J Clin Monit Comput (2013) 27:357–363
DOI 10.1007/s10877-013-9449-2

ORIGINAL RESEARCH

Elucidating the fuzziness in physician decision making in ARDS

David B. Bernstein · Binh Nguyen · Gilman B. Allen · Jason H.T. Bates

Received: 7 December 2012 / Accepted: 28 February 2013 / Published online: 6 March 2013

Abstract The current standard of care for patients suffering from acute respiratory distress syndrome (ARDS) is ventilation with a tidal volume of 6 ml/kg predicted body weight (PBW), but variability remains in the tidal volumes that are actually used. This study aims to identify patient scenarios for which there is discordance between physicians in choice of tidal volume and positive end-expiratory pressure (PEEP) in ARDS patients. We developed an algorithm based on fuzzy logic for encapsulating the expertise of individual physicians regarding their use of tidal volume and PEEP in ARDS patients. The algorithm uses three input measurements: (1) peak airway pressure (PAP), (2) PEEP, and (3) arterial oxygen saturation (SaO_2). It then generates two output parameters: (1) the deviation of tidal volume from 6 ml/kg PBW, and (2) the change in PEEP from its current value. We captured 6 realizations of intensivist expertise in this algorithm and assessed their degree of concordance using a Monte Carlo simulation. Variability in the tidal volume recommended by the algorithm increased for PAP > 30 cmH_2O and PEEP > 5 cmH_2O. Tidal volume variability decreased for $SaO_2 > 90$ %. Variability in the recommended change in PEEP increased for PEEP > 5 cmH_2O and for SaO_2 near 90 %. Intensivists vary in their management of ARDS patients when peak airway pressures and PEEP are high, suggesting that the current goal of 6 ml/kg PBW may need to be revisited under these conditions.

Keywords Acute respiratory distress syndrome · Mechanical ventilation · Fuzzy logic · Low tidal volume ventilation · Clinical decision making

Electronic supplementary material The online version of this article (doi:10.1007/s10877-013-9449-2) contains supplementary material, which is available to authorized users.

D. B. Bernstein · J. H.T. Bates (✉)
School of Engineering, University of Vermont, 149 Beaumont Avenue, HSRF 228, Burlington, VT 05405-0075, USA
e-mail: Jason.H.Bates@uvm.edu; jason.h.bates@med.uvm.edu

B. Nguyen · G. B. Allen
Fletcher Allen Health Care, Burlington, VT 05405, USA

B. Nguyen · G. B. Allen · J. H.T. Bates
Department of Medicine, University of Vermont, Burlington, VT 05405, USA

1 Introduction

Improvements in strategies for ventilatory management of patients with acute respiratory distress syndrome (ARDS) have had a major impact on clinical care in recent years [1–3]. Most importantly, a landmark study in 2000 by the ARDS Network showed that use of a low tidal volume (V_T) ventilation of 6 versus 12 ml/kg predicted body weight (PBW) significantly reduced mortality in these patients [1]. This finding, together with the shift towards evidence-based medicine, has established a V_T of 6 ml/kg PBW as the standard of care in ARDS [4, 5], something that has been estimated to have the potential to prevent 5,500 deaths annually [6]. Nevertheless, there has been some resistance within the medical community to conform to this strategy [7], a reaction that seems to be based on misgivings about a variety of factors. For example, the ARDS Network study only compared 6 ml/kg PBW to a single alternative V_T, which raises the question as to whether some other as yet untested V_T might be even better. Also, physicians continue to debate whether V_T or plateau pressure (P_{plat}) is a better indicator of risk for ventilator-induced lung injury [8]. Adherence to a V_T of 6 ml/kg PBW is further complicated by physician concern about patient comfort, and by the potential failure to identify ARDS early in its course [9, 10].

