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Effect of Parainfluenza Infection on Gas Exchange and FRC Response to Anesthesia in Sheep

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We examined the interaction of viral pneumonitis with the respiratory effects of halothane/N_2O anesthesia in six tracheostomized sheep. Ventilation–perfusion ($\dot{V}_A/\dot{Q}$) distribution, pulmonary artery pressure (PAP), metabolic rate ($\dot{V}_{O_2}$), and functional residual capacity (FRC) measurements were compared in awake and anesthetized animals before and 1 week after inoculation by tracheal instillation of ovine parainfluenza type-3 (PI-3) virus. Awake shunt ($\dot{V}_A/\dot{Q} < 0.005$) was 0.6 ± 0.4% (± standard deviation [SD]) before, *versus* 3.9 ± 2.0% after PI-3 infection ($P < 0.05$). Awake arterial O_2 tension (Pa_{O_2}) was 139.9 ± 14.0 mmHg before and 114.5 ± 8.7 mmHg after infection ($P < 0.05$). Mean PAP increased from 6.0 ± 1.9 mmHg before to 11.5 ± 1.6 mmHg after infection ($P < 0.05$). Anesthesia shunt increased to 5.7 ± 2.3% before and 11.2 ± 3.4% after PI-3 ($P < 0.05$ for the change from awake, and $P < 0.05$ for a PI-3 anesthesia shunt difference). PAP was not significantly different from awake, either before or after infection. Anesthesia also produced an average 14.8 ± 3.8% FRC reduction before and 17.4 ± 6.4% reduction after infection ($P < 0.05$ for FRC reduction with anesthesia, not significantly different for PI-3). Three of the six sheep developed shunt at higher FRCs after infection, both awake and during anesthesia; however, the average slope of the shunt/FRC response to anesthesia was unchanged, suggesting that this was not a neurogenic form of auto-PEEP. We therefore conclude that viral infection significantly enhanced the pulmonary effects of anesthesia. (Key words: Anesthetics, volatile: halothane. Anesthetics, gases: nitrous oxide. Complications, pulmonary: viral respiratory infection; anesthesia. Lung: viral respiratory infection, parainfluenza virus; atelectasis; functional residual capacity; shunting; oxygen consumption. Pulmonary circulation: pulmonary artery pressure.)

GENERAL ANESTHESIA is associated with a highly variable degree of impaired pulmonary gas exchange. Smoking history, obesity, and preexisting chronic obstructive lung disease are well-known potentiating variables for the increased ventilation–perfusion inequality and intrapulmonary shunting.[1,2] The impact of acute lung disease, as might occur with viral respiratory infection, is not so clear. McGill and co-workers reported chest radiographic evidence of atelectasis in pediatric patients with preoperative cough or "cold" symptoms.[3] Tait and Knight have suggested, on the other hand, that there is no increase in pulmonary complications due to preceding viral respiratory illness.[4] Knight's group speculated that inhaled anesthetics such as halothane may actually impair viral replication and thereby reduce the severity of infection.[5] However, pediatric patients do show a significantly higher incidence of desaturation during recovery from general anesthesia.[6]

We speculated that there may be a number of important variables leading to the apparent disparity in these conclusions. First, assessment of the clinical signs and symptoms of viral infection requires subjective interpretation. Second, the pulmonary effects of anesthesia during a viral infection may depend on which viral agent is involved and on the clinical stage of onset, progression or recovery of the disease. Critical pathophysiologic variables may include the volume and consistency of airway secretions, airway reactivity, alveolar filling with edema fluid or cellular debris, and increased O_2 consumption in the lung.[7] Finally, there may be anesthetic agent or administration variables, such as intravenous *versus* volatile agents and mask breathing *versus* tracheal intubation, that could affect the pulmonary response to anesthesia during viral respiratory infection.[8,9]

It is therefore noteworthy that we observed the highest awake and anesthetized shunt in an otherwise healthy young smoker who had myalgia and a mild fever several days prior to surgery.[2] This led us to examine the possible interactions of viral respiratory infection and general anesthesia on pulmonary gas exchange, using a known viral agent and a well-defined sheep model of viral pneumonitis.[10]

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Materials and Methods

Six healthy sheep (24.5–49.5 kg) with negative serum antibody titers to ovine parainfluenza type-3 (PI-3) virus were obtained. Both the sheep and the PI-3 virus cultures were supplied by Howard Lehmkuhl, Ph.D. of the National Animal Disease Laboratory, Ames, Iowa.

Each subject had a chronic tracheostomy[11] and carotid artery exteriorization[12] at least 2 weeks prior to any lung function studies.

