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Review Article

RESPIRATION AND THE AIRWAY

Sex-specific considerations for mechanical ventilation in acute respiratory distress syndrome: a narrative review of implications for female patients in the intensive care unit

Francesca Rubulotta[1,2,*], Luigi Camporota[3], Luciana Mascia[4] and Daniele Guerino Biasucci[5]

[1]Department of Anaesthesia and Intensive Care Medicine, CHIRMED University Hospital Policlinico 'G. Rodolico–San Marco', Catania, Italy, [2]International Women in Intensive and Critical Care Medicine Network (iWIN), Milan, Italy, [3]Centre for Human & Applied Physiological Sciences, School of Basic & Medical Biosciences. King's College London, London, UK, [4]Department of Experimental Medicine, Unisalento University, Lecce, Italy and [5]Department of Clinical Science and Translational Medicine, 'Tor Vergata' University, Rome, Italy

*Corresponding author. E-mail: francesca.rubulotta@unict.it

Summary

Acute respiratory distress syndrome (ARDS) remains a significant clinical challenge, with high morbidity and mortality rates despite advances in supportive care. Mechanical ventilation is central to the management of this condition, yet sex-related differences have been largely overlooked in research and clinical practice. Female patients have smaller lung volumes, different chest wall mechanics, and hormonal modifications that affect inflammation, vascular tone, respiratory compliance, and respiratory drive. These have an impact on treatment and care. This narrative review synthesises current evidence on sex-specific physiological differences affecting ARDS management. It evaluates the impact of physiological differences on lung volumes, chest wall mechanics, and pharmacokinetics and emphasises the importance of personalised ventilation and sedation strategies. Female patients exhibit greater susceptibility to ventilator-induced lung injury. Recent physiological studies show that, despite lower absolute mechanical power, each 1 J min^{-1} increase in mechanical power is associated with a 52.8% higher mortality risk in female patients compared with males, with an excess mortality of 8.2% above a threshold of 17 J min^{-1}. Sex-related sensitivity to sedatives and neuromuscular blocking agents has also been described, with females requiring 20–30% lower opioid doses, 30% increased propofol doses, and a 30% greater sensitivity to neuromuscular blockers. Addressing sex-based differences is crucial for personalised ARDS management. Strategies including normalisation of mechanical power to lung volume and sex-specific analgo-sedation protocols are needed. Equitable access to advanced therapies is essential for all patients. Future research must systematically integrate sex-specific analyses (e.g. the Sex And Gender Equity in Research (SAGER) guidelines) to improve understanding of reported outcomes for critically ill patients.

Keywords: acute respiratory distress syndrome; intensive care unit; mechanical power; mechanical ventilation; sex factors; ventilator-induced lung injury

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Editor's key points

- Females could have an increased susceptibility to ventilator-induced injury because of smaller lung volumes, hormonal influences, and differences in chest wall mechanics compared to males.
- Application of guideline-adherent tidal volumes can result in relatively higher lung strain in female patients.
- Differences in pain, inflammation, coagulation, pharmacokinetics, and pharmacodynamics of commonly used analgesics and sedatives further underscore the importance of considering sex-specific targets in ARDS management.
- Future research in mechanical ventilation of ARDS and non-ARDS patients should incorporate sex-specific analyses to better understand how biological sex-related differences may influence outcomes.
- This review challenges implicit assumptions about current research findings in ARDS and their clinical applicability.

Acute respiratory distress syndrome (ARDS) is a severe inflammatory condition of the lungs, arising from diverse aetiologies such as pneumonia, sepsis, pancreatitis, or trauma, and characterised by refractory hypoxaemia and reduced lung volumes[1] and often associated with multiorgan dysfunction.[2] Despite advances in supportive care, ARDS continues to carry a high morbidity and mortality in ICUs worldwide.[3] Mechanical ventilation (MV) remains the cornerstone of ARDS management, yet its application is complex and challenging.[4] Increasing evidence indicates that sex-related biological differences may influence ARDS outcomes[5] owing to significant variability in MV strategies,[6] response to medication, and recovery. Beyond biological factors,[7] variables such as access to advanced therapies[8] and exposure to implicit bias[9] in clinical decision-making further contribute to differences in care[10] and prognosis across genders.[11,12] In this narrative review, the authors focus on biological sex-related differences, which determine anatomical and physiological responses to MV and the pharmacological effectiveness of drugs needed for analgo-sedation and paralysis of patients with ARDS. Although gender-related factors further influence access to care and clinical decision-making,[10] these sociocultural dimensions are not analysed in depth here and are mentioned only as contextual modifiers. To avoid ambiguity, the terms 'female/male' and 'sex-related' are used throughout when referring to biological differences.

