ORIGINAL RESEARCH

Mechanical Ventilation with Room Air is Feasible in a Moderate Acute Respiratory Distress Syndrome Pig Model – Implications for Disaster Situations and Low-Income Nations

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Abbreviations:
ABG: arterial blood gas
APRV: Airway Pressure Release Ventilation
ARDS: Acute Respiratory Distress Syndrome
ARF: Acute Respiratory Failure
BP: blood pressure
CO_2: carbon dioxide
CPAP: continuous positive airway pressure
Cstat: static lung compliance
$ETCO_2$: end tidal CO_2
FiO_2: fraction of inspired oxygen
HR: heart rate
IACUC: Institutional Animal Care and Use Committee
ICU: intensive care unit
I/E Ratio: Inspirium to Expirium ratio
IV: intravenous
OA: oleic acid
PaO_2: partial pressure of oxygen
PCV: Pressure Controlled Ventilation
PEEP: Positive End Expiratory Pressure
Ppeak: peak airway pressure
SBP: systolic blood pressure
SIMV: Synchronized Intermittent Mandatory Ventilation
SpO_2: peripheral capillary oxygen saturation
Ti: Time of Inspirium

Abstract

Introduction: Patients with respiratory failure are usually mechanically ventilated, mostly with fraction of inspired oxygen (FiO_2) > 0.21. Minimizing FiO_2 is increasingly an accepted standard. In underserved nations and disasters, salvageable patients requiring mechanical ventilation may outstrip oxygen supplies.

Study Objective: The hypothesis of the present study was that mechanical ventilation with $FiO_2 = 0.21$ is feasible. This assumption was tested in an Acute Respiratory Distress Syndrome (ARDS) model in pigs.

Methods: Seventeen pigs were anesthetized, intubated, and mechanically ventilated with $FiO_2 = 0.4$ and Positive End Expiratory Pressure (PEEP) of 5cmH_2O. Acute Respiratory Distress Syndrome was induced by intravenous (IV) oleic acid (OA) infusion, and FiO_2 was reduced to 0.21 after 45 minutes of stable moderate ARDS. If peripheral capillary oxygen saturation (SpO_2) decreased below 80%, PEEP was increased gradually until maximum 20cmH_2O, then inspiratory time elevated from one second to 1.4 seconds.

Results: Animals developed moderate ARDS (mean partial pressure of oxygen [PaO_2]/$FiO_2 = 162.8$, peak and mean inspiratory pressures doubled, and lung compliance decreased). The SpO_2 decreased to <80% rapidly after FiO_2 was decreased to 0.21. In 14/17 animals, increasing PEEP sufficed to maintain SpO_2 > 80%. Only in 3/17 animals, elevation of FiO_2 to 0.25 after PEEP reached 20cmH_2O was needed to maintain SpO_2 > 80%. Animals remained hemodynamically stable until euthanasia one hour later.

Conclusions: In a pig model of moderate ARDS, mechanical ventilation with room air was feasible in 14/17 animals by elevating PEEP. These results in animal model support the potential feasibility of lowering FiO_2 to 0.21 in some ARDS patients. The present study was conceived to address the ethical and practical paradigm of mechanical ventilation in disasters and underserved areas, which assumes that oxygen is mandatory in respiratory failure and is therefore a rate-limiting factor in care capacity allocation. Further studies are needed before paradigm changes are considered.

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Introduction

Acute respiratory failure (ARF) may be divided into two broad types: hypoxemic and ventilatory.[1] Hypoxemic ARF entails impaired diffusion of alveolar oxygen into pulmonary capillary blood and/or mismatch between alveolar ventilation and pulmonary capillary blood flow (V/Q mismatch). Ventilatory failure entails alveolar ventilation, which is insufficient to excrete metabolic carbon dioxide (CO_2) and results in its accumulation. Often, the syndrome is a combination of both mechanisms.

Patients with ARF may require mechanical ventilatory support. The mainstays of such support are enhanced alveolar ventilation and oxygen-enriched positive pressure air. These are coupled with various mechanical adjustments, such as Positive End-Expiratory Pressure (PEEP),[2] variations of Inspiratory Time (T_i), and Inspiratory to Expiratory ratios (I/E Ratio).[3]

The basic assumption in nations with well-developed health care systems is that patients with ARF are treated by experts in an appropriate environment with state-of-the-art mechanical ventilators, and that enough medical oxygen is always available. However, in medically underserved nations and in very extensive disasters (eg, epidemics, earthquakes, wars, or other humanitarian catastrophes), the number of potentially salvageable patients requiring mechanical ventilatory support may outstrip the number of available ventilators[4] and the quantity of available medical oxygen.

