Is gender inequity in ventilator management a “women’s issue”?

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Caregivers involved in artificial ventilation need to pay more and special attention to females: due to their shorter height they are at higher risk of receiving non-protective ventilation, which may affect their outcomes http://bit.ly/2HbkG4n

Cite this article as: Schultz MJ, Karagiannidis C. Is gender inequity in ventilator management a “women’s issue”? *Eur Respir J* 2019; 54: 1901588 [https://doi.org/10.1183/13993003.01588-2019].

Artificial ventilation acts as a double-edged sword in patients with acute respiratory distress syndrome (ARDS). While maintaining oxygenation and unloading the respiratory muscles it may worsen lung injury, especially when the applied volumes are too large or when pressures become too high [1]. The results of the seminal ARMA trial, a clinical study in patients with ARDS comparing ventilation with a low tidal volume (V_T) to ventilation with a high V_T, convinced us that use of low volumes improves survival and shortens duration of ventilatory support [2]. The findings in a recently published meta-analysis, using individual patient data of patients with ARDS under ventilation with a low V_T recruited in nine investigations, made us think that ventilation with a low driving pressure (ΔP) may have additional protective effects [3]. A cut-off of 6 mL per kg of predicted body weight (PBW) for V_T, and of 15 cmH_2O for ΔP, are by now widely proposed as safety limits in patients with ARDS. We cannot think of any reason why a female lung would be different from a male lung, and therefore of no good reason for differences in these safety cut-offs between sexes.

In this issue of the *European Respiratory Journal*, the “Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure” (LUNG SAFE) investigators report on a secondary analysis of their conveniently sized, international, multicentre, prospective cohort study that was conducted during 4 consecutive weeks in the winter of 2014 in a sample of 459 intensive care units (ICUs) from 50 countries across five continents [4]. Here, the LUNG SAFE investigators focused on gender differences in the recognition of ARDS, and ventilator management and outcomes [5]. On the one hand, the results of this secondary analysis are comforting: there are no differences in the recognition of ARDS between sexes. Striking differences, however, were found in ventilator management, and even in outcomes. First, females, compared to males, appeared to have received ventilation with a higher median V_T (a difference of ~1 mL per kg PBW) and also a higher median ΔP (a difference of ~1.5 cmH_2O). Second, when ARDS was confirmed and classified as “severe”, females had higher ICU (64 *versus* 46%) and hospital mortality rates (68 *versus* 50%) than males.

Received: 12 Aug 2019 | Accepted after revision: 15 Aug 2019

The finding that females were more likely to receive "non-protective" ventilation, *i.e.* ventilation with a higher V_T or a higher ΔP, is in line with findings in previous studies focusing on ventilator management. An analysis of open access de-identified data from patients enrolled in ARDS Network trials, conducted after publication of the abovementioned ARMA trial that showed ventilation with a V_T as low as 6 mL per kg PBW to improve outcomes [2], revealed that females were twice as likely to receive ventilation with a V_T >6 mL per kg PBW [6]. Similar gender differences were found in the "Consortium to Evaluate Lung Edema Genetics" (CELEG) study [7]. More recently, gender differences in V_T were also found for patients without ARDS, in the international observational "Practice of VENTilation in patients without ARDS" (PRoVENT) study [8], and even for patients receiving short-lasting intraoperative ventilation during general anaesthesia for surgery, in the "Local Assessment of VEntilatory management during General Anesthesia for Surgery" (LAS VEGAS) study [9]. Why is there a tendency of clinicians to adhere to protective ventilation less strictly in females; why this gender inequity?

It could be suggested that the gender inequity in ventilator management is caused by a difference in patients' height, since females are on average 10 to 15 cm shorter than males, as also shown in LUNG SAFE (median height 160 (155 to 165) *versus* 170 (169 to 178) cm) [4], the CELEG study (average height 162±7 *versus* 177±8 cm) [7], and in the PRoVENT study (median height 155 (150 to 160) *versus* 167 (162 to 170) cm) [8]. The abovementioned analysis of open access de-identified data from patients with ARDS showed that patients of shorter height were least likely to receive ventilation with a low V_T, probably explaining why females were at a disproportional risk of receiving non-protective, unsafe ventilation [6]. In fact, the multivariate analysis of that study revealed that height, and not gender, had an association with ventilation with a too high V_T. Another "disturbing" anthropometric index is weight. Indeed, a higher body weight was associated with more frequent use of non-protective ventilation with high V_T in a French observational study of intraoperative ventilation [10]. In that study, overweight, obesity, severe obesity and morbid obesity were all independent risk factors for use of a high V_T during general anaesthesia. So, it is nothing more than a "height and weight issue", and not *per se* a "gender issue", that causes gender inequity in ventilator management?

