Original Contributions

Description and Evaluation of a Delivery System for Aerosolized Prostacyclin

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INTRODUCTION: Inhaled vasodilators such as nitric oxide and aerosolized prostacyclin (PGI$_2$) are used to treat severe hypoxemia in acute respiratory distress syndrome. Preferential distribution of nitric oxide and PGI$_2$ to ventilated areas of the lung causes selective pulmonary vasodilation, improved ventilation/perfusion matching, and decreased hypoxemia. Because of the technical limitations of previously described methods, we developed a PGI$_2$ delivery technique that allows the aerosolized drug dose to be easily calculated, set, and adjusted. METHODS: A 50 mL solution of PGI$_2$ (3.0×10^4 ng/mL) and a 500 mL normal saline solution were infused by a dual-channel volumetric infusion pump into a MiniHEART jet nebulizer that has a manufacturer-specified output of 8 mL/h at a set flow of 2 L/min. By adjusting the pump infusion rate to achieve a total output of 8 mL/h, the PGI$_2$ concentration was altered to deliver a calculated aerosolized dose of 10–50 ng/kg/min. The effectiveness of the delivery system was retrospectively evaluated by way of the responses of 11 severely hypoxemic acute respiratory distress syndrome patients who received PGI$_2$ via the system we describe. The MiniHEART nebulizer output, particle size, and dose delivery were evaluated in a laboratory bench study, using a set flow of 2 L/min. RESULTS: Aerosolized PGI$_2$ therapy (mean dose 28 $\pm$ 17 ng/kg/min, range 10–50 ng/kg/min) significantly increased the ratio of P$_{aO_2}$ to fraction of inspired oxygen (P$_{aO_2}$/F$_{IO_2}$) (60 $\pm$ 11 mm Hg vs 80 $\pm$ 17 mm Hg, p = 0.003) and arterial oxygen saturation measured via pulse oximetry (86 $\pm$ 8% vs 94 $\pm$ 3%, p = 0.005) (differences evaluated with the Wilcoxon signed rank test). There was no difference in positive end-expiratory pressure, mean airway pressure, or F$_{IO_2}$, before and after aerosolized PGI$_2$ (p > 0.05). Nebulizer output was 6.8 $\pm$ 0.9 mL/h, range 6.0–7.8 mL/h. The inhaled aerosol particles had a mass median diameter of 3.1 μm. Emitted dose was 67 $\pm$ 13% (range 57–81%) of the calculated dose. CONCLUSION: Our system is effective in delivering aerosolized PGI$_2$ to the alveolar-capillary interface, as indicated by significant oxygenation improvements soon after therapy commenced. The performance of the MiniHEART nebulizer varies from the manufacturer's specifications, which may alter the delivered dose. *Key words: acute respiratory distress syndrome, aerosolized prostacyclin, dose delivery, mechanical ventilation, nebulizer.* [Respir Care 2003;48(8):742–753. © 2003 Daedalus Enterprises]

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by severe hypoxemia from intrapulmonary shunting, areas with very low ventilation/perfusion ratio,[1] and by pulmonary hypertension from elevated pulmonary vascular resistance.[2] The use of high positive end-expiratory pressure (PEEP) and/or large tidal volume to recruit atelectatic lung tissue and reverse hypoxemia may exacerbate the disease

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process[3] because lung injury in ARDS is nonhomogenous.[4] Alternatively, severe hypoxemia in ARDS can be treated with inhaled vasodilators such as nitric oxide (NO)[5] or aerosolized prostacyclin (PGI_2).[6] Because these inhaled drugs are distributed preferentially to ventilated areas of the lung, they cause selective pulmonary vasodilation and decrease hypoxemia by improving ventilation/perfusion matching.[6] Inhaled NO and aerosolized PGI_2 also reduce pulmonary arterial pressure.[5,7,8] Previous aerosolized PGI_2 delivery systems were described vaguely[8,9] or had restrictive dose titration capabilities.[10,11] We describe a PGI_2 delivery system that allows the aerosolized dose to be easily calculated, set, and adjusted. We retrospectively evaluated the effectiveness of our PGI_2 delivery system by measuring oxygenation in patients who received aerosolized PGI_2. In this report we also examine relevant clinical issues related to this delivery method, evaluation of nebulizer performance, and predicting actual versus desired dose.

Methods

Equipment Assembly

Our aerosolized PGI_2 delivery system uses routinely available equipment, including a dual-channel volumetric infusion pump (Dual Flo-Gard 6301, Baxter Medical, Deerfield, Illinois), vented and nonvented intravenous tubing, a 3-way intravenous stopcock, a short intravenous tubing extension with a Luer-Lok adapter, a 500 mL normal saline solution, a pharmacy-prepared 50 mL bottle of PGI_2, a jet nebulizer (MiniHEART, Westmed, Tucson, Arizona.), 30.5-cm and 61-cm lengths of corrugated aerosol tubing, an aerosol T-piece, standard oxygen tubing, and an oxygen flow meter (Fig. 1).

The vented intravenous tubing was connected to the bottle of PGI_2, and the standard nonvented intravenous tubing was connected to the normal saline solution. Each intravenous tubing was connected to the 3-way stopcock, which in turn was connected to the short tubing extension. The Luer-Lok adapter on the extension tubing then was connected to the MiniHEART nebulizer (see Fig. 1). The 30.5-cm corrugated aerosol tubing was connected from the nebulizer to the aerosol T-piece, which was placed in-line on the inspiratory limb of the ventilator circuit. A 30.5-cm length of aerosol tubing connected the T-piece to the ventilator Y-piece and served as a reservoir, to improve drug delivery.[12] The nebulizer was secured to the ventilator tubing support arm or intravenous pole as a safety measure to prevent accidental spillage of the nebulizer contents into the ventilator circuit and potential aspiration of the PGI_2 solution.