The causes of respiratory failure in disasters are multiple, and they too may be divided into hypoxemic, hypercapnic, and mixed. Examples include viral pneumonitis in influenza,[5] chemical pneumonitis with chemical agent exposure,[6] near drowning with tsunami wave, and post-operative ventilation.

The issue of the supply of medical oxygen has not been discussed much in the literature. Oxygen is usually generated in commercial plants, though it may be generated locally. In a major disaster, this supply chain cannot be guaranteed. Oxygen is thus a critical resource in disasters, and its unlimited availability cannot be taken for granted.[7] Blakeman notes that there are essentially no national disaster reserves of oxygen in the US, and the system relies on private vendors. These may be unable to supply all the demand, or may have transportation issues, resulting in a total or partial disruption in oxygen supply. It will be the incident manager's task to ration this critical, yet suddenly scarce, commodity. Surprisingly, a paper describing a European consensus process for pandemic preparedness does not even mention oxygen supply issues.[8]

Given an oxygen shortage, the instruction may go out to minimize use of oxygen. Methods to decrease oxygen utilization may include: decreasing flow to oxygen masks; decreasing fraction of inspired oxygen (FiO_2) to patients receiving continuous positive airway pressure (CPAP) and non-invasive ventilation; avoiding oxygen-hungry continuous-flow CPAP systems; discontinuing oxygen as soon as clinically acceptable; and decreasing FiO_2 to mechanically ventilated patients to the minimum compatible with acceptable oxygen saturation, or even to 0.21.

The concept of using the minimum amount of oxygen in ventilated patients in order to avoid oxygen toxicity is an old one.[9] Nevertheless, there is no consensus requiring that FiO_2 not be decreased to less than 0.4. In recent reviews, this is not even mentioned among evidence-based recommendations.[7,10] Even in a study looking specifically at a disaster situation and testing ventilators aimed at such situations, oxygen was used liberally.[4] Ventilating with $FiO_2 = 0.21$ is not an option even discussed in textbooks or most studies.[10]

In ventilated patients, FiO_2 is usually increased if partial pressure of oxygen (PaO_2) drops and does not respond to alveolar recruitment maneuvers such as increased PEEP, increasing inspiratory time up to and including inverting I/E ratio, muscle paralysis, prone position, switching to Pressure Controlled Ventilation (PCV), and Airway Pressure Release Ventilation (APRV).[11]

However, significant variability exists in practice, and often mechanically ventilated patients are ventilated at FiO_2 of at least 0.4. A study of the effect of a restrictive FiO_2 regimen (median $FiO_2 = 0.36$)[12] showed lower mortality and complications in an intensive care unit (ICU). A clinical study of very low FiO_2, and even room air, in ICU patients showed no negative (and no positive) effects of a restrictive FiO_2 regimen that also included $FiO_2 = 0.21$ compared to usual care.[13] Finally, a meta-analysis concluded that high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes.[14]

The objective of the present study was to show in an Acute Respiratory Distress Syndrome (ARDS) model in pigs, that mechanical ventilation with $FiO_2 = 0.21$ is feasible. Pigs are similar to humans in terms of anatomy, genetics, and physiology. As in humans, the porcine lung has extensive inter- and intra-lobular connective tissue, which connects the major vessels and the bronchi to the pleural surface. Hence, the swine lung is considered an excellent model and has served to study lung development, reperfusion injury, and hyperoxia-induced acute lung injury, as well as other diseases.[15]

Methods

Experimental Definition of ARDS

Acute Respiratory Distress Syndrome was defined when two conditions were met: peripheral capillary oxygen saturation (SpO_2) <90% at $FiO_2 = 0.4$, PEEP = 5cmH_2O and PaO_2/FiO_2 ratio <300.

Animals

Experiments were carried out in accordance with Israeli law and approved by the Institutional Animal Care and Use Committee (IACUCs) at the Israel Institute for Biological Research (Ness Ziona, Israel). Treatment of animals was in accordance with regulations outlined in the US Department of Agriculture (USDA; Washington, DC USA) Animal Welfare Act and the conditions specified in the National Institute of Health (NIH; Bethesda, Maryland USA) Guide for Care and Use of Laboratory Animals (2015).