The role of sex in the management of acute respiratory distress syndrome

Epidemiological studies suggest that ARDS incidence, response to treatment, and outcomes differ between male and female patients.[11] Female patients generally have smaller lung volumes and airway dimensions,[13] both factors that can substantially influence respiratory mechanics.[14] Hormonal fluctuations across the menstrual cycle, pregnancy, and menopause impact immune responses, vascular tone, and pulmonary function, potentially altering disease trajectory and response to therapy.

Mechanical ventilation: challenges in female patients

Physiological considerations

Uniform application of lung-protective ventilation strategies, particularly tidal volumes set at 6 ml kg^{-1} predicted body weight (PBW), may not adequately account for sex-specific anatomical variation.[13] Failure to account for sex-specific anatomy may increase the risk of developing ventilator-induced lung injury (VILI).[13] A recent large cohort study provides a critical physiological variable that relates to mortality in ventilated patients, namely, the concept of mechanical power (MP).[14] MP is an integrative measure of the energy delivered by the ventilator to the respiratory system per minute (J min^{-1}).[14] von Wedel and colleagues[13] demonstrated that although absolute MP values were lower in females, each unit increase in MP was associated with a 52.8% higher mortality risk in female patients compared with male patients.[13] The same absolute energy, when applied to a smaller functional lung, imposes greater stress and strain[15] amplifying tissue injury.[16] At a harmful MP threshold of 17 J min^{-1}, mortality was 8.2% higher in female patients.[13] Additionally, chest wall elastance, which is affected by intra-abdominal pressure, is affected by body morphology[13] and is increased during pregnancy. These factors should be considered when selecting driving pressures and PEEP and planning recruitment manoeuvres.[16] According to von Wedel and colleagues,[13] female patients have increased susceptibility to VILI, specifically MP, which has a disproportionately harmful effect at equivalent levels owing to reduced functional lung volume (effect size: standardised mean difference, 0.45; 95% confidence interval [95% CI], 0.25–0.65; $P=0.001$). Moreover, scientific evidence has recently challenged the generalisability of PBW-based formulas for tidal volume prescription across heterogeneous populations.[15] In a large multicohort observational study, Sarma and colleagues[15] demonstrated substantial variability between predicted and physiologically appropriate tidal volumes, particularly in patients at the extremes of body size and lung capacity. This limitation seems to disproportionately affect female patients, who typically have smaller absolute lung volumes for a given PBW.[15] Consequently, even guideline-adherent tidal volumes (6 ml kg^{-1} PBW) can result in relatively higher lung strain in female patients, reinforcing the need to individualise tidal volume based on functional lung size rather than anthropometric estimates alone.[16] As highlighted by Schultz and colleagues[16] in their editorial, these findings underscore the risks of applying uniform ventilatory formulas without accounting for inter-individual and sex-related differences in lung mechanics.[16]

Hormonal influences

Sex hormones modulate inflammatory, vascular, coagulation and metabolic pathways.[17]

Oestrogens can exert protective effects on inflammation,[18] whereas progesterone influences pulmonary compliance,[19] respiratory drive, vascular reactivity, and susceptibility to fluid overload.[20] These variations necessitate adaptive strategies to ventilation and fluid management in women, and this is even more relevant during pregnancy and menopause.