Drug Preparation and Aerosolized Dose Calculation

The pharmacy reconstituted a 1.5 mg (1.50×10^6 ng) vial of PGI_2 (Flolan, GlaxoSmithKline, Research Triangle Park, North Carolina) in a volume of 50 mL of manufacturer-specified sterile diluent solution (94 mg glycine, 73.3 mg sodium chloride, sodium hydroxide to adjust pH, and water to achieve a 3.0×10^4 ng/mL concentration. A concentration of 3.0×10^4 ng/mL PGI_2 provided the most efficient use of drug and diluent and offered the most flexibility in providing the wide range of calculated doses we studied (Table 1). Effective doses of aerosolized PGI_2 have been identified to be between 5 and 50 ng/kg/min,[6–11,13–15] so we calculated PGI_2 and normal saline infusion rates into the nebulizer to achieve a calculated aerosolized PGI_2 delivery between 10 and 50 ng/kg/min (in 10 ng/kg increments) for patients with predicted body weight (PBW) between 40 and 100 kg (see Table 1). The titration charts for PGI_2 and normal saline used to calculate aerosolized dose were based on the manufacturer's specifications for the MiniHEART nebulizer: aerosol output of 8 mL/h at a flow of 2 L/min. PBW was determined by the following formulas:[16]

Male patients: PBW (in kg) = 50

$$+ \ 2.3 \ (\text{height in inches} - 60) \quad [1]$$

Female patients: PBW (in kg) = 45.5

$$+ \ 2.3 \ (\text{height in inches} - 60) \quad [2]$$

If height is measured in centimeters, the formulas are:

Male patients: PBW (in kg) = 50

$$+ \ 2.3 \ [(\text{height in cm} - 152) \div 2.54]$$

Female patients: PBW in kg = 45.5

$$+ \ 2.3 \ [(\text{height in cm} - 152) \div 2.54]$$

The following formulas were used to determine the infusion rate of PGI_2 and normal saline:

PGI_2 infusion rate =

$$[(\text{PBW} \times PGI_2 \text{ dose}) \times 60 \text{ min}] \div PGI_2 \text{ concentration} \quad [3]$$

Normal saline infusion rate

$$= \text{nebulizer output (mL/h)} - PGI_2 \text{ infusion rate} \quad [4]$$
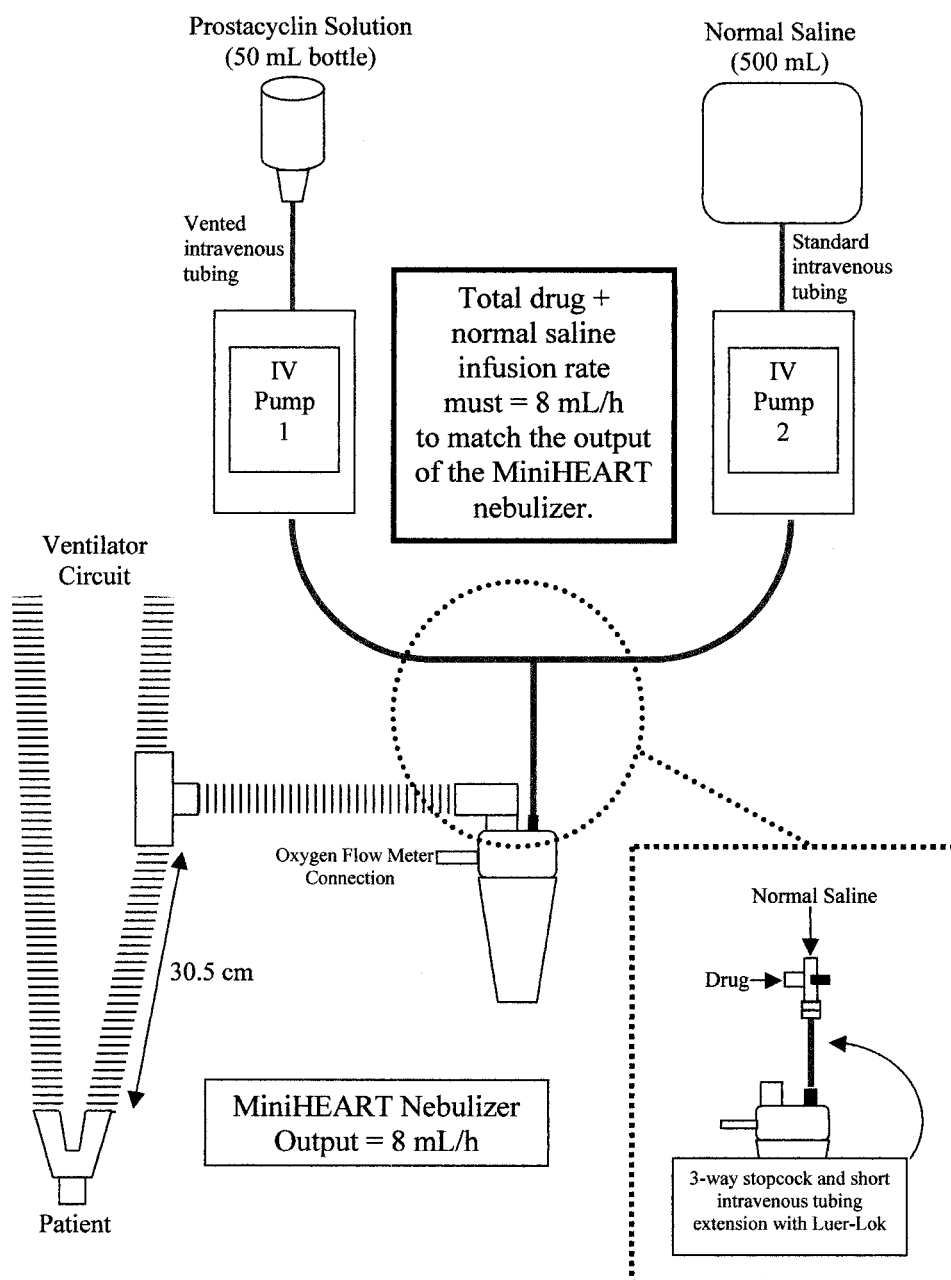
Fig. 1. Delivery system for aerosolized prostacyclin to mechanically ventilated patients. IV = intravenous.

Evaluation

We retrospectively evaluated the effectiveness of our aerosolized PGI_2 delivery system by measuring oxygenation in patients who received aerosolized PGI_2. The retrospective medical record study was approved by the University of California, San Francisco, Committee on Human Research. The medical records were reviewed for mechanical ventilation and arterial blood gas data. Data within 2 h preceding initiation of PGI_2 therapy were compared to data from within 2 h

after PGI_2 therapy commenced. Paired comparisons were made using the Wilcoxon signed rank test.[17] Differences were considered significant when $p < 0.05$.