There currently exists significant discordance between those caregivers who advocate for a V_T of 6 ml/kg PBW in ARDS at all costs, and those who are willing to deviate from it under certain circumstances [7, 9, 10]. This tension is further fueled by current concern about the extent of variation in physician practice [11]. We were thus motivated to determine exactly what is driving variation in the way that physicians choose V_T for ARDS patients. Our approach to this problem was to use the engineering methodology known as fuzzy logic to devise an algorithm encapsulating the decision making process that physicians go through when choosing V_T. By subjecting this algorithm to a spectrum of hypothetical clinical scenarios, we identified those scenarios in which physicians are more inclined to consider the use of a V_T other than 6 ml/kg PBW in ARDS.

2 Methods

2.1 Fuzzy logic algorithm

We have described in previous publications how fuzzy logic control works with respect to pressure support ventilation [12] and fluid administration in the intensive care unit [13]. We used the same approach in the present study to construct a fuzzy logic algorithm for calculating recommended changes to two key ventilator parameters: (1) ΔV_T: the amount by which V_T is to deviate from 6 ml/kg PBW, and (2) ΔPEEP: the amount by which positive end-expiratory pressure (PEEP) is to change from its current setting. The algorithm bases these decisions on the current values of three input variables: (1) peak airway pressure (PAP), (2) PEEP, and (3) arterial oxygen saturation (SaO_2). There are two sets for PAP labeled "Normal" and "High"; three sets for PEEP labeled "Low", "Normal", and "High"; and two sets for SaO_2 labeled "Low" and "Normal". The possible ranges of these three variables are 0–45 cmH_2O for PAP, 0–25 cmH_2O for PEEP, and 0–100 % for SaO_2. Within these ranges, the vertices of the fuzzy sets demarcate the positions of the fuzzy sets and their degrees of overlap. Membership in a set varies from 0 to 1 to reflect the degree of certainty in classifying a particular variable value. Examples of possible overlapping fuzzy sets for each of these variables are illustrated in Fig. 1a.

It should be pointed out that the chosen parameters are not the only factors that might be considered relevant to the management of an ARDS patient. In particular, the inspired oxygen fraction (FiO_2) is also a parameter of major clinical significance which is under physician control. Similarly, one might consider additional input parameters such as end-tidal CO_2 or blood pH. Here, however, we focus our attention on the special case of severe ARDS for which FiO_2 is set to 100 %. We do this partly to limit the complexity of the situation, but also because the stakes of decision making are particularly high in the common clinical scenario of refractory hypoxemia, which may call for unsettling and potentially dangerous deviations from standard practice regarding tidal volume and PEEP. The result is a somewhat simpler fuzzy logic algorithm than would be the case for ARDS in general, but it still enables us to use it to explore areas of concordance in physician decision making.

Once the input variables are fuzzified as described above, they must be related using a rule table that describes what action is to be taken for every possible combination of set memberships for PAP, PEEP and SaO_2. These actions state what is to be done, in qualitative terms, to adjust the output variables V_T and PEEP. These qualitative terms are "Decrease", "Maintain" and "Increase" for both output variables. For example, if PAP is "Normal", PEEP is "High" and SaO_2 is "Low" the decision of an expert physician might be to "Increase" V_T and "Maintain" PEEP, and so on for all other possible combinations of input variable set memberships. An example of a possible rule table is illustrated in Table 1.

Next, the meanings of "Decrease", "Maintain" and "Increase" for both V_T and PEEP are specified in terms of the positions and degrees of overlap of three fuzzy sets defined on the allowable range of values for a change in V_T (in units of ml/kg PBW) relative to 6 ml/kg predicted body weight (ΔV_T), and change in PEEP (in units of cmH_2O) relative to its current value (ΔPEEP). Examples of possible fuzzifications for ΔV_T and ΔPEEP are shown in Fig. 1b.