Study Protocol

The distribution of ventilation–perfusion ratios ($\dot{V}_A/\dot{Q}$), blood gases, and functional residual capacity (FRC) were measured in awake and anesthetized sheep after a 48-h fast, before and after viral infection with ovine PI-3. Carotid artery, flow directed pulmonary artery, and peripheral venous catheters were placed percutaneously with the aid of subcutaneous bupivacaine 0.5%. An 8.5-mm-ID cuffed endotracheal tube was placed in the tracheal stoma with the aid of 0.5% bupivacaine skin infiltration and 4% lidocaine topical tracheal spray. A mixture of six inert gases (sulfur hexafluoride, ethane, cyclopropane, enflurane, ether, and acetone) dissolved in trace concentration in lactated Ringer's solution was infused intravenously at 2.4 ml/min.

Awake control studies were obtained during controlled mechanical ventilation with humidified 30% O_2/balance N_2, with the sheep lying in the left lateral decubitus position. Anesthesia was induced and maintained with 1.25% end-tidal halothane, 30% inspired O_2/balance N_2O. All measurements were obtained after a minimum of 30 min of stable breathing, using tidal volumes of 10 ml/kg and a frequency sufficient to prevent spontaneous breaths in the awake study, *via* an Ohio 200 Anesthesia Ventilator bellows driven by a Bird Mark 14 ventilator.

After recovery from the control study, a 10-ml suspension of ovine PI-3 (with an infectivity titer of $10^{8.5}$ 50% tissue culture infection doses per milliliter, in Hank's buffer solution) was sprayed into the trachea. Virus was assayed by terminal dilution infectivity in Madin Darby Canine Kidney (MDCK) cell tube cultures using hemadsorption of guinea pig erythrocytes. Arterial O_2 tension (Pa_{O_2}) and rectal temperature were measured daily in four sheep. In addition, blood and tracheal secretions were obtained from all six sheep to document the period of virus shedding in airway secretions and to measure serum antibodies to PI-3. Antibody was measured by immunofiltration immunoassay using infected and uninfected MDCK cells as antigen.[13] Repeat awake and anesthetized FRC and gas exchange measurements were obtained (as above) on day 6 (five subjects) or day 7 (one subject) postinoculation.

Measurements

Multiple tracer inert gas analysis was performed with Hewlett-Packard model 5710 FID and 5711 ECD gas chromatographs as described previously.[14] Expired gas volume was measured with a Med Science model 570 wedge spirometer and minute volume ($\dot{V}_E$) determined on-line with a Digital Minc-11 laboratory computer. Inspired, end-tidal, and mixed expired respiratory gas concentrations were measured with a Perkin Elmer model 1100A mass spectrometer. Cardiac output ($\dot{Q}_T$) was determined by the Fick principle from the tracer inert gas elimination data. Computation of 50 compartment distributions of $\dot{V}_A/\dot{Q}$ and indices of $\dot{V}_A/\dot{Q}$ inequality was performed as described by Wagner.[15] Pa_{O_2} was predicted for each distribution of $\dot{V}_A/\dot{Q}$, given the measured mixed venous O_2 tension ($P\bar{v}_{O_2}$), mixed venous CO_2 tension ($P\bar{v}_{CO_2}$), *p*H, hemoglobin, and a value of P_{O_2} at 50% saturation (P_{50}) (normalized for *p*H and body temperature) determined with a Radiometer DCA-1 analyzer from preinfection awake control blood samples. Prediction of Pa_{O_2} for distributions obtained during anesthesia utilized a mixed venous halothane partial pressure determined by gas chromatography and an assumed mixed venous N_2O partial pressure equal to the inspired value. FRC was determined by closed circuit helium dilution using the mass spectrometer to measure He (for 5 seconds) at 3, 4, and 5 min of mixing (with correction for sample loss), and a Collins 9-l spirometer modified with a sealed plastic insert to minimize spirometer dead space.

O_2 consumption rates were calculated in two ways, similar to the methods described by Light[7]:

1) Whole-body O_2 consumption rate ($\dot{V}_{O_{2exp}}$) was estimated from inspired and mixed expired gases using the equation

$$\dot{V}_{O_{2exp}} = (FI_{O_2} \cdot FE_x/FI_x - FE_{O_2})\dot{V}E + (FI_{O_2}/FI_x)\dot{V}_x$$

where $\dot{V}_E$ is measured expired $\dot{V}_E$ (STPD), FI_{O_2} and FE_{O_2} are inspired and mixed expired dry gas O_2 fractions, and FI_x and FE_x are inspired and mixed expired dry gas fractions of N_2 (awake) or N_2O (anesthesia), and $\dot{V}_x$ is rate of uptake of N_2 (awake, = 0) or N_2O (anesthesia).