Coagulation disturbances may be also sex related, with women being relatively hypercoagulable compared with

males, with enhanced platelet aggregation and faster clot dynamics.[21] Female patients have a higher risk of venous thromboembolism during fertile years, with oral contraceptive use increasing the risk four-fold.[21]

Moreover, the presence of sex hormones leads to attenuated sympathoadrenal activation and women are more sensitive to inhibitory stimuli.[22] Notably, hormonal fluctuations during the menstrual cycle affect sympathetic activity and metabolism.[23] These fluctuations cause differences in descending pain modulatory systems and cortex activity influencing responses to nociceptive stimuli. Indeed, females generally report higher pain sensitivity and intensity than males.[24]

Apnoeic sedation and analgesia

Sex impacts anatomy[25] and physiology in ways that directly influence anaesthesia.[26] For example, women have smaller airway diameters,[25] are more prone to exercise-induced hypoxaemia,[27] and have lower cardiac mass,[28] blood pressure, different clinical phenotypes of cardiovascular diseases,[29] and higher resting heart rates,[28,29] which can increase induction and intubation risks.[30] Female patients suffer more from microvascular dysfunction,[29] without obstructive disease, and therefore non-exertional pain or atypical angina is more frequent.[29] Sex differences in pharmacokinetics and pharmacodynamics are well established.[31] Female patients generally exhibit different sensitivity to sedatives,[32] opioids (effect size: odds ratio [OR], 1.8; 95% CI, 1.2–2.7; $P=0.01$),[33–35] and neuromuscular blocking agents,[36,37] predisposing to prolonged sedation or delayed recovery if doses are not adjusted appropriately.[30] Female patients typically require 20–30% lower opioid doses for equivalent analgesia[34] and demonstrate increased sensitivity of up to 30% to neuromuscular blockers such as atracurium,[37] rocuronium, and vecuronium.[36] Conversely, higher propofol doses may be required to achieve loss of consciousness[32] owing to differences in distribution, hepatic clearance, and hormonal modulation of GABAergic[38] and *N*-methyl-D-aspartate (NMDA) pathways, whereas a lower dose of remifentanil can be required for extubation.[35]

Female patients are at higher risk of awareness[32] and post-traumatic stress disorders after general anaesthesia.[30,31] In a meta-analysis of 44 studies, female sex was associated with a greater incidence of awareness (postoperative recall OR, 1.38 and connected consciousness OR, 2.09) under general anaesthesia, which represents 'failure of anaesthesia' and a faster emergence from anaesthesia (time to eye-opening 2.28 min less and time to response to command mean difference 2.84 min).[32] Oestrogen and progesterone have important effects on the central nervous system and hormonal composition plays a role in determining anaesthetic requirements,[39] which are higher during the follicular phase for volatile anaesthetics and propofol, probably through an allosteric modulation of gamma-aminobutyric acid (GABA) type A receptors,[38] a potentiation of NMDA receptor-mediated glutamate neurotransmission,[40] and an inhibition of endogenous sleep mechanisms by oestrogens.[38,40] Female patients in the luteal phase of the menstrual cycle had a lower calculated effect-site median effective concentration of propofol,[40] inversely correlated with progesterone levels, and a shorter emergence time than those in the follicular phase. It is likely that female patients are underdosed particularly at induction, and aim at developing sex-tailored anaesthesia techniques.[32] Female patients have a faster recovery after general anaesthesia even at equivalent Bispectral Index (BIS) levels, suggesting differences in pharmacokinetic (faster clearance)[40] and pharmacodynamic (less response at equal effect site concentrations) factors. Mechanisms that might contribute to this variation include differences in body composition, leading to changes in volume of drug distribution; variations in enzymatic activity, particularly CYP450[40]; altering drug metabolism and elimination kinetic; and differences in cardiac output, hepatic perfusion, and body fat composition, resulting in differences in compartment volumes and clearance. These data suggest the need for reappraisal of anaesthetic care, including whether similar drug dosing for females and males represents best care.[30]

Women experience postoperative nausea and vomiting (PONV) up to three times more frequently than men, a difference attenuated but not abolished after menopause, implicating hormonal influence.[41] Elective procedures scheduled during the luteal phase might therefore reduce PONV risk in susceptible patients.[41]

