	Alveolar stage; microvascular maturation; growth	10, 20, 35 d	NR
Martin *et al.*[62]	Rats	SD	M	Late saccular	6–12 h	150–200 g; age, NR
Garvy and Harmsen[63]	Mice	BALB/c	M	Late saccular	24 h	8–10 wk
Nin *et al.*[64]	Rats	Wistar	M	Aging	22 – 24 mo	3–4 mo
Setzer *et al.*[65]	Rats	Wistar	M	Aging	19 mo	4.4 mo
Cavasani *et al.*[66]	Rats	Wistar	M	Aging	24 mo	4 mo
Andrade *et al.*[67]	Rats	Wistar	M	Late mature	20 mo	8 mo
Moitra *et al.*[40]	Mice	WT/MLCK2 TG*	M/F	Late mature	30–36 wk	8–12 wk
Choi *et al.*[68]	Rats	Wistar	M	Aging	24 mo	6 mo
Canada *et al.*[69]	Rats	Fischer 344	M	Aging	27 mo	2 mo
Otterbein *et al.*[70]	Rats	F-344/SD	M	Aging	24 mo	6 mo
Brock and Di Giulio[71]	Rats	Wistar	M	Late mature	22 mo	3 mo
Elder *et al.*[72]	Rats/mice	F-344/ C57B1/6J	M	Aging	21 mo	2–3 mo
Ito *et al.*[73]	Mice	ICR	M	Late mature	65 wk	11 wk
Ito *et al.*[74]	Mice	ICR	M	Late mature	65 wk	11 wk
Chiu *et al.*[75]	Mice	C57BL/6	M	Aging	20–24 mo	4–5 mo
Ren *et al.*[76]	Mice	C57BL/6j	M	Aging	20 mo	2 mo
Esposito and Pennington[77]	Mice	C57BL/6j	NR	Aging	26–28 mo	6–8 mo

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Pulmonary Insult	Doses	Animals per Group	Time to Measurement	Primary Outcome
Peak inspiratory pressure	15, 30, 45, or 55 cm H_2O	n = 5	60 min	Microvascular permeability
Peak inspiratory pressure	20, 30 cm H_2O	n = 4–6	90 min	Change in compliance; wet to dry, TNFα
Tidal volume	25, 40 ml/kg	n = 4–6	30, 90, 180 min	Cytokine mRNA expression in the lung
Tidal volume	30 ml/kg	n = 4–6	90 min	Clotting cascade
LPS; tidal volume	LPS: aerosol 0.1 mg/ml; 15 ml/kg	n = 10–12	30 min aerosol; 2–3 h MV	Cytokines
Tidal volume + O_2	10 ml/kg; FIO_2, 0.21, 0.30, 0.60	n = 8	3–6 h	Cytokines, oxidative stress
O_2	FIO_2, 0.96–0.98, chamber	n = 4–10	72 h; survival	Antioxidants
O_2	FIO_2, 0.95–0.99, chamber	n = 3–6	24 h; survival	Antioxidants
O_2	FIO_2, >0.95, chamber	n = 3–18	8, 24, 48, 60 h	Oxidative stress
O_2	FIO_2, 1.00, chamber	NR	up to 22 d	Mortality; histology; antioxidants
O_2	FIO_2, >0.98, chamber	n = 3–12	2, 5, 3, 7 d	Injury; neutrophil influx
O_2	FIO_2, >0.95, chamber	n ≥ 3	2–10 d	Cytokine mRNA expression in the lung
O_2	FIO_2, >0.95, chamber	n = 8	4, 7, or 10 d	Chemokine mRNA expression
O_2	FIO_2, 0.75, chamber	n = 6	24 h	Oxidative stress
LPS, *Escherichia coli* 0111:B4	5 mg/ml, 11 μl/100 mg lung weight, i.t.	n = 4–15	6 h	Inflammatory cells
Heat-killed *Moraxella catarrhalis*	1 h aerosol	NR	1 h	Inflammatory cells
LPS, *E. coli* 0111:B4	0.2 g/kg; 2.0 g/kg dry lung weight, i.t.	n = 4–17	1 or 15 d	Inflammation; gelatinase activity
LPS; *Pseudomonas aeruginosa*	1 μg/mg body weight, i.t.	n = 3–4	24 h	Cytokines; apoptosis
Streptococcus pneumoniae; *P. aeruginosa*; *Streptococcus aureus*	Different doses aerosol	n = 4–15	4, 24 h	Inflammatory cells
P. aeruginosa	10^6 CFU/g lung aerosol	n = 6	4 h	PMN recruitment
group B streptococci	Different doses, i.t.	n = 3–12	6 h	Inflammatory cells
S. pneumoniae	Different doses, i.n.	n = 4–5	24 h	Neutrophil
Tidal volume	9, 35 ml/kg	n = 6	1 h	Histology; physiology
Tidal volume	8, 16, 24 ml/kg	n = 15	4 h	Histology; cytokines
Tidal volume + O_2	7 ml/kg; FIO_2, 1.0	n = 7	1, 3 h	Inflammation; oxidative stress
Tidal volume + O_2	6 ml/kg; FIO_2, 1.0	n = 5	3, 6 h	Inflammation; oxidative stress
Tidal volume; LPS	30 ml/kg; 5 mg/kg, i.t.	n = 4–7	24, 2 h	Permeability; inflammatory cells
O_2	FIO_2, 1.0, chamber	n = 3–32	24, 56, 72 h	Inflammation; oxidative stress
O_2	FIO_2, >0·80, chamber	NR	55 h	Survival; histology; antioxidants
LPS; O_2	LPS aerosol; FIO_2, 1.0, chamber	NR	24, 48, 61, 96 h	Histology; apoptosis
O_2	FIO_2, 0.98–1.00, chamber	n = 5	72 h	Edema; mast cells
LPS *P. aeruginosa*	4×10^6 EU/mg aerosol	n = 5–9	24 h	Inflammation; oxidative stress
LPS	200 μg/body, i.t.	n = 4–8	24, 72 h	Histology; VEGF expression
LPS	200 μg/body, i.t.	n = 5–13	2, 6, 12, 24, 72 h	Inflammation
LPS	3 μg/15 μl, i.n.	n = 4–6	6 d	Inflammatory cells
LPS	200 μg/50 μl, i.n.	n = 4–6	0, 5, 4, 24, 72 h	Inflammation; p38 signaling pathway
S. pneumoniae; *Klebsiella*	0.06 ml × different doses	n = 4–6	6, 24, 48 h	Inflammatory cells