2) Fick O_2 consumption ($\dot{V}_{O_{2Fick}}$) was calculated from arterial and mixed venous O_2 contents (Ca_{O_2} and $C\dot{v}_{O_2}$, respectively) and $\dot{Q}_T$, as follows: $\dot{V}_{O_{2Fick}} = Ca_{O_2} - C\dot{v}_{O_2} \cdot \dot{Q}_T$. O_2 contents were calculated from measured P_{O_2}, CO_2 tension (P_{CO_2}), *p*H, hemoglobin, hematocrit, and P_{50}, using Kelman subroutines as described by West.[16]

Statistical Analysis

Mean values of shunt, indices of $\dot{V}_A/\dot{Q}$ inequality, FRC, blood gases, $\dot{Q}_T$, and $\dot{V}_E$ were determined from the duplicate awake measurements, and from duplicate measurements after 60 and 120 min of anesthesia. Statistical significance of differences in awake *versus* anesthesia findings, differences between pre- and postinfection responses, and for differences between 60 *versus* 120 min of anesthesia was determined with one-way analysis of variance. Repeated-measures ANOVA was used for comparison of 1- and 2-h shunt differences, and the difference between $\dot{V}_{O_{2exp}}$ and $\dot{V}_{O_{2Fick}}$ ($\dot{V}_{O_{2lung}}$) before and after infection. Linear regression and analysis of covariance were used to compare predicted *versus* measured Pa_{O_2} values, before

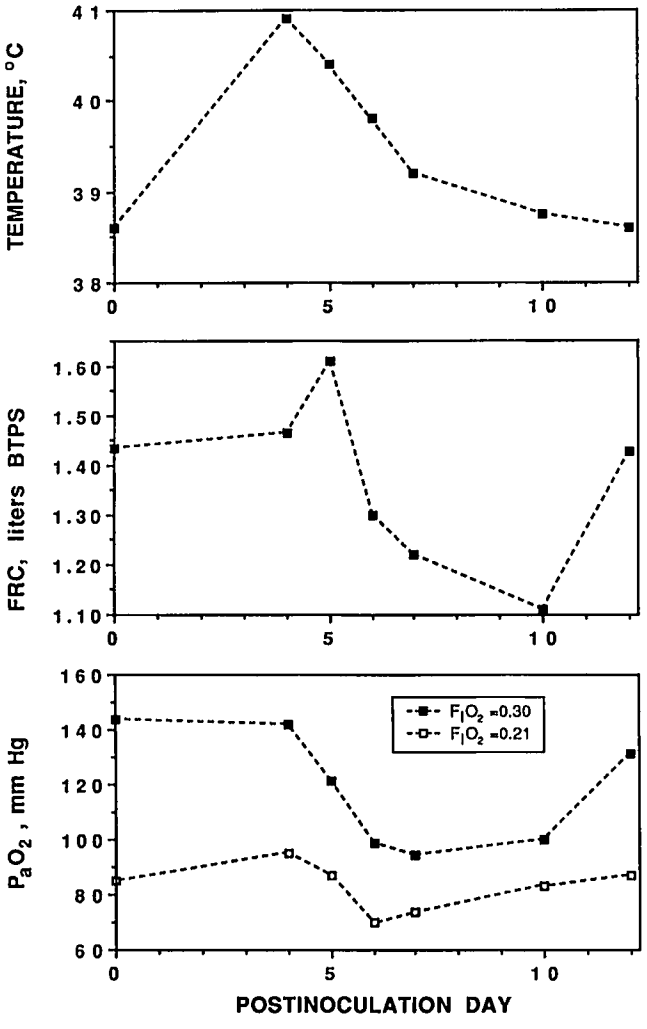

FIG. 1. An example of the clinical profile in one sheep, from day of inoculation (day 0) to postinoculation day 12. *Top:* rectal body temperature; *middle:* shows awake FRC measured *via* tracheostomy; *bottom:* arterial P_{O_2} during room air breathing (FI_{O_2} = 0.21) and at 30% oxygen/balance N_2 (FI_{O_2} = 0.30).

and after infection.[17] Computation of $\dot{V}_A/\dot{Q}$ distributions and analysis of covariance was performed on a Digital Minc-11 computer. Analysis of variance and regression analysis were performed on a Macintosh SE computer using Statview SE software.

Results

Clinical and Virology Findings

Fever developed 3 days after PI-3 inoculation in all six sheep, reached a high of 40.0–40.9 °C, decreased on day 5, and returned to a normal temperature of 38.5–39.0 °C by day 7. Fever was accompanied by tachypnea at approximately 30 breaths per min. Virus could be cultured from tracheal secretions beginning on day 3 or 4, and was cleared by day 7. Serum antibody titers increased from <25 in preinfection specimens to >3,200 following inoculation (except for one subject with a preinoculation titer of 400 and convalescent titer of >25,600). An example of the clinical profile for body temperature, FRC, and Pa_{O_2} is shown in figure 1.