As V_T should be titrated according to the PBW, then it is important to determine PBW of each individual patient when setting the ventilator. There are different ways to determine PBW, resulting in significant potential differences, in particular in females [11]. It may, however, be most reasonable to use the equation as used in the abovementioned ARMA trial [2], which is 45.5+0.905*((height in cm)−152.4) for females, and 50.0+0.905*((height in cm)−152.4) for males. Use of this equation at the bedside could be a bit tough, though, and if one does not want to do the calculation by heart, charts displaying the exact BPW for each height, and of course separated for females and males, could be used. Actually, any type of healthcare software, and yes by now even ventilators can do the simple math. Simple?

But wait for a second. How certain are we about estimating patients' height? There are certainly some challenges here, as repeatedly shown before in several investigations [12–16]. Actually, all these investigations show one thing very clearly: while height is generally better estimated than is weight, overestimation of height occurs, particularly in the shortest patients. And thus, females are more affected by this inaccuracy of estimation.

If estimating patients' heights is so challenging, could we then solve the problem by using a fixed low *and* gender-adjusted V_T when setting the ventilator in patients with ARDS? It has been proposed before that a V_T of 350 mL could be chosen in females, and of 450 mL in males [17]. The mode of V_T, *i.e.* the most frequently used V_T in females was 400 mL, while in males this was 500 mL in LUNG SAFE (personal communication with the LUNG SAFE investigators). So gender adjustment in V_T seemed to have happened in LUNG SAFE, but still with high V_T. This may be still insufficient [6]: in fact, even a V_T of 350 mL and 450 mL for females and males is. For example, as shown in figure 1, when "accepting" a V_T as high as 8 mL per kg PBW as a safe volume, all patients, of any height, receive ventilation with an "adequately sized" V_T. However, when we are stricter in what we call "safe", *i.e.* only accepting a V_T of 7, or even 6 mL per kg PBW, with a V_T of 350 mL and 450 mL for females and males we see more and more patients receiving ventilation with a far too high V_T. And here it is "shorter women first", as due to their shorter height it is they that run the greatest risk of receiving unsafe ventilation. This becomes even more important with more severe ARDS, as demonstrated in the current LUNG SAFE analysis.

Of note, the gender difference in this study does not stand on its own. As one example, there are important differences in outcome from, for example, myocardial infarction [18]. The increased risk of death in females presenting with acute myocardial infarction seems to depend more on the way they are treated in the ward and physicians' behaviour than sex-specific differences in biology. And there are many more examples, like in cardiac arrest and sepsis, partially depending on the pre- and post-menopausal status of females [19, 20]. We can only speculate about the reasons for differences in care, but probably it