Laboratory evaluation of the accuracy of this PGI_2 delivery system was performed using 5 MiniHEART nebulizers (from 4 different manufacturing lots) at a flow of 2 L/min from a 50-psi gas source. Volume output was calculated using the gravimetric method, with timed nebulization over 5 min and extrapolated to 1 hour. The aerosol particles' mass median diameter (MMD) was determined

Table 1. Aerosolized Prostacyclin Infusion Rates for Patients with Predicted Body Weight Between 40 and 100 kg

PBW	PGI$_2$ Dose (ng/kg/min)	PGI$_2$ IV Pump Infusion Rate (mL/h)	NS IV Pump Infusion Rate (mL/h)	PGI$_2$ Total Dose (ng/min)	PGI$_2$ Total Dose (ng/h)
40	10	0.8	7.2	400	24,000
	20	1.6	6.4	800	48,000
	30	2.4	5.6	1,200	72,000
	40	3.2	4.8	1,600	96,000
	50	4.0	4.0	2,000	120,000
50	10	1.0	7.0	500	30,000
	20	2.0	6.0	1,000	60,000
	30	3.0	5.0	1,500	90,000
	40	4.0	4.0	2,000	120,000
	50	5.0	3.0	2,500	150,000
60	10	1.2	6.8	600	36,000
	20	2.4	5.6	1,200	72,000
	30	3.6	4.4	1,800	108,000
	40	4.8	3.2	2,400	144,000
	50	6.0	2.0	3,000	180,000
70	10	1.4	6.6	700	42,000
	20	2.8	5.2	1,400	84,000
	30	4.2	3.8	2,100	126,000
	40	5.6	2.4	2,800	168,000
	50	7.0	1.0	3,500	210,000
80	10	1.6	6.4	800	48,000
	20	3.2	4.8	1,600	96,000
	30	4.8	3.2	2,400	144,000
	40	6.4	1.6	3,200	192,000
	50	8.0	0.0	4,000	240,000
90	10	1.8	6.2	900	54,000
	20	3.6	4.4	1,800	108,000
	30	5.4	2.6	2,700	162,000
	40	7.2	0.8	3,600	216,000
	50	†	–	4,500	270,000
100	10	2.0	6.0	1,000	60,000
	20	4.0	4.0	2,000	120,000
	30	6.0	2.0	3,000	180,000
	40	8.0	0.0	4,000	240,000
	50	†	–	5,000	300,000

PBW = predicted body weight
PGI$_2$ = prostacyclin
IV = intravenous
NS = normal saline
†Unable to deliver dose at a drug concentration of 30,000 ng/mL

using a laser particle analyzer (Malvern Spraytec, Malvern Instruments, Malvern, United Kingdom). Aerosol particle size was measured both at the nebulizer outlet and at the distal end of a 7.5-mm endotracheal tube attached to a test lung during controlled mechanical ventilation, with the nebulizer positioned as in Figure 1. Particle size was measured using normal saline and 3 dilutions of PGI$_2$ solution (3.0×10^4 ng/mL) and normal saline: undiluted, and with ratios of 1 to 1, and 1 to 7. The particle size and aerosol plume emitted at the nebulizer outlet using normal saline solution (MMD = 6.2 ± 0.2 μm) were comparable to the 3 PGI$_2$ solutions (undiluted = 6.3 ± 0.1 μm; 1 to 1 = 6.2 ± 0.1 μm; 1 to 7 = 6.0 ± 0.1 μm). Since there are no chemical assays available for PGI$_2$, a 0.083% solution of albuterol sulfate was used as a surrogate indicator to estimate the emitted and inhaled dose. The quantity of drug collected over 5 min on filters at the nebulizer outlet (emitted dose) and on filters located between the distal end of the endotracheal tube and a test lung (inhaled dose) were measured by assay technique for albuterol sulfate, using a spectrophotometer (Beckman Instruments, Fullerton, California).

The reconstituted solution of PGI_2 has a pH of 10.2–10.8 and is increasingly unstable at a lower pH.[18] To test the effect of normal saline dilution we measured the pH (Beckman pH meter, Beckman-Coulter, Allendale, New Jersey) of undiluted PGI_2 solution (3.0×10^4 ng/mL) and 3 dilutions of PGI_2 solution and normal saline (ratios of 7 to 1, 1 to 1, and 1 to 7) representing the minimum, median, and maximum dilutions used with our delivery system.

Results

Aerosolized PGI_2 was used as rescue therapy in 11 ARDS patients suffering profound respiratory failure (Table 2). Seven patients suffered from pulmonary ARDS and 4 patients from extrapulmonary ARDS. The mean $\pm$ SD lung injury score[19] was 3.7 $\pm$ 0.29. The mean $\pm$ SD dose was 28 $\pm$ 17 ng/kg/min, and the mean duration of treatment was 41 h (range 9–116 h). There was no difference in PEEP, mean airway pressure, or fraction of inspired oxygen (F_{IO_2}) before and after the initial aerosolized PGI_2 treatments (p > 0.05). Aerosolized PGI_2 therapy significantly increased P_{aO_2} (p = 0.002), P_{aO_2}/F_{IO_2} (p = 0.002), and arterial oxygen saturation measured via pulse oximetry (p = 0.001). P_{aO_2} decreased in one patient and was unchanged in another, relative to the change in P_{aCO_2}. In patients whose oxygenation improved, P_{aO_2} increased by an average of 37%. There was a weak correlation between the percent increase in P_{aO_2}/F_{IO_2} and the dose received (r = 0.28, p = 0.41, Fig. 2). Although expired minute ventilation ($\dot{V}_E$) changed significantly (14.6 $\pm$ 3.7 L/min vs 16.3 $\pm$ 5.0 L/min, p = 0.004), P_{aCO_2} (57 $\pm$ 21 mm Hg vs 55 $\pm$ 22 mm Hg, p = 0.13) was unchanged.