(*Continued*)

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Appendix 2. Continued

References	Species	Strain	Gender	Lung Development Stage	Age of the Study Group	Age of the Reference Group
Yokota *et al.*[78]	Mice	ICR	M	Late mature	60 wk	4 wk
Esposito *et al.*[79]	Mice	C57BL/6j	F	Aging	26–28 mo	8–10 mo
Antonini *et al.*[80]	Rats	F-344	M	Late mature; aging	>20 mo	2.5 mo
Hinojosa *et al.*[81]	Mice	Balb/cBy	NR	Aging	19–20 mo	4–5 mo
Mares *et al.*[82]	Mice	C57BL/6	M	Aging	20–24 mo	8–12 wk
Mares *et al.*[83]	Mice	C57BL/6	F	Aging	22–24 mo	6–8 wk
Rottinghaus *et al.*[84]	Mice	C57BL/6	F	Aging	18 mo	2 mo
Shivshankar *et al.*[85]	Mice	Balb/cBy	F	Aging	19–22 mo	4–5 mo
Boyd *et al.*[86]	Mice	BALB/cBy	F	Aging	19–21 mo	4–5; 10–12 mo
Chen *et al.*[87]	Mice	BALB/c	F	Aging	18–20 mo	10–12 wk
Wen *et al.*[88]	Rats	SD	M	Late mature	20–22 mo	5–6 mo
Xu *et al.*[41]	Mice	SAMP8*/ SAMR1*	F	Late mature	12 mo	6 mo
Redente *et al.*[89]	Mice	C57BL6	M/F	Late mature	52–54 wk	8–12 wk
Sueblinvong *et al.*[90]	Mice	C57BL/6j	NR	Aging	24 mo	3 mo

* Genetically modified animals.

CFU = colony-forming unit; EU = endotoxin units; F = female; i.n. = intranasal; i.t. = intratracheal; LPS = lipopolysaccharide; M = male; MLCK2 TG = nonmuscle myosin light chain kinase transgenic; MV = mechanical ventilation; NR = not reported; SAMP = senescence-accelerated prone; SAMR = senescence-accelerated resistant; TLR = toll like receptor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

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Pulmonary Insult	Doses	Animals per Group	Time to Measurement	Primary Outcome
Klebsiella FP221	1.5×10^9 CFU/ml for 20 min, aerosol	n = 5–10	4, 24, 72 h	Inflammatory cells
S. pneumoniae	10^7 CFU/ml 50 μl, i.t.	n = 4–6	24 h, survival	Inflammatory cells
Listeria monocytogenes	10^3; 10^4; 10^5, i.t.	n = 4–9	3, 5, 7 d	Histology; inflammation
S. pneumoniae serotype 4	10^7 CFU, i.n.	n = 4–7	24, 36 h	Inflammation; co-opt proteins
Francisella tularensis	2×10^3 CFU/20 μl, i.n.	n = 16–19	3, 5, 8 d	Inflammation
Francisella novicida	4×10^2; 9×10^2/20 μl, i.n.	n = 3–18	6, 24, 72 h	Inflammation
Mycobacterium tuberculosis	50–100 viable bacteria/lung aerosol, 30 min	n = 4–5	12 d	Inflammation; TLR signaling
S. pneumoniae	$10^{5–7}$ CFU/25–100 μl, i.t.	n = 3–6	2 d	Inflammation
S. pneumoniae	$1.0 \times 10^{5–7}$ CFU, i.n./i.t.	n = 3–8	4 h	Inflammation; TLR signaling
P. aeruginosa	100 μl 10,000–40,000, 100,000 CFU, i.t.	n = 4	24 h	Inflammation
P. aeruginosa	0.2 ml 6×10^8 CFU/ml, i.t.	n = 4–20	2, 6, 9, 12, 24 h	Inflammation
Bleomycin	3.6 units/kg, i.t.	n = 4–7	7, 14 d	Histology; fibrosis
Bleomycin	3.0 units/kg, i.t.	n = 15	2 wk	Histology; inflammation
Bleomycin	3.5 units/kg, i.t.	n = 4–10	14 d	Histology; fibrosis