Having completed the above steps, the fuzzy logic algorithm is ready to use. Using conventional rules for fuzzy logic [13, 14], a particular set of values for the input parameters PAP, PEEP and SaO_2 gives rise to memberships lying between 0 and 1 for the three fuzzy sets of ΔV_T and ΔPEEP. The centroid of the polygonal regions defined by these various members for each output parameter are then taken as the "crisp" output values, i.e. those values of ΔV_T and ΔPEEP that are to be implemented.

2.2 Questionnaire

We created a questionnaire (see Fig. S1 in online supplemental material) designed to gather the fuzzy set vertices (Fig. 1a) and rule table entries (Table 1) that an expert intensivist would need to supply in order to implement the fuzzy logic algorithm described above. We sent this questionnaire to the nine board-certified attending critical care physicians on the Fletcher Allen Health Care MICU Service,

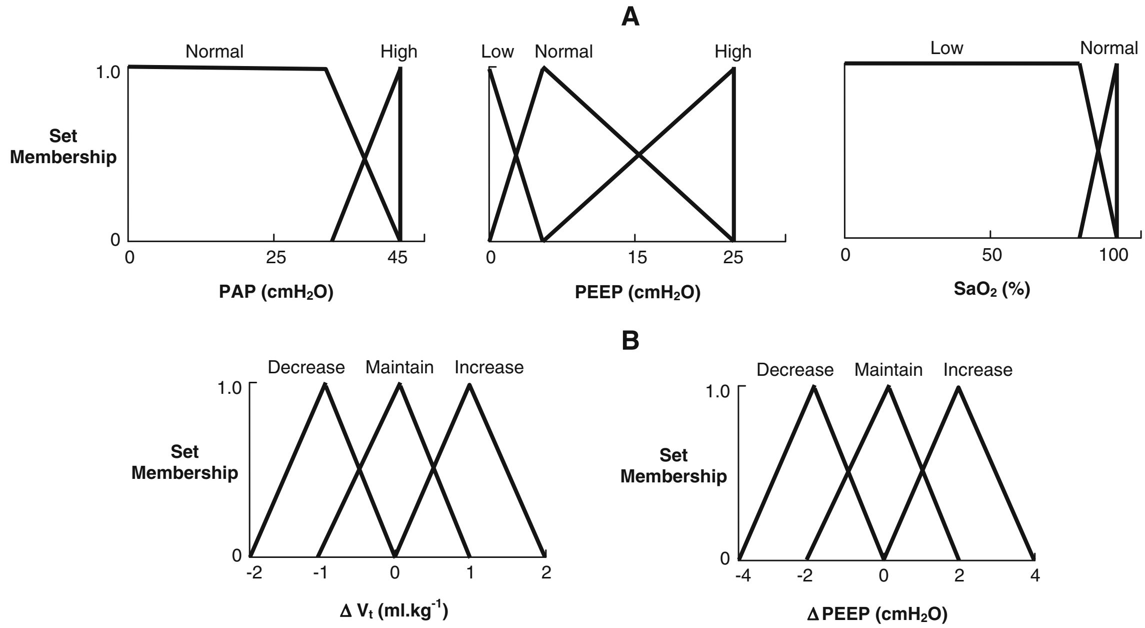

Fig. 1 Fuzzy set structure. **a** The ranges for the input parameters PAP, PEEP and SaO_2 are divided into 2, 3 and 2 overlapping sets, respectively. The sets shown in the figure are illustrative examples; the precise positions of the *vertices* defining the positions of the sets were provided by each of the physicians we studied and used as part of the setting up process for their specific algorithm. **b** The ranges of the output parameters ΔV_t and ΔPEEP are each divided into 3 overlapping sets

Table 1 An example decision table that specifies the actions to be taken in terms of adjusting ΔV_t and ΔPEEP for each combination of set memberships for the input parameters PAP, PEEP and SaO_2