Gas Exchange

Awake shunt ($\dot{V}_A/\dot{Q} < 0.005$) increased an average 3.3% of pulmonary blood flow after infection ($P < 0.05$, see table 1 and fig. 2), while $\dot{V}_A/\dot{Q}$ inequality ($0.005 < \dot{V}_A/\dot{Q} < 0.1$) showed no significant change. Dead space ventilation ($\dot{V}_A/\dot{Q} > 100.0$) decreased an average 5.7% of $\dot{V}_E$ after infection ($P < 0.05$). The awake Pa_{O_2} (at FI_{O_2} = 0.30) decreased from 141 ± 12 mmHg before to 115 ± 9 mmHg after infection ($P < 0.05$).

Anesthesia increased shunt by 5.1 ± 2.0% of pulmonary blood flow before infection to 5.7 ± 2.3% ($P < 0.05$, see table 1 and fig. 2). After infection, anesthesia produced an average 7.3 ± 3.3% shunt increase, to 11.2 ± 3.4%,

TABLE 1. Ventilation–Perfusion Distribution

	Shunt (% $\dot{Q}_T$)	Low $\dot{V}_A/\dot{Q}$ (% $\dot{Q}_T$)	Blood Flow Distribution		High $\dot{V}_A/\dot{Q}$ (% $\dot{V}_E$)	Dead Space (% $\dot{V}_E$)
			Mean $\dot{V}_A/\dot{Q}$	Log SD		
Preinfection						
Awake	0.6 ± 0.4	0.0 ± 0.0	0.58 ± 0.04	0.70 ± 0.08	0.1 ± 0.3	39.8 ± 2.9
Anesthesia	5.7 ± 2.3*	4.1 ± 1.4	0.43 ± 0.10*	0.88 ± 0.15	11.2 ± 7.8*	39.9 ± 4.1
Postinfection						
Awake	3.9 ± 2.0†	2.1 ± 3.2	0.61 ± 0.09	0.84 ± 0.16	0.6 ± 1.5	34.1 ± 4.4†
Anesthesia	11.2 ± 3.4*‡	1.6 ± 1.8	0.45 ± 0.05*	0.85 ± 0.17	17.0 ± 6.2*	35.9 ± 3.6

Mean ± SD intrapulmonary shunt ($\dot{V}_A/\dot{Q} < 0.005$), blood flow to areas with low $\dot{V}_A/\dot{Q}$ ($0.005 < \dot{V}_A/\dot{Q} < 0.1$), mean $\dot{V}_A/\dot{Q}$, log SD of $\dot{V}_A/\dot{Q}$ for blood flow distribution, ventilation to areas with high $\dot{V}_A/\dot{Q}$ ($10 < \dot{V}_A/\dot{Q} < 100$), and dead space ventilation ($\dot{V}_A/\dot{Q} > 100.0$) are presented for awake pre- and postinfection as well as anesthesia pre- and postinfection studies.

* Significant difference between awake *versus* anesthesia.

† Significant difference for awake pre- *versus* postinfection.

‡ Significant difference for anesthesia pre- *versus* postinfection ($P < 0.05$).

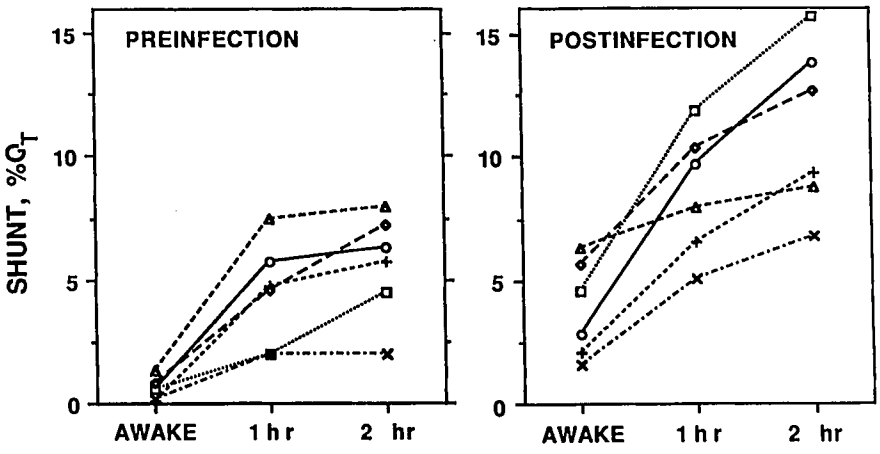

FIG. 2. Awake and anesthesia shunt (1 and 2 h after induction) is shown for each sheep. Mean + SD shunt values increased from 0.6 ± 0.4% awake to 4.4 ± 2.1 and 5.7 ± 2.3% respectively, during anesthesia before infection ($P < 0.05$, *left*); and from 3.9 ± 2.0% awake to 8.6 ± 2.5 and 11.2 ± 3.4% during anesthesia after infection ($P < 0.05$, *right*). The anesthesia shunt was significantly higher after infection ($P < 0.05$), and the increase 1–2 hours after induction also was significant ($P < 0.05$).