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Appendix 3. Outcome Quality Assessment

References	Selection Bias (Randomization)	Performance Bias: House Holding Conditions	Performance Bias: Test Animals Description	Performance Bias: Details on Experimental Protocol	Detection Bias: Blind Outcome Assessment	Detection Bias: All Animals Accounted for	Detection Bias: Samples Size Calculation	Other Bias: Conflict of Interest Disclosure	Other Bias: Compliance with Animal Welfare Requirements	Other Bias: Statistical Model Explained
Adkins *et al.*[42]	No	No	Yes	Yes	No	Yes	No	No	Yes	Yes
Andrade *et al.*[67]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Antonini *et al.*[80]	No	Yes	Yes	Yes	Yes	No	No	No	No	Yes
Berkelhamer *et al.*[55]	No	No	Yes	Yes	No	No	No	No	Yes	Yes
Bodas *et al.*[59]	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Boyd *et al.*[86]	No	No	Yes	Yes	Yes	No	No	No	Yes	Yes
Brock and Di Giulio[71]	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Canada *et al.*[69]	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Cannizzaro *et al.*[47]	No	No	Yes	Yes	No	No	No	Yes	Yes	Yes
Cavassani *et al.*[66]	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Chan *et al.*[45]	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Chen *et al.*[87]	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Chiu *et al.*[75]	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Choi *et al.*[68]	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Copland *et al.*[44]	No	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes
D'Angio *et al.*[54]	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes
Elder *et al.*[72]	No	Yes	Yes	Yes	No	No	No	Yes	No	Yes
Esposito and Pennington[77]	No	Yes	Yes	Yes	No	No	No	Yes	No	Yes
Esposito *et al.*[79]	No	Yes	Yes	Yes	No	No	No	Yes	No	Yes
Franco *et al.*[58]	No	Yes	Yes	Yes	no	No	No	Yes	No	Yes
Frank *et al.*[49]	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes
Garvy and Harmsen[63]	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes
Hinojosa *et al.*[81]	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Ischiropoulos *et al.*[50]	No	Yes	Yes	Yes	No	No	No	Yes	No	Yes
Ito *et al.*[73]	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes
Ito *et al.*[74]	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes
Johnston *et al.*[53]	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes
Keeney *et al.*[52]	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Kornecki *et al.*[43]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Laudert *et al.*[51]	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes
Lee *et al.*[57]	No	Yes	Yes	Yes	No	No	No	No	Yes	No
Mares *et al.*[83]	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Mares *et al.*[82]	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Martin *et al.*[60]	No	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes
Martin *et al.*[62]	No	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes

(*Continued*)

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Appendix 3. Continued

Martin *et al.*[56]	No	No	Yes	Yes	No	Yes	No	Yes	No	Yes
Moitra *et al.*[40]	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes
Nin *et al.*[64]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Otterbein *et al.*[70]	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Redente *et al.*[89]	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Ren *et al.*[76]	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Rottinghaus *et al.*[84]	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes
Setzer *et al.*[65]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Shivshankar *et al.*[85]	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Smith *et al.*[46]	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Sordelli *et al.*[61]	No	No	Yes	Yes	No	Yes	No	Yes	No	Yes
Sueblinvong *et al.*[90]	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Wen *et al.*[88]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Xu *et al.*[41]	No	No	Yes	Yes	No	No	No	No	Yes	Yes
Yam *et al.*[48]	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes
Yokota *et al.*[78]	No	Yes	Yes	Yes	No	Yes	No	No	No	Yes
Total (yes/total)	12/51	37/51	51/51	51/51	15/51	22/51	0/51	33/51	35/51	50/51

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Balanced Anesthesia with Moonflowers and Monkshoods: Behind Hanaoka's *Mafutsusan* (Year 1804, Part 3)

After adding four minor sedating herbs to his gradually ranging ratio from a 2:1 up to a 4:1 mixture by weight of moonflowers to monkshoods, Japan's Seishū Hanaoka (1760–1835) produced an herbal potion now considered the world's first successful *recorded* surgical anesthetic. Not a "slash and dash" surgeon, Hanaoka spent two decades formulating his anesthetic *mafutsusan* ("powder to make go away") in order to minimize his patients' side effects by balancing moonflowers' tachycardia against monkshoods' bradycardia and by allowing monkshoods' aconitine to potentiate moonflowers' anticholinergic delirium. Hanaoka's use of mafutsusan for surgical anesthesia preceded William Morton's ether demonstration by 42 years, but ironically both anesthetic firsts occurred in the same month of the year—October. (Copyright © the American Society of Anesthesiologists, Inc.)

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