Input parameter set memberships			Output parameter adjustments	
PAP	PEEP	SaO2	ΔVt	ΔPEEP
Normal	Low	Low	Maintain	Increase
High	Low	Low	Decrease	Increase
Normal	Normal	Low	Maintain	Increase
High	Normal	Low	Decrease	Increase
Normal	High	Low	Increase	Maintain
High	High	Low	Maintain	Maintain
Normal	Low	Normal	Maintain	Maintain
High	Low	Normal	Decrease	Increase
Normal	Normal	Normal	Maintain	Maintain
High	Normal	Normal	Decrease	Maintain
Normal	High	Normal	Maintain	Decrease
High	High	Normal	Decrease	Decrease

The entries in this table might vary depending on which particular expert is deciding on the decisions that should be taken

and received six anonymous returns. This provided six different information sets that were used to implement six realizations of the fuzzy logic algorithm. In this way, we encapsulated the expertise of the six different intensive care physicians. Approval to gather this information was obtained from the University of Vermont Institutional Review Board.

2.3 Monte Carlo method

The decisions inherent in the 6 different fuzzy logic algorithms were compared to each other using a Monte Carlo approach in which 10,000 hypothetical patient scenarios were generated by choosing 10,000 different sets of values for PAP, PEEP and SaO_2. The values for each parameter were drawn randomly with equal probability from their respective clinically applicable ranges. These ranges are those that define the horizontal axes in the plots in Fig. 1a. The 10,000 patient scenarios were then given to each of the six realizations of the fuzzy logic algorithm, generating 10,000 sets of six recommendations for both ΔV_T and ΔPEEP. The degree of discordance between the physicians for each of the patient scenarios was quantified as the standard deviations of the six recommendations for ΔV_T and ΔPEEP. These standard deviations are designated SD-ΔV_T and SD-ΔPEEP, respectively.

3 Results

Figure 2 shows how the degree of discordance between the six physicians varied as functions of the three input parameters to the fuzzy logic algorithm. Figure 2a, for example, shows where each of the 10,000 values of SD-ΔV_T lies in a plot of SD-ΔV_T versus PAP. The darkness of the plot is proportional to the number of values of SD-ΔV_T that fall on a particular location. We thus see that most values of SD-ΔV_T

are zero for PAP < 30 cmH_2O, indicating strong agreement between the 6 different physicians. By contrast, as PAP climbs above 30 cmH_2O the values of SD-ΔV_T also climb progressively, indicating increasing discordance. Also notable is a dull peak in SD-ΔV_T around a PAP of 35 cmH2O, indicating some disagreement around this value. Figure 2b shows that agreement regarding ΔPEEP was strong over the entire range of PAP investigated. Figures 2c and 2d show that agreement regarding ΔV_T and ΔPEEP was only strong for PEEP < 5 cmH_2O, with discordance developing progressively above this value. Finally, Fig. 2e, f show that agreement regarding ΔV_T and ΔPEEP was relatively strong for all values of SaO_2, although some confusion regarding PEEP control arose around values close to 90 %. There was also a marked decrease in SD-ΔV_T associated with "Normal" SaO_2.

Interactions between input parameters are shown in the three-dimensional color plots of SD-ΔV_T and SD-ΔPEEP versus pairs of input parameter values provided in the online supplemental material (Fig. S2 and S3). These plots provide a more comprehensive view of the data by showing how standard deviations depend simultaneously on two parameters, and show that there is little interaction between PAP and SaO_2. That is, the surfaces in these figures show that SD-ΔV_T depends almost exclusively on variations in PAP (Fig. S2) while ΔSD-PEEP depends almost exclusively on variations in SaO_2 (Fig. S3), and this pertains in both cases regardless of the value of PEEP.