Table 2. Characteristics and Responses of Patients Receiving Aerosolized Prostacyclin As Rescue Therapy

Patient	ARDS Etiology	LIS	Days of MV		Dose (ng/kg/min)	$\dot{V}_E$ (L)	PEEP (cm H_2O)	Arterial pH	P_{aCO_2} (mm Hg)	P/F	S_{pO_2} (%)
1 Expired	P	3.25	4.5	Before	0	15.2	10	7.24	63	49	87
				After	10	18.4	12	7.28	55	70	91
2 Expired	P	4	0.8	Before	0	10.4	15	7.31	91	60	85
				After	20	11.0	15	7.29	96	115	95
3 Survived	EP	3.75	2.6	Before	0	9.6	14	7.38	39	66	97
				After	10	9.5	14	7.39	36	79	98
4 Expired	P	4	10.1	Before	0	12.8	16	7.39	63	49	83
				After	10	13.8	16	7.38	62	63	87
5 Expired	P	4	3.8	Before	0	12.4	20	7.19	66	49	81
				After	50	15.7	22	7.32	59	79	93
6 Expired	P	4	4.9	Before	0	12.2	18	7.19	62	72	86
				After	10	13.2	18	7.32	54	69	95
7 Survived	P	3.5	1.1	Before	0	16.5	12	7.40	36	57	85
				After	30	17.5	12	7.36	41	89	91
8 Expired	P	3.75	10.0	Before	0	19.6	12	7.21	92	64	85
				After	40	21.4	12	7.21	90	76	90
9 Expired	EP	3.75	1.1	Before	0	14.1	10	7.10	43	55	87
				After	50	16.2	14	7.18	43	94	95
10 Survived	EP	3.25	0.3	Before	0	21.6	10	7.06	36	47	87
				After	30	26.9	15	7.19	30	53	95
11 Survived	EP	3.5	3.3	Before	0	16.2	18	7.28	34	83	99
				After	50	16.2	18	7.26	34	94	100
Mean $\pm$ SD		3.7 $\pm$ 0.3	3.9 $\pm$ 3.4	Before	0	14.6 $\pm$ 3.7	14.1 $\pm$ 3.6	7.25 $\pm$ 0.11	57 $\pm$ 21	60 $\pm$ 11	85.7 $\pm$ 7.7
Mean $\pm$ SD				After	28 $\pm$ 17	16.3 $\pm$ 5.0†	15.3 $\pm$ 3.1	7.29 $\pm$ 0.07	55 $\pm$ 22	80 $\pm$ 17†	93.6 $\pm$ 3.3†

ARDS = acute respiratory distress syndrome
LIS = lung injury score
Days of MV = Days of mechanical ventilation prior to PGI_2 treatment
Dose = aerosolized dose of PGI_2 based on predicted body weight
$\dot{V}_E$ = minute ventilation
PEEP = positive end-expiratory pressure
P_{aCO_2} = arterial partial pressure of carbon dioxide
P/F = ratio of P_{aO_2} to fraction of inspired oxygen (F_{IO_2})
S_{pO_2} = arterial oxygen saturation measured via pulse oximetry
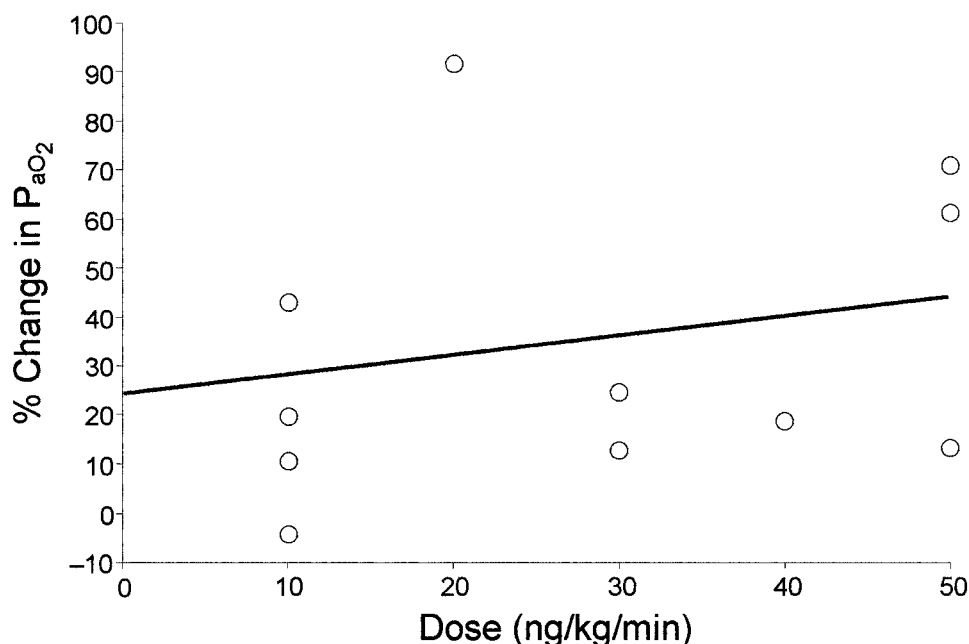P = pulmonary
EP = extra-pulmonary
†p < 0.05

Fig. 2. Linear regression comparing the percent change in P_{aO_2} to the dose received. Correlation coefficient (r) = 0.28, p = 0.41.

The mean $\pm$ SD aerosol volume output from the Mini-HEART nebulizers (6.8 $\pm$ 0.9 mL/h, range 6.0–7.8 mL/h) was below the 8 mL/h needed to deliver the calculated aerosolized dose. Aerosol particles of the undiluted PGI$_2$ solution delivered to the distal tip of the endotracheal tube and available for inhalation had an MMD of 3.12 $\pm$ 0.02 μm. The average emitted dose (360 $\pm$ 69 μg) using albuterol sulfate as a surrogate indicator was 67% (range 57–81%) of the nominal dose (540 μg) (based on the manufacturer's specifications: volume loss from the nebulizer per minute [0.13 mL] times the albuterol concentration [830 μg/mL] times 5 min). The average inhaled dose (74 $\pm$ 0.7 μg) was 14% of the nominal dose and 21% of the average emitted dose. The pH of the 4 dilutions of PGI$_2$ solution (3.0×10^4 ng/mL) and normal saline were: undiluted = 10.48 $\pm$ 0.03; 7 to 1 = 10.45 $\pm$ 0.01; 1 to 1 = 10.35 $\pm$ 0.04; 1 to 7 = 10.13 $\pm$ 0.03. The pH of the normal saline solution was 6.40 $\pm$ 0.0.

Discussion

This PGI$_2$ delivery method allows the aerosolized dose to be easily calculated, set, and adjusted. Aerosolized PGI$_2$ is an alternative to inhaled NO because its effectiveness in treating hypoxemia is comparable,[9,14] and it is less expensive (total cost of drug and disposable equipment approximately \$300/d). However, in many studies aerosolized PGI$_2$ was delivered using premixed, single concentrations of PGI$_2$ solution. Therefore, aerosolized dose adjustments would require mixing each desired concentration. To be clinically practical,

aerosolized PGI$_2$ therapy should allow the clinician to titrate the dose in a manner similar to inhaled NO therapy. Our system does that using a dual intravenous pump to mix PGI$_2$ with a normal saline and a nebulizer with a constant-volume output.