which was significantly different from anesthesia shunt before infection ($P < 0.05$). Anesthesia decreased the mean $\dot{V}_A/\dot{Q}$ of blood flow distribution by an average of 0.16 pre- and 0.17 postinfection (not significantly different; table 1). This change was due to increased ventilation to areas with high $\dot{V}_A/\dot{Q}$ and did not produce a significant increase in pulmonary blood flow to areas with low $\dot{V}_A/\dot{Q}$.

Pa_{O_2} showed only an average 10.7-mmHg reduction with anesthesia before infection and no change with anesthesia after infection (table 2). This lack of change in Pa_{O_2} was in part due to an average 10.2 ± 3.5-mmHg mixed venous P_{O_2} increase before and an 11.5 ± 1.8-mmHg increase after infection ($P < 0.01$ for change from awake, not significantly different for infection) and in part due to a second gas effect of continuing N_2O uptake on alveolar P_{O_2}. The regressions in figure 3 show significant correlation between measured and calculated Pa_{O_2} ($r = 0.86$, $P = 0.03$ for awake; $r = 0.93$, $P = 0.01$ for anesthesia). However, the difference between predicted *versus* measured awake Pa_{O_2} increased from 7.7 ± 7.0 mmHg before to 18.8 ± 7.4 mmHg after infection ($P = 0.03$), whereas pre- and postinfection anesthesia regressions showed no significant change. Pa_{CO_2} increased during anesthesia for both pre- and postinfection, due to the increased ventilation to areas with high $\dot{V}_A/\dot{Q}$ (tables 1 and 2).

Oxygen Consumption

Five of six awake, and all six anesthesia studies, showed increased whole-body $\dot{V}_{O_2exp}$ after infection, while no consistent change was seen in $\dot{V}_{O_2Fick}$, as shown in table 3). Thus, postinfection lung O_2 uptake ($\dot{V}_{O_2exp} - \dot{V}_{O_2Fick}$) showed a significant increase with infection ($P = 0.04$). Anesthesia reduced $\dot{V}_{O_2exp}$ and $\dot{V}_{O_2Fick}$ by more than 30% both before and after infection.

Pulmonary Circulation

Awake mean pulmonary artery pressure (PAP) was an average of 5.5 mmHg higher after infection and anesthesia PAP an average of 4.0 mmHg higher after infection ($P < 0.05$ for both; see table 2 for mean ± SD values), with no difference between awake and anesthesia PAP either before or after infection. There was no significant change in $\dot{Q}_T$, either with anesthesia or due to infection (table 2).

TABLE 2. Standard Physiologic Parameters

	PAP (mmHg)	$\dot{Q}_T$ ($l \cdot min^{-1}$)	FRC ($ml \cdot kg^{-1}$)	$\dot{V}_E$ ($l \cdot min^{-1}$)	Pa_{O_2} (mmHg)	$(P\bar{v}_{O_2})$ (mmHg)	Pa_{CO_2} (mmHg)
Preinfection							
Awake	6.0 ± 1.9	4.29 ± 0.86	32.1 ± 4.9	5.44 ± 1.11	139.9 ± 14.0	50.6 ± 1.7	36.0 ± 3.5
Anesthesia	7.1 ± 1.7	4.63 ± 1.69	27.2 ± 3.3*	5.01 ± 0.64	129.2 ± 19.1	60.8 ± 3.6*	41.3 ± 2.4*
Postinfection							
Awake	11.5 ± 2.4†	4.84 ± 0.86	31.4 ± 3.5	5.84 ± 1.51	114.5 ± 8.7†	52.6 ± 4.7	33.6 ± 4.5
Anesthesia	11.2 ± 1.1‡	4.57 ± 1.17	26.0 ± 3.6*	5.20 ± 0.50	115.0 ± 5.1	64.1 ± 5.1*	41.7 ± 4.0*

Mean ± SD pulmonary artery pressure (PAP), cardiac output ($\dot{Q}_T$), functional residual capacity (FRC, BTPS), arterial O_2 tension (Pa_{O_2}) (at $FI_{O_2} = 0.30$) and CO_2 tension (Pa_{CO_2}), mixed venous O_2 tension ($P\bar{v}_{O_2}$), and minute volume ($\dot{V}_E$) are presented for awake pre- and postinfection as well as anesthesia pre- and postinfection studies.