Female piglets (Topigs 20, 14-24kg, aged 10-15 weeks, n = 17) were obtained from an approved commercial source (van Beek; Netherlands), fed standard pig diet, and housed in a purpose-built animal holding facility for four to eight days prior to the beginning of the experiment. Animals were allowed access to water *ad libitum* and to four percent body weight food per day. Fifteen hours before the experimental procedure, food was withdrawn, while water remained freely available.

Drugs and Chemicals

Drugs used were: Ketamine (Vetoquinol Lure; France), Midazolam (Rafa Laboratories; Israel), Xylazine (Eurovet Animal Health; Netherlands), epinephrine and Standard Solution [0.9% NaCl + 5% glucose] (Teva; Israel), as well as oleic acid (OA) and ethanol (Sigma-Aldrich, Chem-impex, purity 99.5%).

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Surgical Preparations
Pigs were anesthetized with intramuscular ketamine and xylazine (20mg/kg and 2mg/kg, respectively). Anesthesia was maintained with inhaled isoflurane (2%-4% in 100% oxygen) during insertion of arterial and venous catheters. After vascular catheterization, anesthesia was switched to a continuous infusion of Ketamine (3mg/kg/hr) and Midazolam (0.1mg/kg/hr) using a syringe pump (GH Plus, Alaris; Franklin Lakes, New Jersey USA). Five ml/kg/20 minutes infusion 0.9%NaCl/5%Dextrose ("Standard") solution was followed by continuous infusion at 3ml/kg/hr. Endotracheal intubation was performed with a cuffed endotracheal tube (5.5-6.0mm). Tube positioning was verified by capnography and auscultation. A single lumen catheter (16GX20cm, Biometrix; Jerusalem, Israel) was percutaneously introduced into the femoral artery and a triple lumen catheter (8.5FrX20cm, Biometrix) into the femoral vein.

The Improved Technique of OA ARDS Induction (Figure 1)
Repeated intravenous (IV) boluses of OA/saline emulsion is a well-established ARDS model.[16] However, according to the literature and to preliminary experiments, it results in wide variability of individual response. Following a pilot study on four pigs, it has been established that administering a fresh solution of 50% OA in ethanol using syringe-pump into the distal lumen of the central-vein line catheter, simultaneously with standard solution through the proximal lumen of the catheter, is more repeatable and convenient than giving recurrent doses of stirred OA/saline emulsion. This technique allowed a rate-controlled administration adjusted to the individual physiological response of each animal.

A fresh solution of OA in 96% ethanol (1:1) was prepared on the day of the experiment and was administered using syringe pump at 0.17mg/kg/hr. Initial dose was 0.075ml/kg of pure OA. If the ARDS criteria were not met, additional doses of 0.0125ml/kg OA were infused at five-minute intervals, with reassessment of ARDS status. The OA infusion often caused rapid blood pressure (BP) drops; whenever systolic blood pressure (SBP) decreased below 90mmHg, OA administration was stopped for a few minutes, and if SBP dropped below 80mmHg, 5ml/kg fluid bolus was given. If SBP fell below 60mmHg, 0.025mg IV epinephrine boluses were administered. Forty-five minutes after the last administration of OA, to allow development of ARDS, PaO_2/FiO_2 ratio was calculated again before reducing the FiO_2 to 0.21 and the beginning of the experiment.

Experimental Period
After ARDS induction, FiO_2 was reduced from 0.4 to 0.21. When SpO_2 decreased to <80%, PEEP (initially 5cmH_2O) was increased by 3cmH_2O every three minutes, up to 20cmH_2O. If SpO_2 remained <80%, Ti was increased by 0.2 seconds every three minutes (up to 1.4 seconds). If these maneuvers failed to result in $SpO_2 > 80$ (only in three of 17 pigs), FiO_2 was increased by 0.05 increments every three minutes. Hemodynamic variables were monitored (Carescape B650, GE Healthcare; Rehovot, Israel), collected onto a laptop computer at 10-second intervals, via S/5 collection software (GE Healthcare). Ventilator data were recorded manually every 10 minutes from the machine screen. Arterial blood gas (ABG) values and serum lactate were measured using an i-STAT Blood Gas Analyzer (Abbott Laboratories; Chicago, Illinois USA). Data were collected for one hour after room air ventilation was started.

Physiologic Monitoring
Mechanical ventilation was provided with a Hamilton C1 ventilator (Hamilton Medical; Bonaduz, Switzerland). Initial ventilator settings were Synchronized Intermittent Mandatory Ventilation (SIMV), 20 breaths/minutes, $FiO_2 = 0.4$, mandatory tidal volume 10ml/kg, Ti = 1.0 second, PEEP = 5cmH_2O.