4 Discussion

Fuzzy logic is a mathematical engineering discipline that was introduced by Zadeh in the 1960's [15], and has since been used in a variety of control applications [14]. Unlike conventional approaches to servo control that are based on mathematical models of the system being controlled, fuzzy logic allows for the development of control algorithms based on the accumulated experience of experts, and is therefore well suited for applications in medical decision-making [13, 16]. Accordingly, fuzzy logic seemed to us to be an appropriate methodology with which to try to capture the decision processes involved in choosing V_T for ARDS patients, especially as those who make this decision currently appear to be torn between the sole evidence-based recommendation of 6 ml/kg PBW and the doubt they experience arising from a large background of accepted physiological and medical wisdom. Understanding the precise source of this tension is important because ARDS continues to have a substantial impact on public health [17, 18]; a recent cohort study has shown that the incidence of ARDS in the United States could be as high as 190,600 cases per year, with an in-hospital mortality rate of 38.5 %, making the impact of ARDS comparable to that of breast cancer or HIV [17].

Our aim was therefore to use a fuzzy logic-based technique to identify those patient scenarios for which physicians are at odds about how to manage patients with ARDS. Several previous studies have investigated barriers to low V_T ventilation protocols, and have identified a number of contributing factors. One obvious factor is deficit of appropriate knowledge on the part of the health care provider [7], as well as simple carelessness. Also, ARDS is sometimes not diagnosed properly [10], in which case the need for a low V_T protocol may not be acknowledged. On the other hand, much of the resistance to use of low V_T in ARDS arises in the context of careful clinical consideration related to ostensibly justifiable factors such as patient comfort [9, 10]. Nevertheless, the reasons for variability in decisions related to mechanical ventilation settings are not always clear, likely representing lost opportunities to provide the best possible care [19].

An important region of discordance among the six different fuzzy logic algorithms occurred at high values of PAP. Figure 2a shows that SD-ΔV_T increased linearly as PAP increased above 30 cmH_2O. We traced the source of this discordance to variations in the entries the physicians made in the rule tables specifying how V_T should be adjusted when PAP is "High". The ARDS Network ventilation protocol recommends lowering V_T in steps of 1 ml/kg PBW to a minimum of 4 ml/kg PBW when P_{plat} is above 30 cmH_2O [1]. However, research has shown that physicians are often resistant to employing such low V_T because of concerns about hypercapnia, acidosis, hypoxemia, and increased use of sedatives [9, 10]. We speculate that lack of certainty as to what to do in face of these concerns may have contributed to the variation in strategies employed by the six physicians in the present study as PAP increased above 30 cmH_2O.

Another region of substantial discordance began when PEEP reached 5 cmH_2O, above which SD-ΔV_T and SD-ΔPEEP increased linearly (Fig. 2c, d). This result is again traceable to differences among the rule table entries, this time related to adjustment of V_T and PEEP when PEEP is "High". There are several adverse effects associated with high PEEP, notably lung over distension [20], decreased venous return caused by high intra-thoracic pressure [21], and decreased oxygenation from pulmonary blood flow being redirected to regions of limited ventilation [22]. While these adverse effects are widely appreciated, intensivists may react to them in different ways, which could account for the variability we encountered in the present study. Another potential source of discordance may arise from the apparent disagreement between the results of several studies regarding the use of PEEP in ARDS. The most widely cited study by the ARDS Network