* Significant difference between awake *versus* anesthesia.
† Significant difference for awake pre- *versus* postinfection.
‡ Significant difference for anesthesia pre- *versus* postinfection ($P < 0.05$).

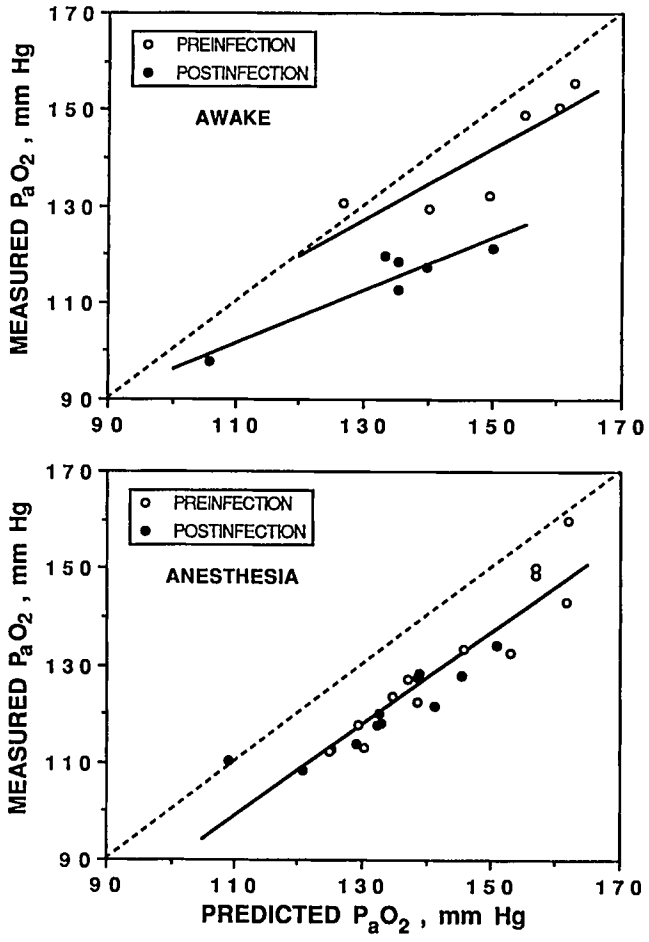

FIG. 3. Measured arterial P_{O_2} was compared with predicted Pa_{O_2} from distributions of $\dot{V}_A/\dot{Q}$ for each sheep during awake and anesthesia conditions, before and after PI-3 infection. Linear regression showed:

1) measured Pa_{O_2} = 0.742 · predicted Pa_{O_2} + 30.759 (r^2 = 0.74) for awake preinfection;

2) measured Pa_{O_2} = 0.548 · predicted Pa_{O_2} + 41.518 (r^2 = 0.86) for awake postinfection; and

3) measured Pa_{O_2} = 0.94 · predicted Pa_{O_2} − 4.341 (r^2 = 0.86) for anesthesia.

Analysis of covariance showed a significant difference in elevation of the regression for awake before *versus* after PI-3 ($P < 0.05$, but difference in slope not significant), and no difference between anesthesia before *versus* after PI-3.[17]

Lung Volume

Anesthesia produced a 14.8 ± 3.8% FRC reduction before and 17.4 ± 6.4% after infection ($P = 0.03$ for the FRC change due to anesthesia, not significantly different for PI-3; table 2). Infection did not alter either awake or anesthesia FRC despite a significant increase in shunt. The individual shunt/FRC responses before and after infection are shown in figure 4. The average slope of the individual response curves was similar before and after infection. Three sheep showed accentuation of shunt and FRC along the preinfection curves, whereas the other three postinfection curves were displaced to higher FRCs but without change in the slope from preinfection. Displacement of the shunt/FRC response curves to higher FRC averaged 3.5 ± 4.4 (range −0.5 to 7.2) ml · kg^{-1}. The fact that the displaced response curve slopes remained the same as with preinfection suggests that the increase in FRC was not influenced by anesthesia; *i.e.*, it was not due to a conscious or subconscious (neurogenic) form of "auto-PEEP".