Threshold SpO_2
The lower limit of SpO_2 was arbitrarily set at 80%, in order to simulate rather severe disease, which would challenge caregivers in a disaster or low-resource situation and require a resource-allocation decision. The model was thus calibrated to "start low" and show that PEEP alone or slight elevation of FiO_2 will maintain life. There is physiological evidence that saturation in the 80% range does not adversely affect brain metabolism,[17] and clinicians encounter these levels often.

Statistical Analysis
Data are presented in Figure 2 and Figure 3 as means and 95% confidence intervals (CI). For each pig, the momentary measurements of the hemodynamic variables were aggregated into 15-minute groups. Such a one-quarter of an hour group, *t*, contained all the measurements taken in the time range [*t*–7.5 min, *t*+7.5 min). For each group *t*, a temporal average value was calculated. Then, for each one-quarter of an hour *t*, the mean and standard deviation (SD) of the temporal means over the pigs were calculated. The statistical calculations were performed with Microsoft Office Professional Plus 2013 Excel (Microsoft Corp.; Redmond, Washington USA) using the functions: AVERAGEIF and STDEV.

Ethical Approval and Consent to Participate
Animal Study—Experiments were carried out in accordance with Israeli law and approved by the IACUC at the Israel Institute for Biological Research.

Availability of Data and Materials—The data generated or analyzed during this study are included in this published article (and its supplementary information file; available online only).

Results

Induction of ARDS
The experimental paradigm is depicted in Figure 1. Mean PaO_2/FiO_2 ratio after OA infusion was 169 (SD = 42). Forty-five minutes later, the mean PaO_2/FiO_2 ratio was 163 (SD = 34). Thirty minutes after FiO_2 was reduced to 0.21, mean PaO_2/FiO_2 ratio was 237 (SD = 41), and 30 minutes later 248 (SD = 59; Table S1 [available online only]). Peak airway pressure (Ppeak) was 17.7 (SD = 3.4) cmH_2O immediately after OA infusion and increased to 30 (SD = 6) cmH_2O. Static lung compliance (Cstat) was reduced by approximately one-half, from 17.2 (SD = 3.8) to 9.4 (SD = 2.3) ml/cmH_2O (Table 1).

Cardiorespiratory Responses
Intermittent, rapid BP drops were noted during OA infusion (Figure S1; available online only), then BP stabilized. Figure 2 shows the average heart rate (HR), mean arterial pressure, and end tidal CO_2 ($EtCO_2$) of 14 pigs that maintained $SpO_2 > 80\%$ at $FiO_2 = 0.21$ (additional data are provided in the supporting information; available online only).

Arterial Blood Gas (ABG) Analysis
No acidosis or hypercarbia were detected during the entire process, with arterial pH starting at 7.48 (SD = 0.03) and being

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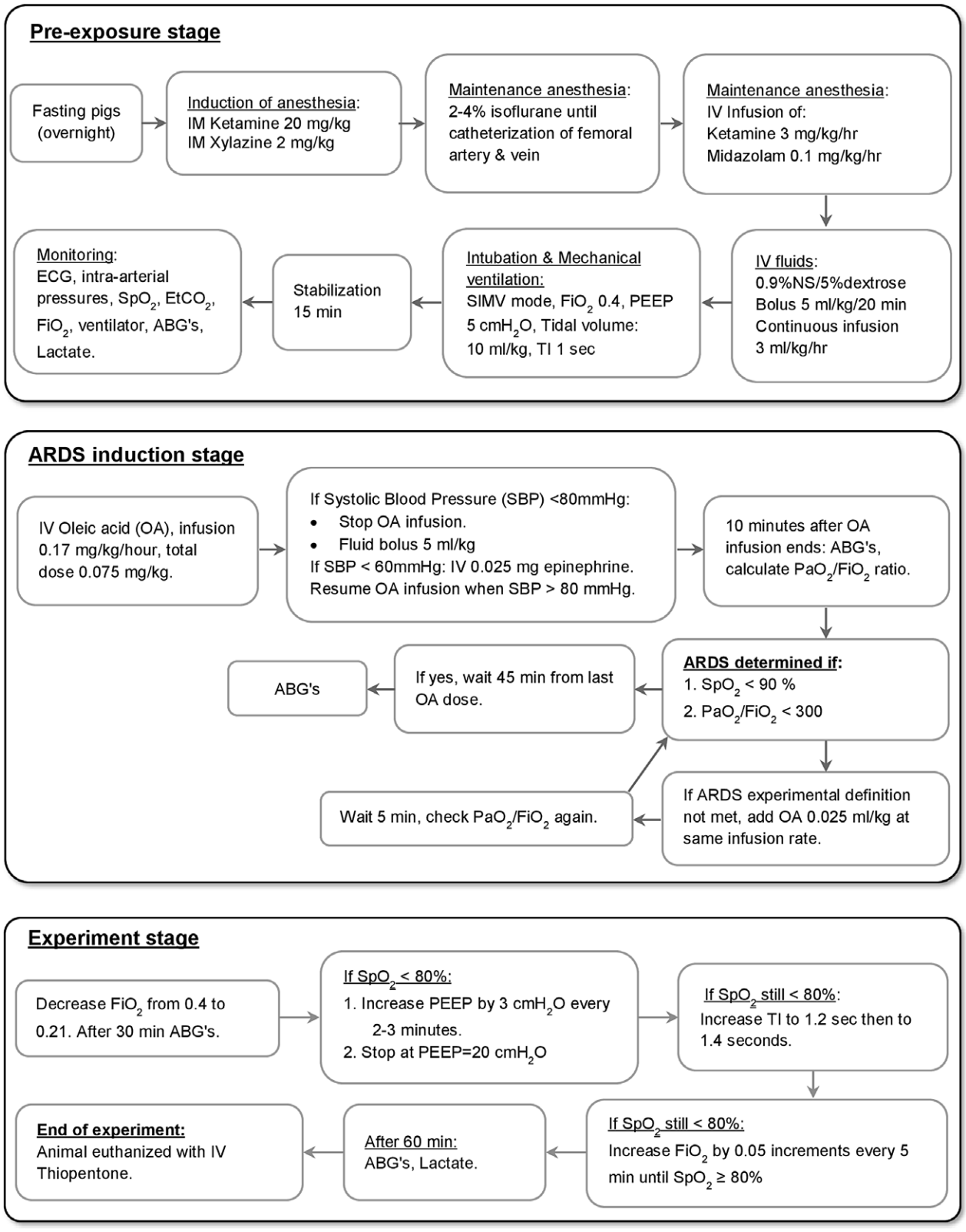

Figure 1. Experimental Paradigm.
Abbreviations: ABG, arterial blood gas; ARDS, Acute Respiratory Distress Syndrome; ECG, electrocardiogram; $ETCO_2$, end tidal CO_2; FiO_2, fraction of inspired oxygen; IM, intramuscular; IV, intravenous; OA, oleic acid; PaO_2, partial pressure of oxygen; PEEP, Positive End Expiratory Pressure; SBP, systolic blood pressure; SIMV, Synchronized Intermittent Mandatory Ventilation; SpO_2, peripheral capillary oxygen saturation; Ti, Time of Inspirium.

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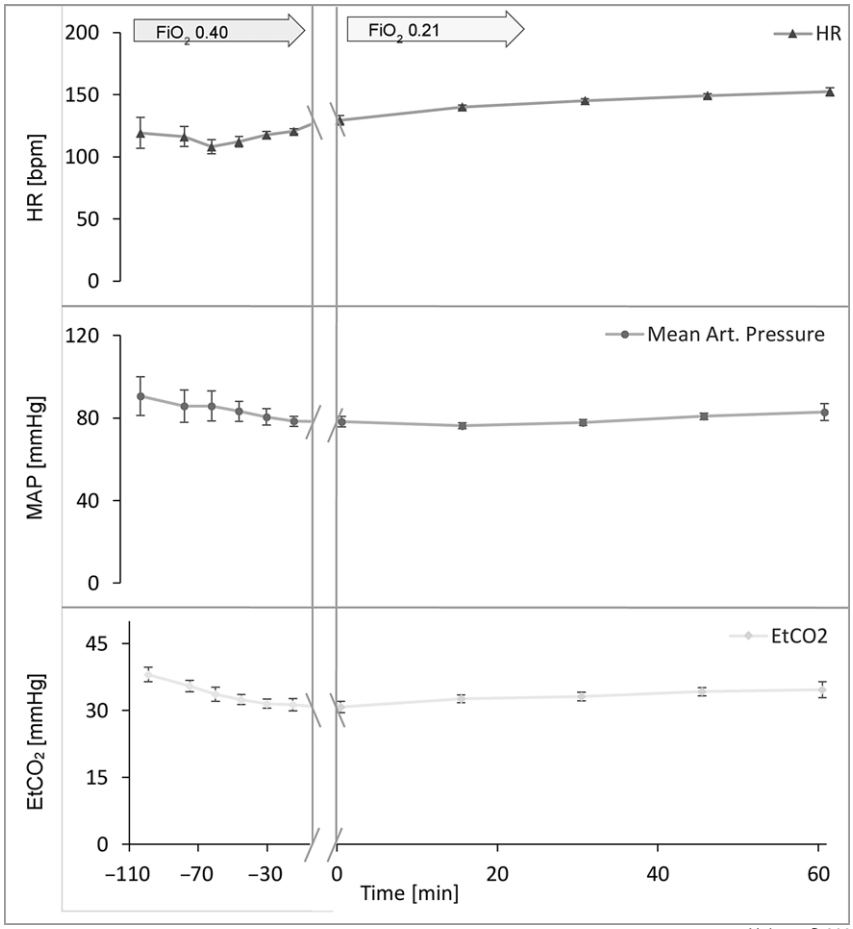

Figure 2. Cardiorespiratory Data of 14 Pigs [mean (95% CI)] During and After Oleic Acid-Induced Acute Respiratory Distress Syndrome.
Abbreviations: $ETCO_2$, end tidal CO_2; FiO_2, fraction of inspired oxygen; HR, heart rate.

7.42 (SD = 0.05) at the end of the experiment (Table 2). As expected, the PaO_2 decreased after the FiO_2 decrease. Lactic acid increased during induction of ARDS from 0.7 (SD = 0.3) mmol/L to 4.7 (SD = 2.5) after OA, then remained unchanged at 4.9 (SD = 3.0).

SpO_2 versus Interventions

The SpO_2 decreased during ARDS induction period, then it further dropped sharply with FiO_2 reduction to 0.21 (Figure 3). Increasing PEEP resulted in increased SpO_2 back to >80%. In some pigs, when the SpO_2 increased, even a reduction in PEEP was possible. Only in three of 17 pigs, PEEP elevations and Ti prolongation were not sufficient and a minimal elevation of FiO_2 was required (Figure S19; available online only).

Discussion

The present study aimed to employ a validated animal ARDS model to determine the feasibility of using room air to mechanically ventilate subjects with moderately severe ARDS. The conceptual framework of the study was the need to conserve scarce medical oxygen in situations such as major disasters, prolonged humanitarian crises, and in regions suffering from chronic medical oxygen shortages in normal times, as well as bolster the emerging understanding of the need to minimize FiO_2.

Medical oxygen scarcity is a reality. Mowafi found that in 2015, most Syrian hospitals in the civil war zone did not have reliable access to medical oxygen.[18] Contini reported that 30% of rural Afghan hospitals do not have oxygen supplies on an assured basis.[19] Tran showed that less than one-half of the hospitals in Haiti had a reliable oxygen supply in 2015,[20] as did only one-third of hospitals in Gambia in 2011,[21] and 17% of sub-district hospitals in Bangladesh in 2017[22] or Cameroon.[23] The experience of the first author in this study (PH) while operating an ICU in Turkey during the 1999 earthquake there indicated that critical oxygen shortages occurred frequently and were often unpredictable.[24]

The issue of "permissive hypoxemia" is still under study, with variable results.[25] The present study was, however, explicitly undertaken to address a scenario whereby multiple patients require respiratory support, mechanical or manual ventilators are available, but oxygen is not or is in limited supply. The alternatives are, to put it bluntly, either to allow many or most of these patients to die, or to provide them with a viable chance of survival, if research shows this option to be feasible at all. The authors thus chose a rather arbitrary lowermost value of SpO_2 of 80% as a pragmatic, though physiologically acceptable, threshold for the study.

The two most important initial interventions when mechanically ventilated patients become hypoxemic are increasing FiO_2 and

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FiO_2	0.4			0.21			
Experiment Time	**Pre-Experiment Base Line**	**End OA Infusion**	**0 min**	**15 min**	**30 min**	**45 min**	**60 min**
Ppeak [cm H_2O]	17.7 (SD = 3.4)	26.6 (SD = 5.3)	29.2 (SD = 5.9)	31.4 (SD = 6.5)	32.8 (SD = 7.0)	29.8 (SD = 5.1)	30.0 (SD = 5.6)
Pmean [cm H_2O]	8.8 (SD = 1.2)	14.9 (SD = 4.8)	17.4 (SD = 2.9)	19.7 (SD = 5.0)	20.5 (SD = 6.3)	18.9 (SD = 4.7)	18.4 (SD = 6.2)
Cstat [ml/cm H_2O]	17.2 (SD = 3.8)	8.9 (SD = 1.8)	8.9 (SD = 3.4)	8.9 (SD = 4.1)	9.1 (SD = 2.4)	9.3 (SD = 2.2)	9.4 (SD = 2.3)

Table 1. Ventilation Parameters of 14 Pigs
Note: The parameters exhibited as Mean (SD).
Abbreviations: Cstat, Static Lung Compliance; OA, oleic acid; Pmean, Mean Airway Pressure; Ppeak, Peak Airway Pressure.

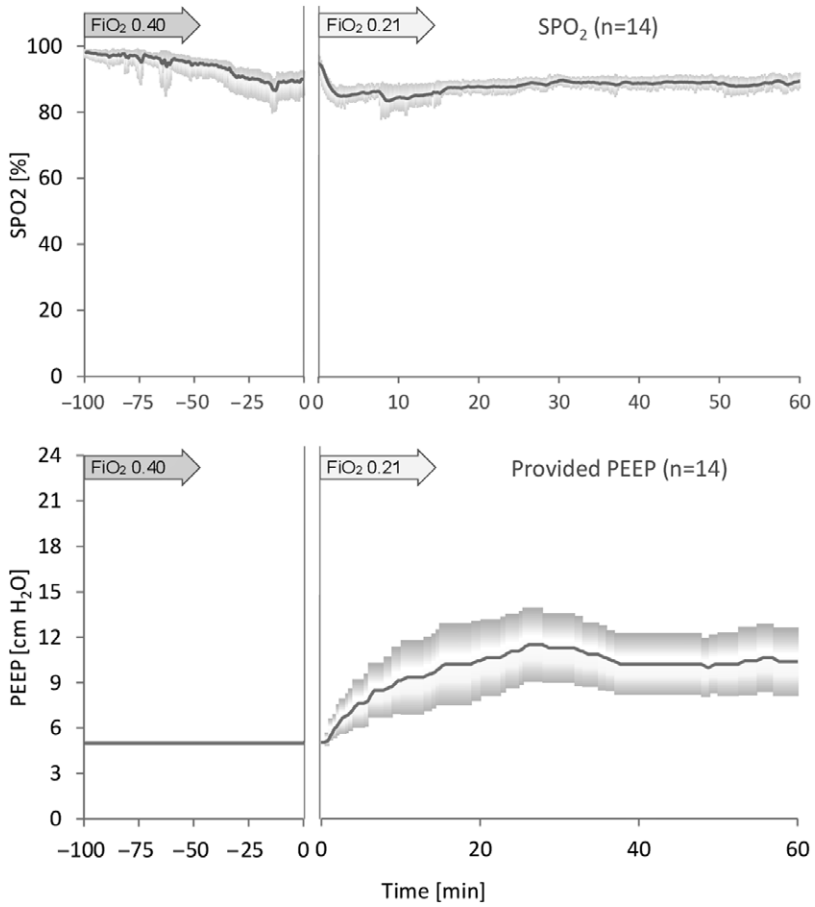

Figure 3. Oxygen Saturation and Positive End Expiratory Pressure of 14 Pigs [mean (95% CI)] During and After Oleic Acid-Induced Acute Respiratory Distress Syndrome.
Abbreviations: FiO_2, fraction of inspired oxygen; PEEP, Positive End Expiratory Pressure; SpO_2, peripheral capillary oxygen saturation.

increasing PEEP. In a study by Lawless[26] in an OA-induced ARDS model in pigs exposed to a simulated altitude of 2440 meters, PEEP was increased gradually from 5cmH_2O to 12.5cmH_2O, or FiO_2 was increased from 0.21 to 1.0. Fifty percent of FiO_2 interventions did not reach target PaO_2 while all PEEP animals did. The authors concluded that increases in PEEP are more reliable than increases in FiO_2 for correcting altitude-induced hypoxia in this model. Admittedly, the response to PEEP is variable and difficult to predict. Among other variables, it depends on the recruitable lung fraction.[27] A systematic review[28] showed that both PEEP and lung recruitment maneuvers were beneficial in ARDS.

Most studies on ARDS, as well as reviews and textbooks, do not mention the possibility, and certainly not the need, to decrease FiO_2 to very low levels even when possible. In spite of the many

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FiO_2	0.4			0.21	
Experiment Time	Pre-Experiment Base Line	End OA Infusion	0 min	30 min	60 min
pH	7.48 (SD = 0.03)	7.38 (SD = 0.07)	7.38 (SD = 0.06)	7.40 (SD = 0.05)	7.42 (SD = 0.05)
$PaCO_2$ mmHg	46 (SD = 3)	46 (SD = 5)	48 (SD = 6)	44 (SD = 4)	43 (SD = 5)
PaO_2 mmHg	211 (SD = 16)	76 (SD = 23)	73 (SD = 22)	53 (SD = 7)	52 (SD = 11)
Lactate mmol/l	0.7 (SD = 0.3)	4.4 (SD = 1.7)	4.3 (SD = 2.1)	4.7 (SD = 2.5)	4.9 (SD = 2.5)

Table 2. Arterial Blood Gas (ABG) Analysis (N = 14)
Note: The parameters exhibited as Mean (SD).
Abbreviations: OA, oleic acid; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen.

studies cited above indicating that lowering FiO_2 in critically ill patients may be beneficial, it seems that it is usually assumed that oxygen is non-toxic at FiO_2<0.4 and there is therefore no incentive, and certainly no imperative, to decrease FiO_2 to below 0.4, even when clinically feasible. Helmerhorst, et al showed that physicians in ICUs believe they should use the lowest possible FiO_2, yet analysis of actual data indicated that the average FiO_2 administered in >100,000 instances was 0.4-0.5, higher than the studied physicians indicated as optimal.[29]

In disasters and in underserved regions, some casualties may perhaps not need oxygen supplementation at all, or only very little, provided that mechanical ventilatory maneuvers are employed. If it were to be shown that at least some patients may not require oxygen enrichment or only minimal amounts, precious oxygen might be saved. Additionally, lives may be saved by not triaging potentially salvageable casualties as "expectant" (ie, not expected to survive) because of the perceived futility of instituting mechanical ventilation in the face of limited oxygen supplies.

The actual use of $FiO_2 = 0.21$ in ventilated patients has rarely been tested, and no studies have been found of a validated laboratory ARDS model looking at this issue. The purpose of the present study was therefore to test the assumption that in a moderately-severe ARDS model in pigs, mechanical ventilation with room air is feasible in most instances, or that only slight increases in FiO_2 may be sufficient when mechanical ventilatory maneuvers, such as adjusting PEEP and Ti, are not sufficient.

In the present study, PaO_2/FiO_2 ratio improved during the experimental procedure. This is either attributable to the increasing PEEP or to the well-known effect of FiO_2 on the P/F ratio, whereby decreasing FiO_2 to below 0.4 results in an increase in the ratio.[30] Also, other indicators of the severity of ARDS remained constant, such as decreased lung compliance.

In a small subgroup of animals, increasing PEEP was insufficient to increase SpO_2 to the predetermined level, but a slight increase of FiO_2 was enough. This group exemplifies the need for dynamic clinical decision making with such patients, but does not invalidate the basic message of the study.

Limitations

From practical reasons, the study period was relatively short and did not address possible further deterioration of ARDS for extended period of time. Also, other lung volume recruiting maneuvers were not applied, which might potentially further facilitate oxygen sparing. Further studies need to look at these issues, as well as use other models of respiratory failure (eg, infectious or primary ventilatory failure).

Conclusions

The present study indicates that in a relevant and well-established animal model of hypoxemic respiratory failure, mechanical ventilation with room air or with small amounts of added oxygen was feasible. Admittedly in humans, some patients with respiratory failure go on to develop worsening ARDS due to the original insult, Ventilator Associated Pneumonia (VAP), or lung atelectasis. This may necessitate additional oxygen supplementation, even after an initial period of satisfactory oxygenation on $FiO_2 = 0.21$. Regardless, the data shown here indicate that automatic use of high FiO_2 and the high oxygen utilization it entails may not be obligatory. Increased PEEP may be used in lieu of increased FiO_2, as well as other interventions that had not been explored in the present study, such as high I:E ratios, ventilatory modes such as PCV, APRV, the prone position, and other lung volume recruiting maneuvers. The present study thus addresses the practical basis for the ethical and practical paradigm of mechanical ventilation in disasters and underserved areas, which assumes that oxygen is mandatory in respiratory failure and is a rate-limiting factor in care capacity allocation. Further studies are needed before any paradigm changes are considered.

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Authors' Contribution (using the CRediT Taxonomy)

PH: Conceptualization, Methodology, Validation, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization. MG: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Data Curation, Visualization. KB: Conceptualization, Methodology, Investigation. AR: Validation, Resources. AW: Methodology, Validation, Formal Analysis. GY: Methodology, Validation, Resources, Data Curation. SK: Conceptualization, Methodology, Validation, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project Administration. All authors read/approved final manuscript.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1049023X20001016

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