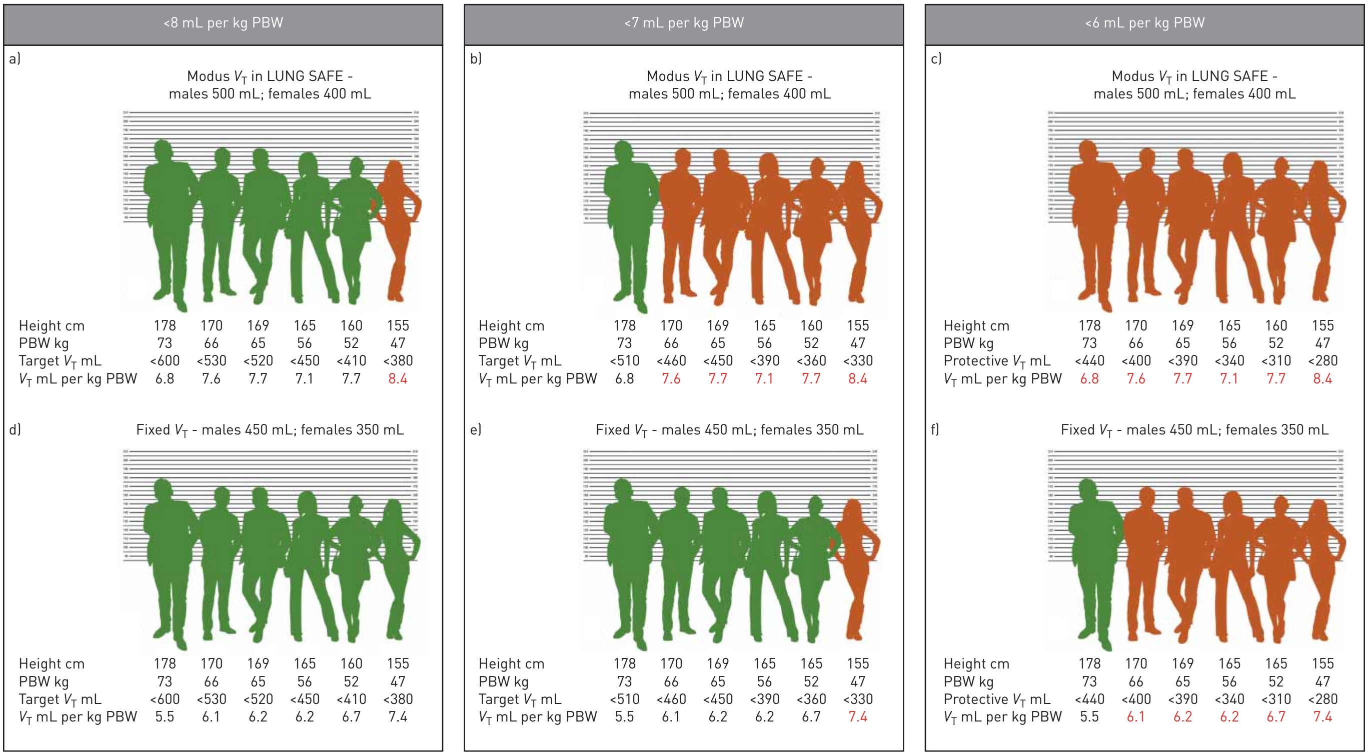

FIGURE 1 The effects of ventilation with a tidal volume of 500 mL in males, and of 400 mL in females, the modus tidal volume (V_T) in LUNG SAFE (upper panels), and a fixed low *and* gender-specific absolute tidal volume, as previously suggested (lower panels) [17], on the size of V_T expressed per kg of predicted body weight (PBW). Each panel shows silhouettes for females (right) and males (left) representing patients as tall as the 75% interquartile, the median and the 25% interquartile for height, as in LUNG SAFE. A red silhouette means that a patient, male or female, receives a too large V_T per kg PBW at a fixed tidal volume when a V_T <8 mL per kg is seen as "acceptable" (a and d), or when a V_T <7 mL per kg (b and e), or <6 mL per kg is seen targeted (c and f). The modus V_T and heights of patients are obtained after personal communication with the LUNG SAFE–investigators.

is not the cultural background of the caregivers. Indeed, LUNG SAFE was a worldwide study, including many countries. It seems we are dealing with fundamental differences in general "recognition" of females and males in the ICU and emergency department. Certainly, we should not ignore that there are also biological differences between the sexes, such as pain processing [21] and hormonal differences [20, 22, 23]. As an example, estradiol modulates the lung inflammatory response in an experimental model of acute lung injury [24] and during experimental human endotoxaemia, females show a more pronounced proinflammatory innate immune response associated with less norepinephrine sensitivity [25].

There is one important caveat to all this. The "best" V_T is calculated based on an estimation of body height, and this may reflect the actual lung size, which differs from individual to individual. But again, females might be more affected by inaccurate estimations than males. And also, the effects of "mis-estimations" and "mis-calculations" could be worse in more critically ill patients, in this case patients with severe ARDS. This calls for individualised or precision medicine.

In summary, caregivers involved in artificial ventilation need to pay more and special attention to females. We need to change our minds, it is not "one size fits all". Being a female is a risk factor, *per se*, to receive ventilation with unsafe settings, even if differences are driven by height. Maybe it is time for a campaign like "Save the Life of Females in the ICU"? Meanwhile, manufacturers of ventilators could help "visualising" the issue of gender, and of height, by mandating gender and height input when setting the ventilator. Last, but not least, translational researchers could focus on effects of gender in the context of ARDS, and also in harm caused by artificial ventilation.

Conflict of interest: None declared.

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