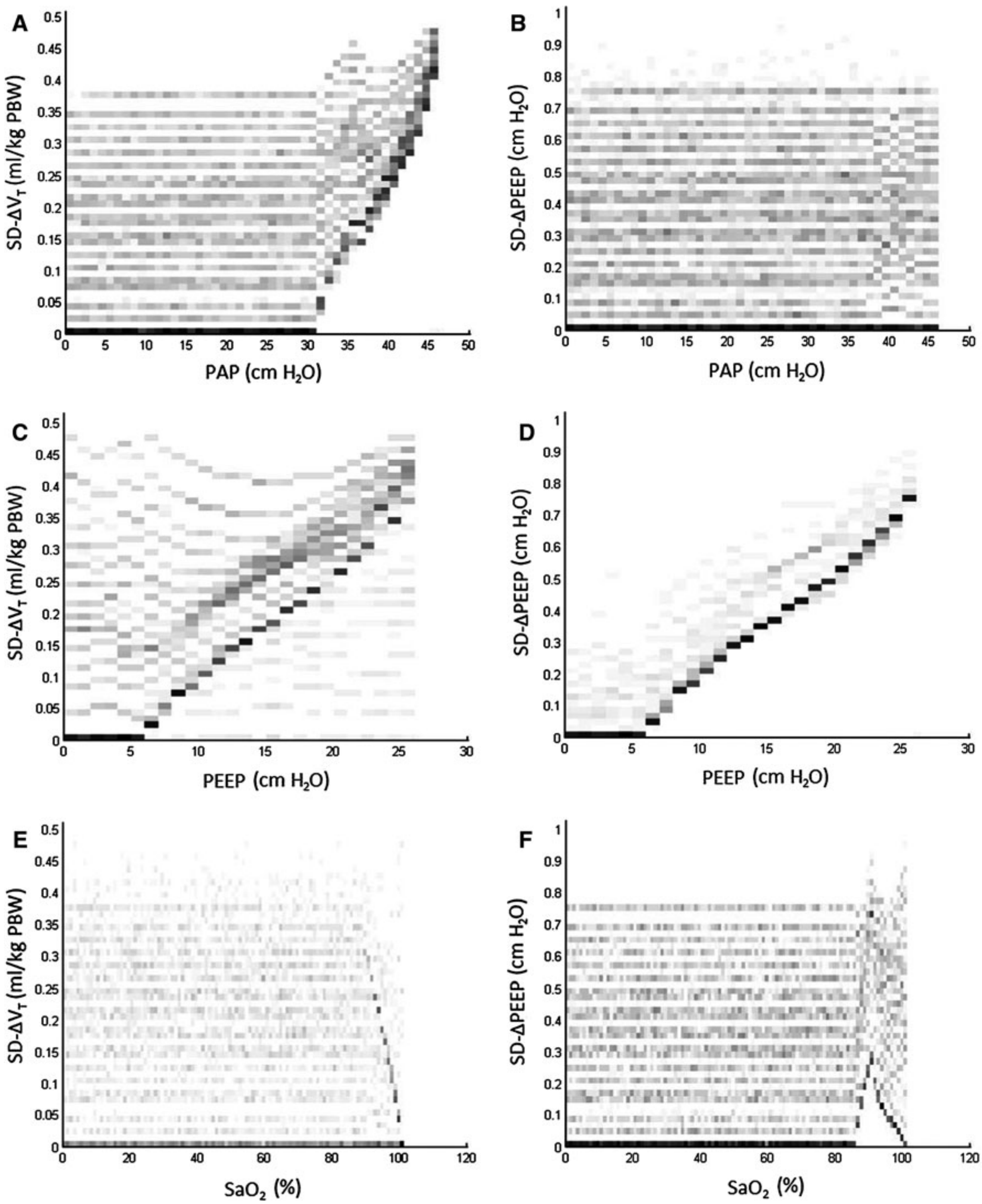

Fig. 2 SD-ΔV_T and SD-ΔPEEP plotted against each of the input parameters PAP, PEEP, and SaO_2. The *darkness of the plot* is proportional to the number of the 10,000 individual patient scenarios that fall on a given value

demonstrated no benefit of higher PEEP over modest PEEP when the level of PEEP was arbitrarily driven by FiO_2 requirement [23]. However, subsequent studies have suggested a benefit of higher PEEP when guided by airway pressure [24] or esophageal pressure [25].

Discordance did not appear to be strongly related to SaO_2 apart from an elevation in SD-ΔPEEP when SaO_2 was around 90 % (Fig. 2f). This disagreement was due to differences in the way the physicians specified the lowest value at which SaO_2 could possibly be defined as being "Normal". By contrast, there was strong agreement about what action to take for ΔV_T when SaO_2 was "Normal" (Fig. 2e). This result can be traced to agreement among the rule tables for how to adjust V_T when SaO_2 is "Normal".