TABLE 3. Oxygen Consumption Rate

	$\dot{V}_{O_2exp}$ (ml · min^{-1} · kg^{-1})	$\dot{V}_{O_2Fick}$ (ml · min^{-1} · kg^{-1})	$\dot{V}_{O_2lung}$ (ml · min^{-1} · kg^{-1})
Preinfection			
Awake	4.18 ± 0.46	4.01 ± 0.48	0.17 ± 0.17
Anesthesia	2.79 ± 0.40*	2.49 ± 0.30*	0.30 ± 0.21
Postinfection			
Awake	4.47 ± 0.45	3.97 ± 1.01	0.50 ± 0.63†
Anesthesia	3.13 ± 0.44*	2.34 ± 0.32*	0.79 ± 0.34‡

Mean ± SD O_2 consumption rates, normalized to body weight, are presented for values obtained from inspired and mixed expired O_2 and CO_2 (V_{O_2exp}), from arteriovenous O_2 content difference · cardiac output (V_{O_2Fick}), and for the difference (assumed to be V_{O_2lung}).

* Significantly different from awake ($P < 0.05$).

†‡ Significantly different from preinfection ($P = 0.04$).

Note N_2O uptake (V_{N_2O} ml · min^{-1} · kg^{-1}) increases anesthesia V_{O_2exp} and V_{O_2lung} by 0.445 · V_{N_2O}.

Discussion

PI-3 viral infection produced a significantly higher intrapulmonary shunt, lower Pa_{O_2} and higher PAP in both awake and anesthetized sheep. Pa_{O_2} was lower than expected for the amount of shunting, due to increased lung O_2 uptake after viral infection. Three of six sheep developed shunt at higher FRCs after infection, both awake

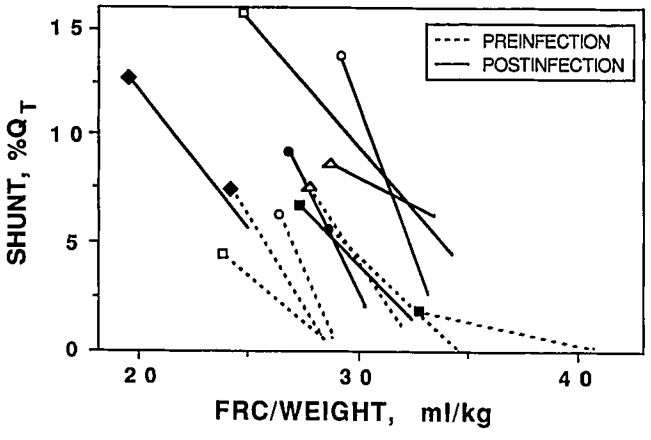

FIG. 4. The change in intrapulmonary shunt and FRC from awake (beginning of each line) to anesthetized (symbols) is compared for each sheep before (dashed line) and after (solid line) viral infection. Note that three sheep show progression of shunt and FRC changes along the same shunt/FRC lines seen before infection, whereas three sheep developed shunt at higher FRCs both awake and during anesthesia.

and during anesthesia; but the slope of the shunt/FRC response to anesthesia was unchanged, suggesting that this was not a neurogenic form of auto-PEEP. Finally, mean PAP was significantly increased by ovine PI-3 viral infection.

The pathology of ovine PI-3 infection involves viral inclusions and buds in both ciliated and nonciliated bronchial epithelial cells and type I and type II alveolar cells.[8] Specific immunofluorescence shows the most intense viral antigen staining on postinfection day 3, with more diffuse fluorescence on day 5, and minimal staining on day 7. The bronchiolitis involves the terminal airways and consists of necrosis and sloughing of epithelial cells followed by hyperplasia of the epithelium. There is also an interstitial lesion comprised of extensive infiltration of alveolar septa and alveoli with macrophages and necrosis of alveolar epithelium. This pattern of progression of the pulmonary pathology was entirely consistent with the clinical profile of fever, Pa_{O_2}, and FRC shown in the example in figure 1.

The ovine PI-3 viral respiratory infection model was chosen in part because of the observation that viral "upper respiratory tract infection" frequently alters lower respiratory function, including abnormal frequency dependence of dynamic compliance,[18] diminished steady-state diffusing capacity,[19] abnormal closing volumes, and abnormal density-dependent expiratory flow rates.[20] We therefore anticipated that airway closure would be enhanced during anesthesia in subjects with viral respiratory infection. Our shunt and FRC values did not provide evidence of synergism between the effects of anesthesia and viral infection. However, the enhanced relationship between shunt and FRC after viral infection in sheep (fig. 4) suggests that acute lung disease may be an important factor in the gas exchange effects of FRC reduction due to anesthesia, much like the effects of smoking in young surgical patients.[2]