The retrospective analysis of our delivery method showed significant improvement in oxygenation shortly after aerosolized PGI$_2$ therapy commenced. There was no change in PEEP, mean airway pressure, or F$_{IO_2}$, which suggests that our system effectively delivers aerosolized PGI$_2$ to the lung parenchyma.

There was a significant change in $\dot{V}_E$, which was partially due to nebulizer flow. The change in $\dot{V}_E$ can also be explained by the fact that aerosolized PGI$_2$ was instituted as rescue therapy in critically ill patients in whom ventilator settings were not necessarily held constant. Seven of the 12 patients were on pressure-targeted ventilation, with which $\dot{V}_E$ may vary. As ventilation parameters were not controlled, adjustments in peak inspiratory pressure, PEEP, tidal volume, and respiratory frequency resulted in $\dot{V}_E$ changes in some patients. Although $\dot{V}_E$ increased significantly, P$_{aCO_2}$ was lower but not statistically different. A decrease in P$_{aCO_2}$ lowers alveolar carbon dioxide and increases alveolar oxygen, which had the potential for introducing a bias toward improvement in oxygenation. However, in 4 patients P$_{aCO_2}$ increased by 5–6 mm Hg or was unchanged, yet P$_{aO_2}$/F$_{IO_2}$ increased by an average of 34 mm Hg (see Table 2). In the other 7 patients, if the change in P$_{aO_2}$ was adjusted for the reduction in P$_{aCO_2}$, the change in P$_{aO_2}$/F$_{IO_2}$ remained significant (57 $\pm$ 10 mm Hg vs 68 $\pm$ 10 mm Hg, p = 0.016). Therefore, the oxygen-

ation improvement cannot be explained solely by the effects of altered $\dot{V}_E$ on P_{aCO_2}.

Alveolar deposition of aerosol particles is optimized when the particles are 1–2 μm in diameter.[20] The MiniHEART nebulizer reportedly delivers an aerosol particle size of 2.5 μm (mass median aerodynamic diameter), delivered through a 30-cm length of 22-mm inner-diameter tubing,[21] which is similar to our test results. The oxygenation improvements we observed are consistent with other reports,[6–11,22] suggesting that various nebulizers can deliver aerosolized PGI_2 to the lung parenchyma. The estimated inhaled dose (using albuterol sulfate as a surrogate indicator) of 14–21% is also consistent with characteristics of nebulized medication delivery during mechanical ventilation.[12,23,24]

We use the MiniHEART nebulizer because it is designed for continuous aerosolization at low flow rates. Nebulizer performance was evaluated using a 2 L/min flow from a 50-psi gas source. Under these conditions the aerosol output of the nebulizers tested was below the 8 mL/h needed to deliver the calculated aerosolized dose using our system, but was within the manufacturer's specified variance of ± 20%. The manufacturer-measured performance characteristics of the MiniHEART nebulizer specify a total liquid consumption of 7.9 ± 0.2 mL/h at a flow of 2 L/min with a pneumatic pressure of 39.2 ± 0.6 psi, and up to 10.3 ± 0.5 mL/h at a flow of 2.5 L/min with a pneumatic pressure of 52.8 ± 2.9 psi.[21] The effect of pneumatic pressure on nebulizer performance was not assessed or verified. However, our laboratory testing shows that the method used to set flow can affect the pneumatic pressure with the MiniHEART nebulizer. We tested 4 standard oxygen flow meters (15 L/min scale) with a single MiniHEART nebulizer and measured the pneumatic pressure when setting flow directly to 2 L/min versus opening the flow meter valve to flush and then lowering the flow to 2 L/min, and we found a 5.5-psi difference (34.4 ± 2.1 psi vs 39.9 ± 1.8 psi). It is not common clinical practice to measure pneumatic pressures during nebulization, so we recommend using the latter method to set flow. Additionally, in our experience we often find it necessary to run the nebulizer flow at higher than 2 L/min to maintain a constant nebulizer reservoir volume. Because individual nebulizer performance varies, close monitoring of the volume in the nebulizer reservoir is necessary to detect when the volume emitted from the nebulizer is higher or lower than the fill rate from the infusion pumps. Our practice is to use a flow meter with a low-flow graduated scale (maximum 3.5 L/min) so that small incremental changes (± 0.25 L/min) in flow can be made when necessary. Occasionally, when nebulizer overfill goes undetected (or nebulizer output is insufficient despite adjusting the pneumatic pressure and flow to maximum), we temporarily suspend nebulizer filling by turning off the infusion pumps until the problem is resolved.

The effects of evaporation during jet nebulization are often unrecognized and usually ignored, especially during continuous aerosolization. The total liquid consumption from any jet nebulizer is the sum of aerosol produced plus the evaporative loss of solvent. As water vapor does not carry any drug, the amount of drug emitted from a jet nebulizer does not equal the calculated amount based on the volume loss from the nebulizer. The initial aerosolized dose delivered is therefore always lower than the intended dose. As a result of solvent evaporation the concentration of drug in the nebulizer solution increases. The desired aerosolized dose is eventually achieved when the drug concentration increases to the level at which the aerosol emitted contains the intended amount of drug (Fig. 3).

When administering aerosolized PGI_2, we intentionally fill the nebulizer with a volume of 8 mL of the calculated dose concentration as a safety mechanism to maintain a 1-hour supply of drug solution in the nebulizer reservoir, in case of unforeseen problems with infusion pump function or drug acquisition. If a smaller reservoir volume is used, the rate of drug concentration is accelerated and the time required to achieve the desired dose is shortened. When using nebulizer reservoir volumes of 2, 4, 6, or 8 mL, the calculated times to achieve 98% of the desired dose of 50 ng/kg/min are 45, 85, 130, and 170 min, respectively (Fig. 4).

The MiniHEART nebulizer has a reservoir capacity of 30 mL and therefore can deliver 3 hours of aerosolized PGI_2 (without continuous infusion into the nebulizer) by filling the nebulizer with 24 mL of a 3.0×10^4 ng/mL solution (total drug mass = 7.2×10^5 ng), but this can result in a large variation in the delivered dose (Fig. 5). To avoid large variation in delivered dose we do not recommend filling the MiniHEART nebulizer with that large a volume of solution. Other large-reservoir jet nebulizers designed for continuous aerosolization would suffer similar evaporative concentration (and therefore escalating dose delivery) and are also not recommended.