Strategies for individualised care

A precision approach to ARDS management requires moving beyond traditional 'one-size-fits-all' lung-protective ventilation,[42] which is primarily based on PBW and population-level averages.[43] Individual variation in lung size, compliance, and chest wall mechanics,[43] particularly pronounced between sexes, necessitates patient-specific titration of ventilatory energy delivery,[44] or MP.[45]

Scaling tidal volume to functional lung capacity

Tidal volumes should ideally be referenced to the *functional* (aerated) lung volume rather than PBW alone.[16] This is particularly relevant in female patients, who typically have smaller total lung capacities[25] and can therefore be inadvertently overventilated even when 'protective' PBW-based settings are applied.[46] Quantifying recruitable lung volume through compliance analysis,[47] electrical impedance tomography (EIT), or CT-derived aeration estimates allows more accurate adjustment of tidal volume[15] and driving pressure to the actual ventilated compartment.[16]

Normalisation of mechanical power to lung compliance

Recent data from von Wedel and colleagues[13] provide a mechanistic explanation for sex-related mortality differences in ARDS. Although absolute MP values were lower in females, each unit increase in MP conferred a disproportionately greater mortality risk,[13] reflecting higher strain energy per unit of functional lung. Normalising MP to static compliance (MP/Crs) largely eliminated this discrepancy.[44] This supports the concept that energy load should be indexed to the mechanical properties of the respiratory system, moving beyond fixed MP[45] thresholds toward a physiologically meaningful, sex-neutral target.[46]

Transpulmonary pressure monitoring

Use of **oesophageal manometry** enables partitioning of respiratory mechanics into lung and chest wall components, allowing clinicians to estimate *transpulmonary pressure (PL)*, the true distending pressure of the lung.[47] By guiding PEEP

titration to maintain end-expiratory PL near zero and avoiding excessive end-inspiratory PL, clinicians can minimise regional overdistension and collapse.[45,47] This approach also refines the assessment of MP by identifying the proportion of ventilatory energy transmitted to the lung parenchyma rather than dissipated in the chest wall. In females, who often exhibit higher chest wall elastance (especially during pregnancy or with elevated intra-abdominal pressure), PL-guided ventilation may prevent overestimation of driving pressure and inappropriate PEEP escalation, aligning mechanical load with reduced functional lung size.[47] In practice, this method provides real-time insight into individual load–capacity balance, offering a powerful adjunct for controlling MP delivery at the lung level.[13] Pregnancy introduces additional alterations in respiratory mechanics and gas exchange targets; however, a detailed discussion is beyond the scope of this review and warrants dedicated analysis.

Electrical impedance tomography

EIT offers noninvasive, bedside, radiation-free monitoring of regional ventilation distribution. It provides dynamic feedback on the spatial distribution of tidal volume, regional compliance, and recruitment/derecruitment patterns.[48] In ARDS, EIT can identify focal overdistension or dependent collapse, facilitating fine-tuning of PEEP and tidal volume to achieve the lowest regional MP gradient and minimise heterogeneity of strain.[44,48] Recent studies have explored EIT-derived indices, such as regional MP or energy homogeneity as emerging metrics for personalised ventilator management.[48] In female patients, EIT may be particularly useful to detect subtle regional disparities related to anatomical differences in thoracic shape and lung–chest wall coupling, which are not captured by global mechanics.[48]

PEEP and driving pressure optimisation

PEEP should be carefully titrated to balance alveolar recruitment with haemodynamic tolerance, acknowledging the narrower window between de-recruitment and overdistension in smaller lungs.[25] Driving pressure should be limited relative to measured compliance rather than absolute thresholds,[13] as women may reach injurious strain[43] at lower absolute pressures.[46] Integrating intra-abdominal pressure assessment can further refine ventilator settings when chest wall load is increased.[16,45]