A mild peak in SD-ΔV_T also occurred around PAP values of 35 cmH_2O (Fig. 2a) due to variations in the way that physicians defined the maximum value of PAP that is unquestionably "Normal". It is possible that we would have found less variation among the physicians had we used P_{plat} instead of PAP in our algorithm because the ARDS Network protocol specifies the maximum acceptable P_{plat} to be 30 cmH_2O whereas no such value is specified for PAP [1].

The findings of our study reflect the benefits of the fuzzy logic approach to encapsulating physician expertise in an algorithm, as well as the advantages of using a computer to exhaustively explore the vast space of possible clinical scenarios. This approach is not without its limitations, however. For example, we assumed that the decisions made by the fuzzy logic algorithm when it is parameterized by a specific physician for a particular patient would mirror the decisions the physician would make when actually in the presence of the patient. This would not necessarily be the case, particularly if the physician based their decision on information other than that encapsulated in PAP, PEEP and SaO_2. Our assumption is that this extra information plays a relatively small role in decision-making, as was suggested for control of pressure support mechanical ventilation in our previous study using fuzzy logic in that context [12], but we cannot be sure this applies in the present application. Of course, we can always include additional information in our algorithm by incorporating additional clinical parameters, but this rapidly increases the complexity of the algorithm.

Our algorithm also purports to apply to ARDS patients in general, but in fact ARDS is a heterogeneous disease that affects different patient groups in different ways (e.g. obese vs. lean). Working with a single fuzzy algorithm suits our purposes for the present study because we are simply looking for areas of overall concordance in physician decision making, but in the actual application of fuzzy logic to control V_T in ARDS one might want to construct particular algorithms to suit various clinical situations, and this might include consideration of additional parameters such as FiO_2 and end-tidal CO_2. Nevertheless, SaO_2 may often be what drives clinicians to manipulate PEEP in an effort to improve regional lung recruitment and ventilation-perfusion matching, so arbitrarily linking PEEP levels to FiO_2 is likely not the most appropriate method for regulating PEEP in a mixed population of patients consisting of those who respond to PEEP and those who do not [26].

Our study is also limited by our small sample size of only six physicians. We felt the advantage of our sample is that these physicians all work together and so likely have knowledge bases and skill sets that overlap about as much as one is likely to find in the profession. Our results therefore probably represent a best-case scenario in terms of levels of contention in the management of ARDS. The power of our study would certainly have been greater had it included additional physicians from other centers. Indeed, physicians with different training backgrounds might make decisions based on quite different considerations than those favored at our own institution, in which case we might expect the degree of discordance to be commensurately higher if multiple institutions were included, similar to the situation found by Allerod et al. [27]. This would significantly increase the complexity of the study, but assessing variations in discordance within and between centers could certainly be an interesting area for future research.

In conclusion, we developed a fuzzy logic algorithm to investigate sources of discordance among physicians who manage ARDS patients. Using a Monte-Carlo method, we determined the ranges of PAP, PEEP and SaO_2 values that led to significant degrees of discordance among physicians in terms of their decisions about setting ΔV_T and ΔPEEP. We related the sources of this discordance to variations in how physicians define overlapping fuzzy sets of PAP, PEEP and SaO_2 as well as how they specify the actions to be taken in the face of combinations of set membership for PAP, PEEP and SaO_2. Our findings may have identified patient scenarios for which the current standard of care of V_T less than or equal to 6 ml/kg PBW will need to be re-examined for a possible alternative recommendation, or for deficits in physicians' knowledge bases that need to be more aggressively targeted through training and continual medical education.

Acknowledgments We thank all of the pulmonary critical care physicians at Fletcher Allen Health Care who completed the survey. This research was funded by the National Institutes of Health grant P30 GM103532.