When PGI_2 is reconstituted with the specified diluent the drug is stable for 8 hours at room temperature or 48 hours with refrigeration. PGI_2 is photosensitive, so the drug bottle, the intravenous tubing, and the nebulizer must be protected from direct sunlight to prevent decomposition. Any drug solution not administered within 8 hours must be discarded, so the PGI_2 bottle, intravenous tubing, and nebulizer are changed every 8 hours or whenever a new solution bottle is started.

After changing doses it is our practice to discard the contents of the nebulizer and fill the reservoir with 8 mL of the new dose concentration. As the initial delivered dose is approximately 20% less than the desired dose (Fig. 6), this practice results in unintended alterations of actual dose administered. This effect is more important when decreasing the set dose. For example, if a patient is at a set dose of 50 ng/kg/min for 4 hours and the set dose is reduced to 40 ng/kg/min, the initial dose at the new setting
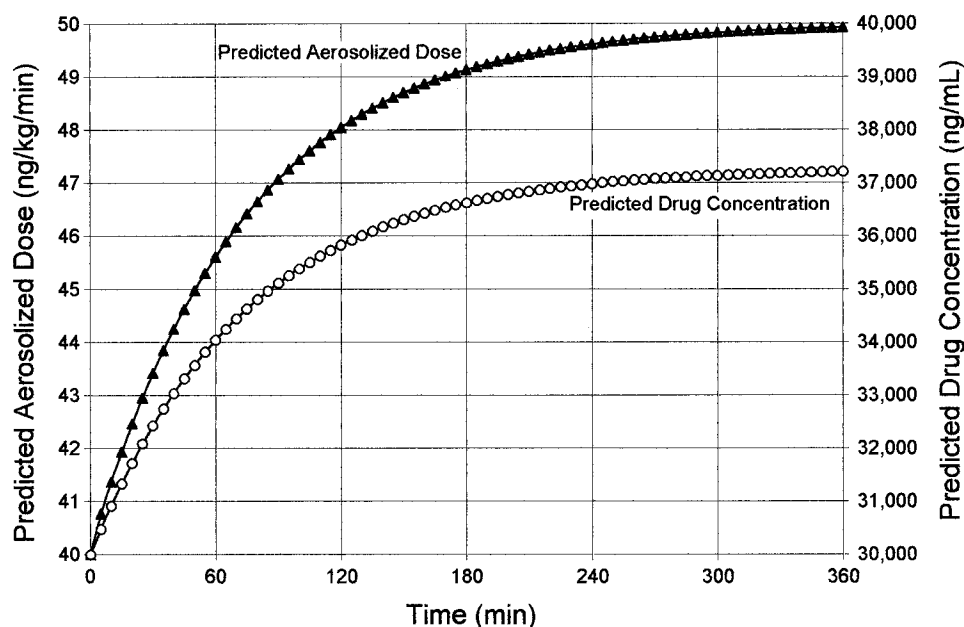
Fig. 3. Predicted change in aerosolized prostacyclin dose and nebulizer drug concentration due to evaporative volume loss from the MiniHEART nebulizer with a set dose of 50 ng/kg/min for an 80-kg patient and a nebulizer reservoir volume of 8 mL. See Appendix 1 for calculations.

is actually 32.6 ng/kg/min (see Fig. 6). We have not experienced any adverse effects while decreasing dose, but abrupt and complete discontinuation of aerosolized PGI_2 must be avoided, because acute deterioration in oxygenation can occur within 10 min.[11,22]

It is difficult to assess the effects of normal saline dilution on the PGI_2 solution pH and drug stability

and potency. At the lowest PGI_2 concentration we used (1 mL PGI_2 solution and 7 mL normal saline), the measured pH (10.13 ± 0.03) was below the pH at which the drug becomes unstable (10.2). Our retrospective patient data showed that patients responded at all doses administered (see Table 2). Linear regression shows a weak correlation between dose and the percent
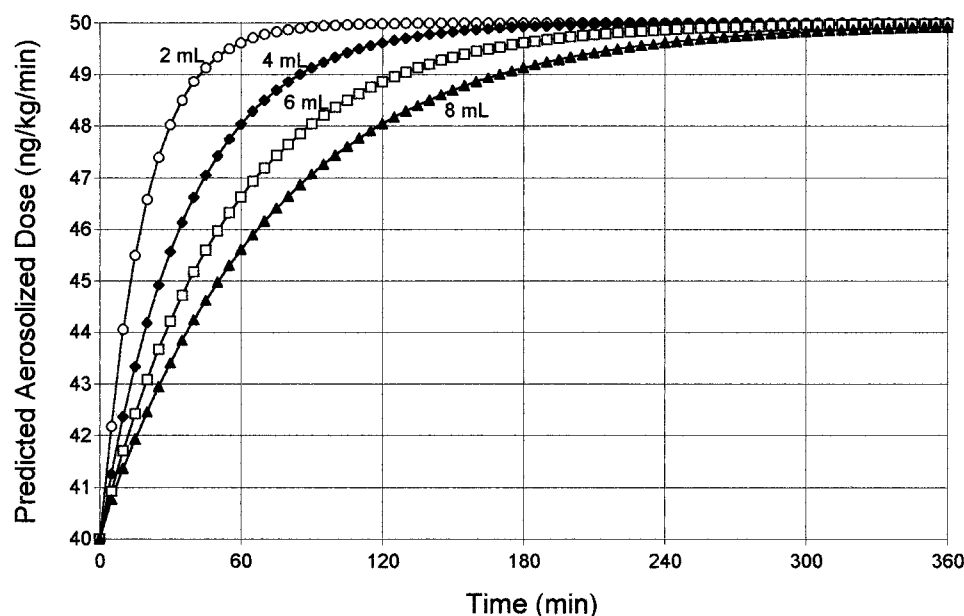