The ovine PI-3 viral infection model differs somewhat from parainfluenza type-2 (PI-2) viral bronchiolitis seen in pediatric epidemics as well as from the canine "kennel cough" model of PI-2 infection.[21] Both of these PI-2 models show primarily a bronchiolitis pattern, with very little evidence of pneumonitis. However, the canine model shows FRC reduction during the acute disease, whereas children with acute bronchiolitis have hyperinflation.[22] This may be in part a reflection of differences in pathology induced by PI-2 *versus* PI-3 viral infection or a difference in airway reactivity between species. Furthermore, the ovine PI-3 model did show evidence of hyperinflation in some of the sheep (fig. 4). These intersubject differences could have been partly a function of timing; *i.e.*, hyperinflation occurred shortly after the onset of clinical symptoms and was followed by FRC reduction in the subsequent course of illness (fig. 1). Thus, some of the variability of FRC values obtained in our postinfection studies may have been due to variability in the clinical course of PI-3 infection.

The severity of hypoxemia due to viral infection was greater than expected for the relatively modest intrapulmonary shunt, especially in awake studies. Since rigorous analysis showed that this was not explained by differences in precision of blood gas or tracer inert gas measurements, we explored the feasibility of two entirely different explanations: 1) O_2 uptake within the lung, or 2) change in P_{50} secondary to infection. The first explanation was derived from an earlier study of bacterial pneumonia in dogs by Light,[7] who found a significant increase in lung O_2 consumption rate ($\dot{V}_{O_2exp} - \dot{V}_{O_2Fick}$), presumably due to free radical formation from neutrophil-scavenging of bacteria. We used an identical method for estimating whole-body $\dot{V}_{O_2exp}$, and calculated the $Ca_{O_2} - C\dot{v}_{O_2}$ difference to derive $\dot{V}_{O_2Fick}$. Our estimates of lung O_2 consumption showed an average 0.33 $ml \cdot min^{-1} \cdot kg^{-1}$ (approximately 10 $ml \cdot min^{-1}$) increase after viral infection, which corresponds to a 0.2-$ml \cdot dl^{-1}$ Ca_{O_2} reduction, sufficient to account for a 20-mmHg reduction in Pa_{O_2}. This is approximately one third of the lung O_2 uptake reported by Light.[7]

Next, we looked at the effects of a 5-mmHg rightward shift of the oxyhemoglobin dissociation curve due to viral infection, using a computer subroutine described earlier by West.[16] This hypothetical shift would account for a 10-mmHg reduction in Pa_{O_2} for the measured $\dot{V}_A/\dot{Q}$ distributions but would be accompanied by a 1.13 ± 0.13 $ml \cdot min^{-1} \cdot kg^{-1}$ (40.0 ± 9.4 $ml \cdot min^{-1}$) increase in $\dot{V}_{O_2Fick}$. This is four times more than the amount needed to account for the increase in $\dot{V}_{O_2lung}$. That is, a 1.25-mmHg increase in P_{50} would be sufficient to account for the increase in $\dot{V}_{O_2lung}$ but would produce only a 2.5-mmHg reduction in Pa_{O_2}. This would not be sufficient to account for the increased difference in postinfection awake predicted *versus* measured Pa_{O_2}. We cannot rule out a small change in P_{50}, but we conclude that the change in measured and predicted awake Pa_{O_2} (fig. 3) was probably due to increased lung O_2 uptake. This lung O_2 uptake may have either: 1) accentuated the effect of intrapulmonary shunt on pulmonary end-capillary O_2 content, or 2) enhanced the shunting of bronchial venous blood flow (postpulmonary shunt), since $\dot{V}_A/\dot{Q}$ distribution measurements do not account for bronchial and Thebesian anatomic shunting.[23] We do not feel that bronchial venous drainage is a likely mechanism, however, since detailed studies of bronchial blood flow in sheep suggest that the dominant bronchial venous drainage is *via* the azygos vein and that the distal bronchial venous plexus outflow is either pulmonary capillary or precapillary.[24]

Increased lung O_2 uptake also occurred during the postinfection anesthesia study (table 3). However, the re-

duction in O_2 consumption rate from awake to anesthesia, without a reduction in $\dot{Q}_T$, raised Ca_{O_2} sufficiently to prevent arterial desaturation despite the significantly higher intrapulmonary shunt. We note that this $P\bar{v}_{O_2}$ effect of halothane/N_2O anesthesia is a significant though unexplained difference from human subjects and has also been observed with halothane/N_2O anesthesia in dogs.[25]

Earlier studies have also demonstrated significant increases in PAP and pulmonary vascular resistance induced by endotoxin infusion in sheep, similar to our viral infection-induced changes in mean PAP.[26] We speculate that pulmonary vascular resistance was increased also with PI-3 viral infection, since $\dot{Q}_T$ was unchanged. It is noteworthy, however, that halothane/N_2O anesthesia had no apparent effect on PAP. