Severity of Hypoxemia and Other Factors That Influence the Response to Aerosolized Prostacyclin in ARDS

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BACKGROUND: ARDS is characterized by decreased functional residual capacity (FRC), heterogeneous lung injury, and severe hypoxemia. Tidal ventilation is preferentially distributed to ventilated alveoli. Aerosolized prostaglandin I_2 exploits this pathophysiology by inducing local vasodilation, thereby increasing ventilation-perfusion matching and reducing hypoxemia. Therefore, aerosolized prostaglandin I_2 efficacy may depend upon FRC. Both P_{aO_2}/F_{IO_2} and compliance of the respiratory system (C_{RS}) are indirect signifiers of FRC and thus may partly determine the response to aerosolized prostaglandin I_2. METHODS: We reviewed the records of 208 ARDS subjects who received aerosolized prostaglandin I_2 and had arterial blood gases done before and after the initiation of therapy, without other ventilator manipulations. Subjects were grouped according to baseline P_{aO_2}/F_{IO_2} (lowest: < 60, intermediate: 60–90, highest: > 90 mm Hg) and C_{RS} (< 20, 20–29, 30–39, and ≥ 40 mL/cm H_2O) and by other factors, such as sepsis. Comparisons were analyzed by paired *t* tests, or Kruskal-Wallis and Dunn post-tests. Multivariate logistic regression modeling was done to determine which of 18 clinically relevant factors were most predictive for responding to aerosolized prostaglandin I_2. α was set at .05. RESULTS: Mean P_{aO_2}/F_{IO_2} increased by 33 mm Hg (42%) upon initiation of prostaglandin I_2, with a responder rate of 62%. P_{aO_2}/F_{IO_2} increased significantly in all oxygenation groups. The highest baseline P_{aO_2}/F_{IO_2} group had the greatest improvement and responder rate (51 ± 63 mm Hg, and 82%). In addition, those with sepsis had a smaller improvement in P_{aO_2}/F_{IO_2} compared with those without sepsis (18 ± 35 vs 40 ± 55 mm Hg, $P = .002$). Both P_{aO_2}/F_{IO_2} and responder rate increased as C_{RS} improved, but between-group improvements were not as consistent. In the final model, the only factors that predicted a positive response to aerosolized prostaglandin I_2 were baseline P_{aO_2}/F_{IO_2} (odds ratio 1.10 [1.004–1.205], $P = .042$) and C_{RS} (odds ratio 1.04 [1.01–1.08], $P = .02$). CONCLUSIONS: Aerosolized prostaglandin I_2 improves oxygenation in approximately 60% of ARDS cases. A favorable response was most strongly associated with baseline P_{aO_2}/F_{IO_2} and C_{RS}. *Key words: ARDS; aerosolized prostacyclin; inhaled Flolan.* [Respir Care 2017;62(8):1014–1022. © 2017 Daedalus Enterprises]

Introduction

ARDS is characterized by severe hypoxemia from altered permeability pulmonary edema leading to decreased functional residual capacity (FRC), which in turn causes hypoxemia from intrapulmonary shunting, and areas of low alveolar ventilation to perfusion.[1] Pulmonary hyper-

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tension is also a common feature of ARDS resulting from pulmonary vascular endothelial injury as well as from the effects of hypoxemia, hypercapnia, and acidosis that, if sustained, leads to cor pulmonale and increased mortality risk.[2]

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Because lung injury in ARDS is non-homogeneous[3], portions of the lungs may remain functionally normal, so that tidal ventilation is preferentially distributed to these alveoli. Inhaled vasodilators, such as nitric oxide (NO)[4] and aerosolized prostaglandin I_2,[5] exploit this pathophysiology by inducing local pulmonary vasodilation, thereby increasing alveolar ventilation/perfusion matching.[6] These agents also reduce pulmonary arterial pressure in ARDS.[7] In addition, aerosolized prostaglandin I_2 possesses both anti-inflammatory properties[8] and anticoagulant properties.[9] In theory, these characteristics may lessen the impact of pulmonary vascular endothelial injury and abnormal pro-coagulation that are prominent features of ARDS.[10]

Because of its heterogeneous nature, the extent and distribution of lung injury in ARDS is relatively unique in individual cases. Therefore, the effectiveness of aerosolized prostaglandin I_2 in ARDS may be determined in part by the magnitude of FRC loss. In ARDS, mean FRC is reduced to between 1.8 and 0.6 L (or approximately 75 to 25% of normal).[11] Because FRC is essentially the alveolar volume and the primary determinant of oxygenation and compliance of the respiratory system (C_{RS}),[12] we hypothesized that the initial response to aerosolized prostaglandin I_2 in ARDS would be greater in those with less impaired oxygenation. We used both P_{aO_2}/F_{IO_2} and C_{RS} as indirect correlates of FRC status.

In addition, we evaluated whether ARDS etiology (particularly sepsis) or classification as direct versus indirect injury mechanisms modifies the response to aerosolized prostaglandin I_2. Inhaled NO and aerosolized prostaglandin I_2 cause vasodilation through similar pathways.[13] Prior studies reported that inhaled NO was less effective in sepsis-associated ARDS,[14,15] due to both the blunting effects of endogenous NO overexpression during sepsis[14] and sepsis-induced cardiac dysfunction.[15] Yet others reported that aerosolized prostaglandin I_2 improved oxygenation only in those with indirect or extrapulmonary etiologies for ARDS (78% of whom had sepsis).[16] Therefore, we also investigated the response to aerosolized prostaglandin I_2 in ARDS subjects with and without evidence of sepsis.

QUICK LOOK

Current knowledge

Aerosolized prostaglandin I_2 has been used to improve oxygenation in subjects with ARDS for > 20 y. Most studies have been small and generally have consisted of case series and retrospective reports. Various dosing regimens have been used and have produced modest-to-moderate improvements in oxygenation.

What this paper contributes to our knowledge

The majority of subjects administered aerosolized prostaglandin I_2 had an improvement in oxygenation. Both the magnitude of response and the response rate decrease as the degree of oxygenation dysfunction worsens. This suggests that the efficacy of aerosolized prostaglandin I_2 is dependent upon the amount of aerated lung. The response to aerosolized prostaglandin I_2 was weaker in those with sepsis and stronger in those with trauma-associated ARDS.

Methods

We utilized our hospital's ARDS quality assurance database to examine the effectiveness of aerosolized prostaglandin I_2 in ARDS. This database registered all patients who met the American-European Consensus Conference definition of acute lung injury from June 2002 to April 2016.[17] For the purposes of this study, all subjects were reclassified post hoc according to the current Berlin definition of ARDS.[18] The database was reviewed to identify all patients who received aerosolized prostaglandin I_2 during that time period. Approval to use our quality assurance data was granted by our institutional review board. Of the 1,820 patients in the database, 279 had received aerosolized prostaglandin I_2. After excluding those who died during the therapy; had intervening increases in PEEP, recruitment maneuvers, or prone positioning; or had missing data/medical record, there were 208 subjects who had an arterial blood gas before and after the initiation of aerosolized prostaglandin I_2 and thus were available for analysis (Fig. 1).

Acute Physiology and Chronic Health Evaluation (APACHE II),[19] Simplified Acute Physiology Score II (SAPS II),[20] and lung injury scores[21] were calculated on the day of ARDS onset. Basic demographic information as well as the primary etiology of ARDS and the presence of severe sepsis/septic shock also were collected. Lung injury score was again calculated just before initiating aerosolized prostaglandin I_2. In addition, the medical records were

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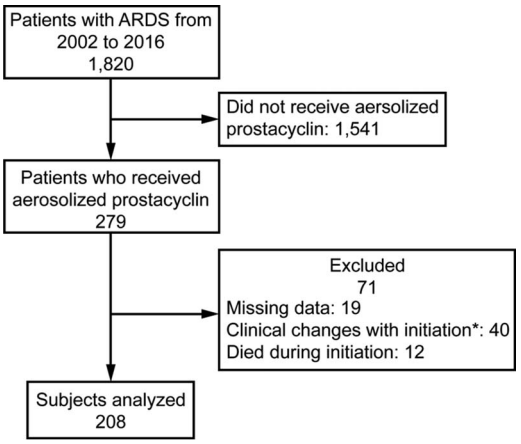

Fig. 1. Flow chart. * = changes in PEEP, prone position, or recruitment maneuvers concurrent with aerosolized prostacyclin initiation.

reviewed to determine all potential mechanisms that might have contributed to the development of ARDS so that lung injury could be classified as being direct, indirect, or mixed. All subjects were managed with one of the ARDSNet ventilator protocols, which is a standard of care at our institution.[22,23]

The aerosol delivery system used was described previously.[24] In brief, a 50-mL solution of prostacyclin (3.0×10^4 ng/mL) and a 500-mL normal saline solution were infused by a dual-channel volumetric infusion pump into a Mini-HEART (Westmed, Tucson, Arizona) jet nebulizer connected to the ventilator circuit with a T-adapter. We found this nebulizer to generate an aerosol with a mass median diameter of 3.12 ± 0.02 μm.[24] In 2010, the delivery system was modified using an Aerogen (Mountain View, California.) vibrating mesh technology (mass median diameter of 3.1 μm)[25] with a fixed concentration of prostacyclin infused through a single volumetric infusion pump. Therapy commenced at the highest recommended dose (50 ng/kg/min) and titrated downward. This approach was based on our early experiences with aerosolized prostacyclin indicating that subjects tend to respond quickly to the highest dose. Therefore, our strategy was based on clinical expediency.

Response to aerosolized prostaglandin I_2 was assessed primarily by changes in P_{aO_2}/F_{IO_2} and also by variables considered to indirectly reflect changes in physiologic dead space: namely the gradient between P_{aCO_2} and end-tidal carbon dioxide tension and corrected minute ventilation ($\dot{V}_E \times P_{aCO_2}/40$).[26] Data were analyzed according to two categories used as signifiers of FRC impairment. The hypoxemia groups were determined a priori to ensure both reasonably approximate sample sizes and clinically informative cutoffs in baseline P_{aO_2}/F_{IO_2} for severe ARDS and were classified as follows: lowest (< 60 mm Hg), intermediate (60–90 mm Hg), and highest (> 90 mm Hg). The compliance groups were based upon clinically informative cutoffs in C_{RS}: < 20 mL/cm H_2O, 20–29 mL/cm H_2O, 30–39 mL/cm H_2O, and ≥ 40 cm H_2O. Marked improvement in oxygenation was defined pre hoc as a P_{aO_2}/F_{IO_2} response of ≥ 10 mm Hg based on the observations of Walmrath et al.[27]

Statistical analysis was done using either Stata 9.0 (Stata Corp, College Station, Texas) or Instat (GraphPad Software, La Jolla, California). Data are reported as mean $\pm$ SD. Pre-post analysis of variables was done using paired *t* tests, whereas comparisons between 2 groups (eg, responders and non-responders) were done with unpaired *t* tests. For non-normally distributed data variables, comparisons were analyzed using either 2-sided Wilcoxon signed-rank tests (pre-post comparisons) or 2-sided Mann-Whitney tests (between-group comparisons). Multiple group comparisons were made using Kruskall-Wallis and Dunn's post-test. Categorical variables were assessed by chi-square tests. α was set at .05.

Backward, step-wise logistic regression modeling was used to determine which variables differentiated aerosolized prostaglandin I_2 responders from non-responders. Variables included in the initial model were age, sex, ethnicity, APACHE II, SAPS II, lung injury score, ARDS etiology, injury category, Berlin definition category, duration of ARDS, presence of sepsis, mean arterial blood pressure, use of vasopressors (both dichotomous classification and number of agents), neuromuscular blockade, baseline P_{aO_2}/F_{IO_2}, C_{RS}, V_T, PEEP, and nebulizer type. The final model included all variables with a $P \leq .10$.

Results

General Characteristics

The majority of our 208 study subjects presented with severe ARDS, as judged by lung injury score at the onset of ARDS and its deterioration at the time that aerosolized prostaglandin I_2 was initiated (Table 1). The proportion of subjects classified as having severe ARDS according to the Berlin definition[17] increased to over four fifths by the time aerosolized prostaglandin I_2 was initiated. An equal proportion of subjects could be categorized as direct or indirect injury, whereas a quarter of all subjects had lung injury attributable to both mechanisms. No primary etiology of ARDS was disproportionately represented. Responders also had significantly lower APACHE II, SAPS II, and lung injury scores at ARDS onset (Table 2).

Hemodynamics and the Response to Aerosolized Prostaglandin I_2

Sixty-five percent of all subjects required vasopressors (Table 1). Of these, 36% required a single agent, 27%

Table 1. Demographics, Baseline Characteristics at ARDS Onset, and Outcome

Variable/Characteristic	Value
Age, mean ± SD y	48 ± 18
Male/female/transgender, %	71/28/1
Racial/ethnic characteristics, %	
European descent	38
Hispanic descent	23
Asian descent	21
African descent	15
Middle-eastern descent	2
Vasopressor use, %	65
APACHE*	26.2 ± 9.0
SAPS*	53.0 ± 18.6
LIS*	3.0 ± 0.6
LIS†	3.3 ± 0.5‡
ARDS classifications and primary etiologies, %	
Severe	59*/83†
Moderate	35*/16†
Mild	5*/1†
Direct injury	34
Indirect injury	32
Mixed injury	34
Aspiration	16.4
Pneumonia	27.4
Sepsis	14.9
Trauma	26.9
Other	14.4§
Hospital mortality, %	56

* Determined at ARDS onset.
† Determined at onset of aerosolized prostacyclin therapy.
‡ $P < .001$ compared with lung injury score at ARDS onset.
§ Sources included burns/inhalation injuries, hemorrhagic shock, neurogenic, and pancreatitis.
APACHE = Acute Physiology and Chronic Health Evaluation
SAPS = Simplified Acute Physiology Score
LIS = lung injury score

required a dual agent, 27% required a triple agent, 7% required 4 agents, and 2% required 5 agents. Although the proportion of subjects requiring vasopressors was not different between responders and non-responders, the later required significantly more vasopressor agents (Table 2).

With the exception of higher epinephrine and vasopressin dosages (which reflected 5 subjects who started therapy after aerosolized prostaglandin I_2 commenced), vasopressor dosages were not different (Table 3). The incidence of hypotension (mean arterial blood pressure < 65 mm Hg) was not different before (29%) or after initiation (28%) and had no impact on the magnitude of improvement in P_{aO_2}/F_{IO_2} (29 ± 44 vs 34 ± 52 mm Hg, respectively; $P = .59$). In the multivariate logistic regression model results, mean arterial blood pressure, vasopressor use, and number of agents used did not determine the responder rate (see below).

Table 2. Characteristics of Responders and non-Responders to Aerosolized Prostaglandin I_2

Variable	Non-Responders	Responders	*P*
Age, mean ± SD y	51 ± 16	46 ± 19	.065
Female/male/transgender, %	35/63/1	23/75/2	.16
APACHE II	30 ± 10	24 ± 8	<.001
SAPS II	60 ± 19	49 ± 17	<.001
Sepsis (co-diagnosis), %	38	30	.25
Mortality, %	70	48	.002
Vasopressor use, %	66	64	.95
Required number of vasopressors, mean ± SD	2.3 ± 1.1	1.8 ± 1.0	.007
LIS*	3.13 ± 0.52	2.93 ± 0.54	.01
LIS†	3.40 ± 0.38	3.28 ± 0.48	.08
ARDS etiology, %			.059
Aspiration	18	16	
Pneumonia	29	26	
Sepsis	22	11	
Other	15	14	
Trauma	16	33	
Injury category, %			.066‡
Direct	33	35	
Indirect	40	26	
Mixed	27	39	
C_{RS}, mean ± SD mL/cm H_2O	25 ± 9	29 ± 10	.01
P_{aO_2}/F_{IO_2}, mean ± SD mm Hg	69 ± 31	83 ± 40	.008

* Determined at ARDS onset.
† Determined at onset of aerosolized prostacyclin therapy.
‡ Versus indirect injury.
APACHE = Acute Physiology and Chronic Health Evaluation
SAPS = Simplified Acute Physiology Score
LIS = lung injury score
C_{RS} = compliance of the respiratory system

Table 3. Vasopressor and Inotropic Dosages Before and After Initiation of Aerosolized Prostaglandin I_2 Therapy

Treatment	*n*	Pre	Post	*P*
Norepinephrine, μg/m	106	13.9 ± 7.0	14.6 ± 6.9	.16
Neosynephrine, μg/m	47	136 ± 95	132 ± 103	.73
Epinephrine, μg/m	33	6.7 ± 7.2	8.4 ± 7.7	.02
Dopamine, μg/kg/m	27	11.0 ± 8.3	11.2 ± 6.4	.39
Dobutamine, μg/kg/m	3	7.33 ± 6.81	7.33 ± 6.81	.82
Vasopressin, units/m	68	0.037 ± 0.012	0.040 ± 0.003	.03

Results are mean ± SD.

Oxygenation and Ventilation Response to Aerosolized Prostaglandin I_2

There were no differences between pre- and post-aerosolized prostaglandin I_2 measurements of F_{IO_2}, PEEP, V_T, and mean arterial blood pressure (Table 4). Oxygenation improved markedly after the introduction of aerosolized prostaglandin I_2, with mean P_{aO_2}/F_{IO_2} increasing by 33 mm Hg (42%) for the entire sample and by 56 mm Hg (80%) when only responders were considered. A modest

Table 4. Gas Exchange and Ventilator Variables Before and After Initiation of Aerosolized Prostaglandin I_2 Therapy

Variable	Pre	Post	*P*
pH	7.29 ± 0.11	7.31 ± 0.11	<.001
P_{aCO_2}, mm Hg	46 ± 12	45 ± 12	<.001
P_{aO_2}, mm Hg	71 ± 29	101 ± 59	<.001
F_{IO_2}	0.94 ± 0.11	0.95 ± 0.11	.41
PEEP, cm H_2O	14 ± 4	14 ± 4	.18
V_T, mL	430 ± 92	427 ± 97	.46
V_T, mL/kg	6.7 ± 1.2	6.7 ± 1.2	.95
P_{aO_2}/F_{IO_2}, mm Hg	78 ± 37	110 ± 67	<.001
$\dot{V}_E$, L/m	12.1 ± 2.8	12.4 ± 3.0	.003
$\dot{V}_{Ecorr}$, L/m	13.9 ± 4.5	13.8 ± 4.9	.26
P_{ETCO_2}, mm Hg	29 ± 9	28 ± 9	.006
$P_{(a\text{-}ET)CO_2}$, mm Hg	17 ± 10	16 ± 11	.26
MAP, mm Hg	74 ± 16	74 ± 16	.87

Results are mean ± SD.
V_T = tidal volume
$\dot{V}_E$ = minute ventilation
$\dot{V}_{Ecorr}$ = minute ventilation corrected ("normalized") to a P_{aCO_2} of 40 mm Hg,
P_{ETCO_2} = end-tidal carbon dioxide tension
$P_{(a\text{-}ET)CO_2}$ = arterial-to-end tidal carbon dioxide tension gradient
MAP = mean arterial pressure

reduction was observed in both P_{aCO_2} and end-tidal carbon dioxide pressure that coincided with a significant, but negligible, increase in $\dot{V}_E$, yet the relative change in $\dot{V}_E$ (ie, corrected to a P_{aCO_2} of 40 mm Hg) was not different. The mean time between pre- and post-arterial blood gas measurements was 2.2 ± 2.0h. Sixty-seven percent of the pre-/post-arterial blood gas measurements were done within 2 h, and 89% were done within 4 h.

Impact of Baseline Oxygenation on the Response to Aerosolized Prostaglandin I_2

Those with the least impaired oxygenation (highest group), had a significantly greater improvement in P_{aO_2}/F_{IO_2} (51 ± 63 mm Hg) than those in either the intermediate (34 ± 46 mm Hg, $P = .002$) or lowest group (19 ± 37 mm Hg, $P < .001$) (Fig. 2). When only responders were considered, the increase in P_{aO_2}/F_{IO_2} was 70 ± 49 (highest group), 58 ± 46, (intermediate group) and 39 ± 45 for (lowest group). Among responders, when compared with the lowest group, the magnitude of increase in P_{aO_2}/F_{IO_2} was significantly greater in both the intermediate ($P = .039$) and highest groups ($P = .005$).

Impact of Baseline C_{RS} on the Response to Aerosolized Prostaglandin I_2

All four C_{RS} groups also had a significant improvement ($P < .001$) in oxygenation with aerosolized prostaglandin I_2 (Fig. 3). Unlike the oxygenation groups, however, there was

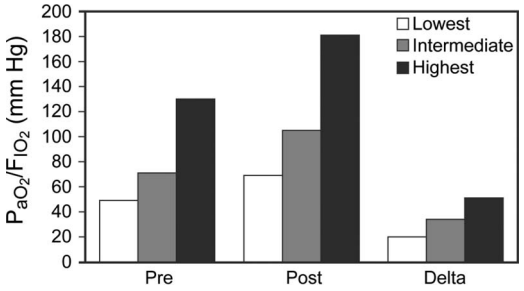

Fig. 2. Mean ratio of P_{aO_2}/F_{IO_2} before and after the initiation of aerosolized prostacyclin and the magnitude of change based on the severity of oxygenation defects in Group A (P_{aO_2}/F_{IO_2} < 60 mm Hg), Group B (P_{aO_2}/F_{IO_2} 60–90 mm Hg), and Group C (P_{aO_2}/F_{IO_2} > 90 mm Hg).

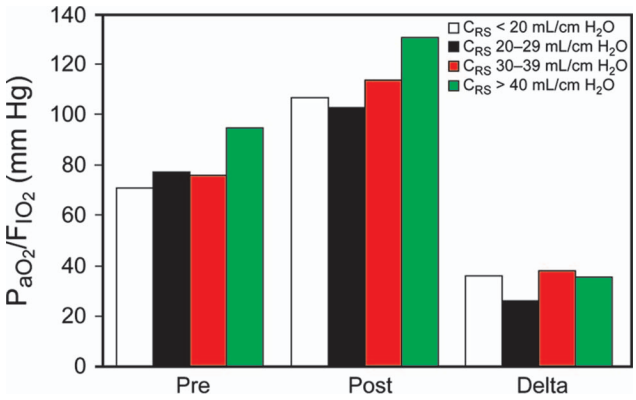

Fig. 3. Mean P_{aO_2}/F_{IO_2} before and after the initiation of aerosolized prostacyclin and the magnitude of change based on groupings according to derangements in compliance of the respiratory system (C_{RS}).

not a steadily increasing improvement in the magnitude of P_{aO_2}/F_{IO_2} response, since C_{RS} increased whether all subjects ($P = .27$) or only responders ($P = .58$) were considered. This was readily apparent when comparing the columns marked "Delta" between Figure 2 and Figure 3. Nonetheless, the number of aerosolized prostaglandin I_2 responders tended to increase as C_{RS} improved: 53% (C_{RS} < 20 mL/cm H_2O), 56% (C_{RS} = 20–29 mL/cm H_2O), 75% (C_{RS} = 30–39 mL/cm H_2O), and 68% ($C_{RS} \geq 40$ mL/cm H_2O). Among responders, there was an impressive increase in P_{aO_2}/F_{IO_2}: 67 ± 64 (C_{RS} < 20 mL/cm H_2O), 49 ± 37, (C_{RS} = 20–29 mL/cm H_2O), 53 ± 49 (C_{RS} = 30–39 mL/cm H_2O), and 62 ± 49 mm Hg ($C_{RS} \geq 40$ mL/cm H_2O). Significant differences were observed between C_{RS} groups: C_{RS} < 20 versus C_{RS} = 30–39 mL/cm H_2O ($P = .009$); C_{RS} = 20–29 versus C_{RS} = 30–39 mL/cm H_2O ($P = .02$).

ARDS Etiology and the Response to Aerosolized Prostaglandin I_2

Regardless of ARDS etiology, P_{aO_2}/F_{IO_2} increased significantly in response to aerosolized prostaglandin I_2 (Ta-

Table 5. Oxygenation Response to Aerosolized Prostaglandin I_2 Based on Etiology of ARDS

Etiology	*n*	P_{aO_2}/F_{IO_2} (pre)	P_{aO_2}/F_{IO_2} (post)	$\Delta P_{aO_2}/F_{IO_2}$	Responders
Trauma	57	86 ± 44	135 ± 77*	49 ± 54	77%
Aspiration	33	70 ± 30	109 ± 60†	39 ± 58	60%
Other	29	71 ± 38	108 ± 82*	37 ± 15	59%
Pneumonia	57	78 ± 33	102 ± 55*	24 ± 39‡	56%
Sepsis	32	77 ± 38	87 ± 47§	10 ± 39‖	50%

Results are mean ± SD.
* $P < .001$ compared with P_{aO_2}/F_{IO_2} (pre).
† $P = .002$ compared with P_{aO_2}/F_{IO_2} (pre).
§ $P = .008$ compared with P_{aO_2}/F_{IO_2} (pre).
‡ $P = .006$ compared with the trauma cohort.
‖ $P = .001$ compared with the trauma cohort.

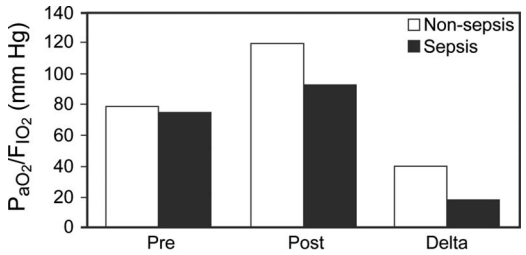

Fig. 4. Mean P_{aO_2}/F_{IO_2} before and after the initiation of aerosolized prostacyclin and the magnitude of change based on the presence or absence of sepsis.

ble 5). Subjects with trauma-associated ARDS had the largest increase in P_{aO_2}/F_{IO_2}, which was significantly greater compared with those with ARDS associated with either pneumonia or sepsis. Although the baseline P_{aO_2}/F_{IO_2} also was higher in subjects with trauma-associated ARDS, the differences between etiologies in baseline P_{aO_2}/F_{IO_2} was not significant ($P = .28$).

Subjects with sepsis as the primary source of ARDS had both the smallest increase in P_{aO_2}/F_{IO_2} and lowest responder rate. All subjects who had sepsis as a contributing factor in the development of ARDS ($n = 68$) were compared with those without sepsis ($n = 139$). Despite having a similar baseline oxygenation, those with sepsis had a significantly smaller improvement in P_{aO_2}/F_{IO_2} in response to aerosolized prostaglandin I_2 than those without sepsis (18 ± 35 vs 40 ± 55, $P = .02$) (Fig. 4). Subjects with sepsis as a primary or secondary source of ARDS also tended to have a lower responder rate compared with those without sepsis (55% vs 65%), although this was not significant (odds ratio 0.78 [95% CI 0.55–1.11], $P = .23$).

Direct and indirect sources of ARDS each accounted for 37% of the sample, whereas mixed mechanisms accounted for 26%. Regardless of etiology, all groups experienced significant increases in P_{aO_2}/F_{IO_2} in response to aerosolized prostaglandin I_2 ($P < .001$). The magnitude of improvement in P_{aO_2}/F_{IO_2} for direct, indirect, and mixed was 34 ± 51, 22 ± 45, and 41 ± 51 mm Hg, respectively, and was significant only between indirect and mixed mechanisms ($P = .03$). In addition, the respective responder rate was 64, 55, and 67% and was not statistically significant.

Impact of ARDS Duration Before Commencing Aerosolized Prostaglandin I_2

In the majority of subjects (55%), aerosolized prostaglandin I_2 was initiated on the day of ARDS onset, and 82% of initiations occurred in the early phase of ARDS (ie, days 1–4). Initiation during either the early or later phases of ARDS was associated with significant improvements in P_{aO_2}/F_{IO_2} (77 ± 37 vs 111 ± 69 mm Hg, $P < .001$; 82 ± 39 vs 109 ± 57 mm Hg, $P < .001$, respectively). Also, the magnitude of P_{aO_2}/F_{IO_2} improvement was not different between ARDS phases (34 ± 53 mm Hg vs 27 ± 29 mm Hg, respectively, $P = .96$).

Multivariate Regression Model

Most variables of interest included in the initial model failed to predict aerosolized prostaglandin I_2 responders. Of particular interest, factors such as nebulizer type (mini-Heart vs Aerogen), baseline PEEP, V_T, ARDS etiology, injury mechanism (ie, direct, indirect, mixed), sepsis, mean arterial blood pressure, and vasopressor use fell out of the initial model. In the final model, aerosolized prostaglandin I_2 responders were associated with baseline P_{aO_2}/F_{IO_2}, C_{RS}, lower APACHE II score, and absence of neuromuscular blockade (Table 6). For every 10 mm Hg increase in baseline P_{aO_2}/F_{IO_2}, the odds of responding to aerosolized prostaglandin I_2 increased by 10%, whereas for every 1-mL/cm H_2O increase in baseline C_{RS}, the odds of responding increased by 4%. For every 1-point increase in APACHE II measured at ARDS onset, the odds of responding to aerosolized prostaglandin I_2 diminished by 7%. Although only approaching statistical significance, the absence of neuromuscular blockade also decreased the odds of responding by 42%.

Table 6. Adjusted Analysis of Aerosolized Prostaglandin I_2 Response as a Function of Baseline P_{aO_2}/F_{IO_2} and Compliance of the Respiratory System

Variable	Odds Ratio	95% CI	*P*
P_{aO_2}/F_{IO_2}	1.10*	1.004–1.205	.042
C_{RS}	1.04†	1.01–1.08	.02
APACHE II	0.93‡	0.90–0.97	<.001
NMB	0.58§	0.31–1.08	.09

* Per 10-mm Hg change in baseline value.
† Per 1-mL/cm H_2O change in baseline value.
‡ Per 1-unit change in score.
§ Signifies the impact of an absence of neuromuscular blockade therapy.
C_{RS} = compliance of the respiratory system
APACHE = Acute Physiology and Chronic Health Evaluation
NMB = neuromuscular blockade

Discussion

Inhaled pulmonary vasodilators commonly are used for treating refractory hypoxemia despite limited data indicating precisely which ARDS patients may benefit. In the present study, approximately 60% of subjects had significantly improved oxygenation with aerosolized prostaglandin I_2. Moreover, we demonstrated that 2 of the classic signifiers of FRC in ARDS, baseline oxygenation (as measured by P_{aO_2}/F_{IO_2}) and C_{RS}, are the most salient determinants of a positive response to aerosolized prostaglandin I_2. The magnitude of improvement in P_{aO_2}/F_{IO_2} in our ARDS subjects was greater than that found in some studies of ARDS ($\Delta P_{aO_2}/F_{IO_2}$ of 10–21 mm Hg),[7,16,24,27-29] but was consistent with others (28–44 mm Hg).[6,30-32] In addition, those with least impaired oxygenation had a significantly greater improvement in P_{aO_2}/F_{IO_2} and a substantially higher responder rate than those with more severely impaired baseline oxygenation. Although the C_{RS} groups did not demonstrate the same pattern of a proportional increase in the magnitude of oxygenation improvement, nonetheless there was a distinct increase in the *response rate* to aerosolized prostaglandin I_2 as C_{RS} improved.

Our findings support the study hypothesis that the effectiveness of aerosolized prostaglandin I_2 is dependent upon the amount of aerated lung parenchyma, signified by FRC. They are also in accord with the classic studies on lung mechanics and gas exchange in ARDS demonstrating that oxygenation efficiency and C_{RS} are directly related to FRC.[33,34] From this, it follows that the effectiveness of aerosolized prostaglandin I_2 might be enhanced when combined with lung recruitment strategies, such as higher PEEP, prone positioning, and/or recruitment maneuvers. A review of prone positioning cited several studies where combining inhaled NO with prone position had an additive effect on improving oxygenation.[35] Therefore, when initiation of aerosolized prostaglandin I_2 therapy fails to improve oxygenation sufficiently, clinicians might consider additional therapies (eg, prone position, higher PEEP, or recruitment maneuvers) that may enhance the effects of either aerosolized prostaglandin I_2 or inhaled NO in very severe cases of ARDS.

Our subjects with sepsis had smaller improvement in P_{aO_2}/F_{IO_2} and a tendency toward a lower response rate to aerosolized prostaglandin I_2. Sepsis causes endothelial dysfunction, leading to deregulated release of both nitric oxide and prostacyclin.[36] Therefore, our results are consistent with other studies that found that inhaled NO is less effective in improving gas exchange in sepsis-associated ARDS.[14,15] This appears to be a novel finding, since we are unaware of any aerosolized prostaglandin I_2 study reporting diminished response in sepsis-associated ARDS. In contrast, subjects with trauma-associated ARDS tended to have both a greater improvement in P_{aO_2}/F_{IO_2} and response rate. This also appears to be a novel finding, though it shares similarities with other studies. Trauma-associated ARDS is distinct from other etiologies in terms of often having both a less severe clinical course and lower systemic inflammatory response[37] as well as lower dead-space ventilation[38] and lower mortality.[39,40]

Both the magnitude of improvement and response rate of P_{aO_2}/F_{IO_2} to aerosolized prostaglandin I_2 were not different when subjects were classified as having either direct or indirect injury. This is in contrast to the findings of Domenighetti et al,[16] who found that aerosolized prostaglandin I_2 was only effective in those with indirect injury. However, only 14 subjects were studied. Given our findings that approximately 40% of subjects with ARDS are non-responders, this may only reflect an artifact from a small sample size.

A meta-analysis[41] of aerosolized prostaglandin I_2 in ARDS concluded that there was insufficient evidence supporting the routine use of aerosolized prostaglandin I_2, because there is no indication that it improves outcomes despite improving oxygenation. However, complex phenomena, such as determinants of mortality in ARDS, are not necessarily amenable to a single therapy. Aerosolized prostaglandin I_2 might be useful in concert with other therapies targeting a specific goal known to impact mortality. In the absence of demonstrable harm or excessive cost/benefit ratio, there is a justifiable rationale to pursue using inhaled vasodilators in subsets of ARDS described below.

There is persuasive evidence that cor pulmonale is associated with mortality in ARDS and is present in approximately 50% of severe cases.[42-44] Also, preclinical research has demonstrated the additive effects of high-stretch tidal ventilation and hyperoxia in promoting ventilator-induced lung injury.[45] Given the heterogeneous nature of lung injury and maldistribution of V_T despite achieving lung-protective goals,[46] it remains plausible that prolonged, regional exposure to both excessive stretch and hyperoxia

may impact outcomes in ways not yet appreciated. The ability of aerosolized prostaglandin I_2 to improve oxygenation and reduce right-ventricular afterload at a less toxic F_{IO_2} might yet be shown to improve outcomes when incorporated into a multitargeted approach. In the interim, we would suggest that aerosolized prostaglandin I_2 be considered in these situations, particularly when right-heart dysfunction is suspected or demonstrated by echocardiography.

The majority of our subjects (68%) were studied within 48 h of ARDS onset, with 83% of all subjects meeting severe ARDS criteria at the time aerosolized prostaglandin I_2 therapy commenced. However, our mortality was higher than the ranges reported both by the Berlin Definition Study Group[18] and the more recent LUNG SAFE Investigators[47] (56% vs 42–48% and 42–50%, respectively). Direct comparisons between our cohort and these studies are problematic because the latter were based on classifications determined on the day of ARDS onset. Moreover, our subjects were a distinct subset of severe ARDS that could be classified as non-responders to traditional therapy, hence the need for ancillary strategies traditionally considered to be salvage or rescue therapies.

The limitations of our study stem from its retrospective nature and its being based upon a single center. However, our study is by far the largest ever done on aerosolized prostaglandin I_2 in ARDS with diverse, well-represented etiologies, as well as having subjects of diverse racial/ethnic backgrounds. It also was done predominantly in highly unstable subjects early in the course of severe ARDS. These represent the cohort of ARDS patients most in need of effective therapies to stabilize gas exchange and in whom evidence suggests that other therapies (higher PEEP,[48] prone positioning,[49] recruitment maneuvers,[50] and neuromuscular blockade[51]) improve outcomes. Our results, therefore, provide uniquely detailed information that might inform the design of a future trial to assess whether aerosolized prostaglandin I_2 might improve outcomes in a *highly circumspect* subset of ARDS.

Conclusions

In summary, aerosolized prostaglandin I_2 improved oxygenation in approximately 60% of subjects presenting with moderately severe or severe ARDS. Its efficacy was apparent regardless of the severity of impairment in baseline oxygenation or C_{RS}; subgroupings of ARDS based upon etiology, early versus late, or direct versus indirect injury; or type of aerosol delivery system used. Its effectiveness also appears to be higher in those with less severely impaired oxygenation and C_{RS}. This only suggests that the effectiveness of aerosolized prostaglandin I_2 is dependent upon FRC and therefore may be improved when used together with strategies that improve FRC (eg, prone positioning, recruitment maneuvers, and high PEEP).

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