Fig. 4. Predicted effect of varying nebulizer reservoir volume on the rate of change in actual versus set prostacyclin dose of 50 ng/kg/min for an 80-kg patient, using 2, 4, 6, and 8 mL reservoir volumes. See Appendix 2 for calculations.
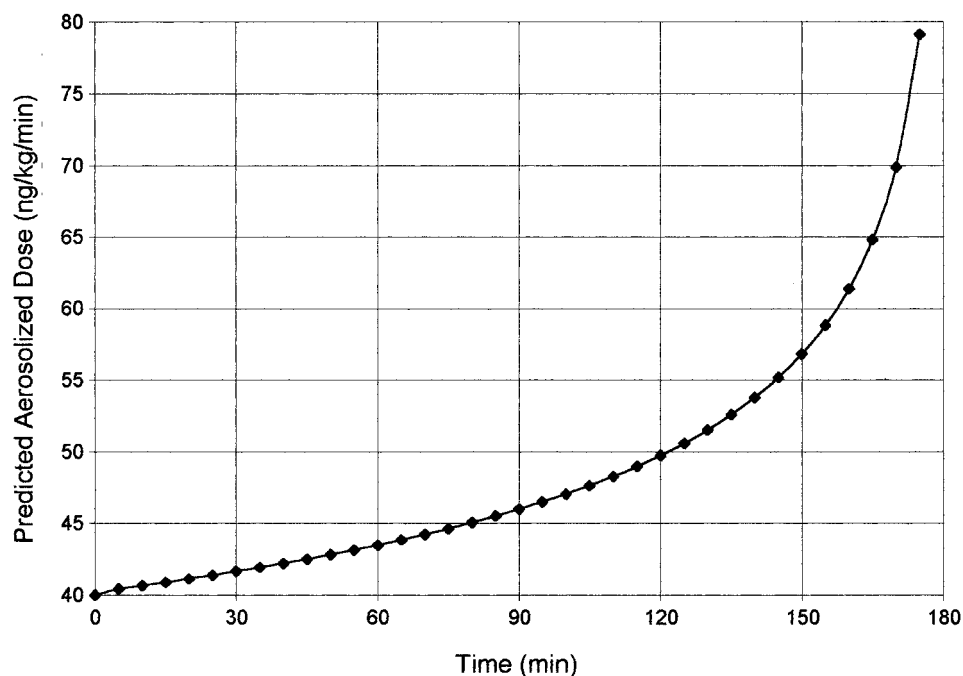
Fig. 5. Predicted change in aerosolized prostacyclin dose with the MiniHEART nebulizer (without continuous infusion) filled to a volume of 24 mL (total drug mass = 7.2×10^5 ng) to deliver a set dose of 50 ng/kg/min to an 80-kg patient. See Appendix 3 for calculations.

change in P_{aO_2} (see Fig. 2), suggesting that drug stability and potency was not affected by solution pH at the lower doses.

Several limitations of this study should be considered. The clinical evaluation of the delivery system was uncontrolled and based on retrospective data on a small number of patients. The report does not include data on the effects on pulmonary hypertension, pulmonary vascular resistance, or hemodynamic function. Additionally, the laboratory testing of the MiniHEART nebulizer
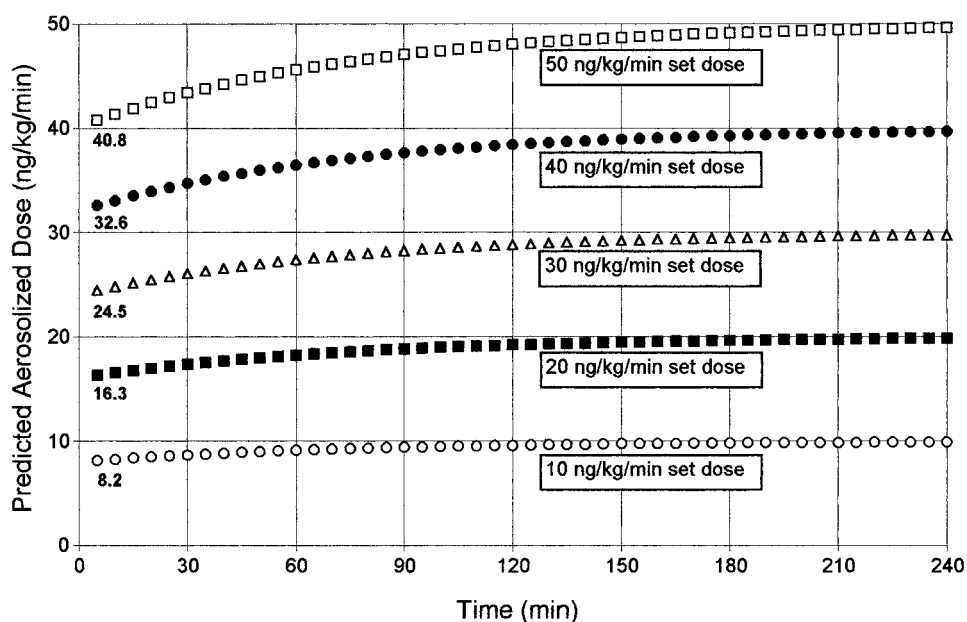

Fig. 6. Predicted change in aerosolized prostacyclin dose, showing that the initial dose is approximately 20% less than the set dose. This relationship is constant for all the dose-per-kg values listed in Table 1.

was performed under conditions that may not have optimized performance (setting flow to pneumatic pressure) or duplicated conditions in clinical practice (using flow rates > 2 L/min). Also, our use of albuterol sulfate as a surrogate indicator to estimate dose delivery may not reflect actual emitted and inhaled dose while aerosolizing different dilutions of PGI_2 solution. Furthermore, the predicted changes in aerosolized dose secondary to evaporative concentration were calculated based on the manufacturer's specifications of nebulizer performance and were not verified. Until a chemical assay method for PGI_2 becomes available, further assessment of dose delivery and nebulizer performance cannot be verified. Moreover, we used aerosolized PGI_2 as an alternative to inhaled NO for supportive care of extremely ill patients, based on the difference in cost, but neither therapy has been proven efficacious in altering outcome beyond short-term improvement in physiologic variables.

When administering aerosolized drugs to mechanically ventilated patients, the exact inhaled dose is often unknown because of the many variables that affect drug delivery to the lungs. The dose delivered via nebulization during mechanical ventilation is far less than the amount placed in the nebulizer, so the dose is considered the amount of drug placed in the nebulizer and aerosolized, not the actual amount delivered to the patient.

Establishing dose ranges to achieve a desired clinical effect is accomplished by analysis and comparison of dose response. This was not the intended purpose of this report. At our institution aerosolized PGI_2 is indicated for rescue treatment of profound hypoxemia in ARDS patients, defined as a P_{aO_2}/F_{IO_2} of < 100 mm Hg. Initial doses were determined at the ordering physician's discretion, based on previous reports of dose response. Aerosolized PGI_2 therapy was initiated at doses of 10–50 ng/kg/min. Patients had various responses at all doses administered, despite the predicted dose variance we calculated.

Conclusions

We have described a practical method for aerosolized PGI_2 delivery to mechanically ventilated ARDS patients. The dual-channel volumetric infusion pump system allows easy titration of drug dosage. The simple design of the nebulizer system allowed our staff to quickly begin aerosolized PGI_2 therapy, and with only a modest amount of training. Evidence for the effectiveness of our system in delivering PGI_2 to the alveoli was the significant improvement in oxygenation that occurred shortly after aerosolized PGI_2 therapy commenced.

Further investigation is warranted to develop technologies for continuous aerosolization that eliminate dose variance from evaporative concentration, reduce interference with ventilator function, increase inhaled dose delivery, and improve targeted deposition within the lung. Additional study focusing on optimizing dosing strategies and long-term outcome is essential to validate the efficacy of aerosolized PGI_2 therapy.

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APPENDIX 1

Calculations for Predicting the Effect of Evaporation on Drug Concentration and Actual Dose Delivered (as Illustrated in Figure 3)

When delivering a 50 ng/kg/min dose to an 80-kg patient (4,000 ng/min) with a nebulizer reservoir volume of 8 mL (total mass of drug in nebulizer = 240,000 ng), using evaporation rate for the MiniHEART (13 μL per liter of gas flowing through the nebulizer),[21] the predicted initial aerosolized dose is approximately 20% less than the desired dose. Assuming a volume loss of 8 mL/h at a nebulizer flow of 2 L/min, the volume loss per minute equals:

$$8 \text{ mL/h} \div 60 = 0.13333 \text{ mL/min} \qquad [1]$$

The actual aerosol output equals the volume loss per minute minus the evaporation rate or:

$$0.13333 \text{ mL/min} - (0.013 \text{ mL/L} \times 2 \text{ L/min}) = 0.10733 \text{ mL/min} \qquad [2]$$

The actual aerosolized mass of drug during the first minute equals the actual aerosol output times the concentration of drug in the nebulizer (30,000 ng/mL):

$$30,000 \text{ ng/mL} \times 0.10733 \text{ mL/min} = 3,220 \text{ ng/min} \qquad [3]$$

The actual dose per minute is calculated by the mass of drug delivered divided by the predicted body weight:

$$3,220 \text{ ng/min} \div 80 \text{ kg} = 40.25 \text{ ng/kg/min} \qquad [4]$$

During the second minute, the concentration of drug in the nebulizer is now higher because the mass of drug emitted is less than the mass of drug infused (3,220 ng vs 4,000 ng):

$$(4,000 \text{ ng} - 3,220 \text{ ng}) + 240,000 \text{ ng} = 240,780 \text{ ng} \qquad [5]$$

Assuming the volume in the nebulizer remains constant at 8 mL, the mass of drug and therefore the concentration of drug in the nebulizer increases by the following:

$$240,780 \text{ ng} \div 8 \text{ mL} = 30,098 \text{ ng/mL} \qquad [6]$$

By using the new concentration (30,098 ng/mL) in equation [3], the new dose (40.38 ng/kg/min) can be calculated using equation [4] for the third minute of nebulization. This process of increasing drug concentration and dose progresses over time until the emitted drug mass per minute approaches the infused drug mass in equation [5]. At the 360-min point in Figure 3 the predicted nebulizer drug mass, drug concentration, aerosolized mass, and actual aerosolized dose are 297,689 ng, 37,211 ng/mL, 3,994 ng, and 49.92 ng/kg/min, respectively.

APPENDIX 2

Calculations for Predicting the Effects of Varying Nebulizer Reservoir Volume on the Rate of Change in Actual Versus Set Prostacyclin Dose (as Illustrated in Figure 4)

By using a smaller reservoir volume, the rate of drug concentration is accelerated. Using equations [5] and [6] from Appendix 1 and inserting the initial drug mass and the reservoir volume, the change in concentration after the first minute can be estimated by the following:

2 mL reservoir volume:

$$(4,000 \text{ ng} - 3,220 \text{ ng}) + 60,000 \text{ ng} = 60,780 \text{ ng} \qquad [7]$$

$$60,780 \text{ ng} \div 2 \text{ mL} = 30,390 \text{ ng/mL} \qquad [8]$$

4 mL reservoir volume:

$$(4,000 \text{ ng} - 3,220 \text{ ng}) + 120,000 \text{ ng} = 120,780 \text{ ng} \qquad [9]$$

$$120,780 \text{ ng} \div 4 \text{ mL} = 30,195 \text{ ng/mL} \qquad [10]$$

6 mL reservoir volume:

$$(4,000 \text{ ng} - 3,220 \text{ ng}) + 180,000 \text{ ng} = 180,780 \text{ ng} \qquad [11]$$

$$180,780 \text{ ng} \div 6 \text{ mL} = 30,130 \text{ ng/mL} \qquad [12]$$

8 mL reservoir volume:

$$(4,000 \text{ ng} - 3,220 \text{ ng}) + 240,000 \text{ ng} = 240,780 \text{ ng} \qquad [13]$$

$$240,780 \text{ ng} \div 8 \text{ mL} = 30,098 \text{ ng/mL} \qquad [14]$$

APPENDIX 3

Calculations for Predicting the Effects of Using the MiniHEART Nebulizer Filled to a Volume of 24 mL (total drug mass = 720,000 ng) (Without Continuous Infusion) to Deliver a Set Dose of 50 ng/kg/min to an 80-kg Patient (as illustrated in Figure 5).

After 2 hours the predicted aerosolized dose equals the desired dose, but at the end of the last hour of nebulization the predicted dose is approximately doubled. By using a modified equation [6], the predicted drug concentration after 174 min of nebulization is calculated as the drug mass remaining divided by the volume remaining in the nebulizer.

$$47,216 \text{ ng} \div [24 \text{ mL} - (174 \times 0.13333 \text{ mL})] = 58,977 \text{ ng/mL} \qquad [15]$$

The predicted aerosolized drug mass and dose for the next minute of nebulization are calculated using equations [3] and [4] from Appendix 1:

$$58,977 \text{ ng/mL} \times 0.10733 \text{ mL/min} = 6,330 \text{ ng/min} \qquad [16]$$

$$6,330 \text{ ng/min} \div 80 \text{ kg} = 79.13 \text{ ng/kg/min} \qquad [17]$$