Ethical standards The experiments of this study comply with the laws of the country in which they were preformed.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
2. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338:347–54.
3. Holcomb BW, Wheeler AP, Ely EW. New ways to reduce unnecessary variation and improve outcomes in the intensive care unit. Curr Opin Crit Care. 2001;7:304–11.
4. Kallet RH. Evidence-based management of acute lung injury and acute respiratory distress syndrome. Respir Care. 2004;49:793–809.

5. Guyatt G, Cairns J, Churchill D, et al. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA. 1992;268:2420–5.
6. Pronovost PJ, Rinke ML, Emery K, Dennison C, Blackledge C, Berenholtz SM. Interventions to reduce mortality among patients treated in intensive care units. J Crit Care. 2004;19:158–64.
7. Dennison CR, Mendez-Tellez PA, Wang W, Pronovost PJ, Needham DM. Barriers to low tidal volume ventilation in acute respiratory distress syndrome: survey development, validation, and results. Crit Care Med. 2007;35:2747–54.
8. Steinberg KP, Kacmarek RM. Respiratory controversies in the critical care setting. Should tidal volume be 6 mL/kg predicted body weight in virtually all patients with acute respiratory failure? Respir Care. 2007;52:556–64. Discussion 565–557.
9. Mikkelsen ME, Dedhiya PM, Kalhan R, Gallop RJ, Lanken PN, Fuchs BD. Potential reasons why physicians underuse lung-protective ventilation: a retrospective cohort study using physician documentation. Respir Care. 2008;53:455–61.
10. Rubenfeld GD, Cooper C, Carter G, Thompson BT, Hudson LD. Barriers to providing lung-protective ventilation to patients with acute lung injury. Crit Care Med. 2004;32:1289–93.
11. Kohn LT, Corrigan J, Donaldson MS. To err is human : building a safer health system. Washington, D.C.: National Academy Press; 2000.
12. Nemoto T, Hatzakis GE, Thorpe CW, Olivenstein R, Dial S, Bates JH. Automatic control of pressure support mechanical ventilation using fuzzy logic. Am J Respir Crit Care Med. 1999; 160:550–6.
13. Bates JH, Young MP. Applying fuzzy logic to medical decision making in the intensive care unit. Am J Respir Crit Care Med. 2003;167:948–52.
14. Nguyen HT, Walker E. A first course in fuzzy logic. Boca Raton, FL: Chapman & Hall/CRC; 2006.
15. Zadeh LA. Fuzzy sets. Inf Control. 1965;8:338.
16. Steimann F. On the use and usefulness of fuzzy sets in medical AI. Artif Intell Med. 2001;21:131–7.
17. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ, Hudson LD. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353:1685–93.
18. Vasudevan A, Lodha R, Kabra SK. Acute lung injury and acute respiratory distress syndrome. Indian J Pediatr. 2004;71:743–50.
19. Khemani RG, Sward K, Morris A, Dean JM, Newth CJ. Variability in usual care mechanical ventilation for pediatric acute lung injury: the potential benefit of a lung protective computer protocol. Intensive Care Med. 2011;37:1840–8.
20. Mergoni M, Martelli A, Volpi A, Primavera S, Zuccoli P, Rossi A. Impact of positive end-expiratory pressure on chest wall and lung pressure-volume curve in acute respiratory failure. Am J Respir Crit Care Med. 1997;156:846–54.
21. Lutch JS, Murray JF. Continuous positive-pressure ventilation: effects on systemic oxygen transport and tissue oxygenation. Ann Intern Med. 1972;76:193–202.
22. Hawker FH, Torzillo PJ, Southee AE. PEEP and "reverse mismatch". A case where less PEEP is best. Chest. 1991;99:1034–6.
23. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004;351:327–36.
24. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008;299:646–55.
25. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med. 2008;359: 2095–104.
26. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med. 2006;354:1775–86.
27. Allerod C, Karbing DS, Thorgaard P, Andreassen S, Kjaergaard S, Rees SE Variability of preference toward mechanical ventilator settings: a model-based behavioral analysis. J Crit Care. 2011;26: 637 e635–637 e612.