Sedation, multidisciplinary care, and future directions

Sex-based differences in pharmacokinetics and pharmacodynamics underscore the need for sedation and analgesia protocols that explicitly account for heightened female sensitivity to commonly used agents.[30] Women often exhibit greater responsiveness to opioids,[34] benzodiazepines, and neuromuscular blocking agents,[37] which can result in prolonged sedation or delayed recovery if dosing is not carefully titrated.[30] Closer and more frequent monitoring of sedative depth and neuromuscular block is therefore essential to avoid oversedation, weakness, and complications associated with prolonged immobility. Tailoring sedation to sex-specific physiology represents an important step toward equitable and personalised critical care.[30] Optimal ARDS management also extends beyond ventilatory parameters. Female patients appear to experience higher rates of anxiety, depression, and post-intensive care psychological sequelae, highlighting the importance of a holistic, multidisciplinary approach.[49] Incorporating psychological and social support as integral components of ICU care can help mitigate these long-term effects.[49] Early engagement of mental health professionals alongside physiotherapists and rehabilitation teams should become standard practice in the continuum of critical care recovery. Cultivating reflective practice and ensuring equitable access to advanced interventions, such as extracorporeal membrane oxygenation (ECMO),[8] can substantially narrow outcome gaps between male and female patients.[50,51] Finally, sustained progress will depend on embedding sex and gender considerations within the research agenda.[52] This is the rationale for the systematic use of the sex and gender equity in research guidelines (SAGER).[52] The prospective validation of normalised MP (MP/Crs) as a sex-inclusive target for mitigating VILI is a priority.[16]

Outcomes and prognosis

The LUNG-SAFE study demonstrated that female patients were more frequently exposed to non-protective ventilation with higher tidal volumes,[53] with increased mortality in severe ARDS.[46] This clinical observation is strongly supported by new physiological data showing that the energy load from ventilation (MP) is more injurious at comparable levels in females, explaining their higher mortality risk.[45] A 2023 review emphasised the multidimensional impact of sex and gender differences in critical care, including ARDS.[9]

Limitations

Authors do not explore gender-related factors, which can extend beyond biology to influence care delivery and outcomes.[54] Gender determines access to health care, help-seeking behaviours, and individual use of the health care system, including preventive measures and invasive therapeutic strategies. Women are less likely to be referred for advanced therapies such as ECMO.[8,50,51] Implicit biases in the perception of illness severity and intervention candidacy may partially explain such disparities. Comparable inequities are well documented in cardiovascular medicine[55]: women with acute myocardial infarction receive less evidence-based treatment for acute myocardial infarction,[56] including reperfusion therapy, and they have worse outcomes and increased rates of readmission, reinfarction, and death in the first year after acute myocardial infarction,[55] and higher in-hospital mortality after cardiogenic shock complicating acute myocardial infarction.[56] Recognition of similar biases in ARDS and critical care is essential to ensure equitable access to life-saving interventions.[56]

Conclusions

Optimising mechanical ventilation in female ARDS patients requires recognition of sex-based physiological differences, the impact of hormonal influences, and the role of sedation, analgesia, and neuromuscular drugs in this population. Crucially, new evidence demonstrates that the injurious effects of mechanical power are magnified in females, necessitating a move towards personalised targets normalised to functional lung size. A precision approach to ARDS should account for these variables to prevent VILI, improve survival,

and reduce long-term sequelae. These observations and implications could also extend to patients without ARDS, even if the focus of this manuscript is this complex lung condition. Future research must systematically incorporate sex- and gender-specific analyses, including the validation of normalised mechanical power, alongside attention to drugs, fluids, and hormonal fluctuations, to ensure that advances in ARDS management benefit all patients equitably. Only through such multidimensional integration can clinicians evolve toward genuinely personalised and equitable practice. This is also the rationale for promoting the systematic use of SAGER guidelines.[52]

Authors' contributions

Conceived and led the review, developed the review question and overall methodology, supervised the literature synthesis, and critically revised all manuscript drafts for important intellectual content: FR
Performed the literature search, screened and organised data, drafted substantial sections of the manuscript: LC
Edited the manuscript into its final submitted form: LC, LM, DGB
Verified data, integrated co-author and reviewer feedback: LM
Provided methodological expertise for the review design, advised on data synthesis and interpretation, assessed study quality and risk of bias, contributed to revising the manuscript: DGB

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Declaration of interest

The authors declare that they have no conflicts of interest.

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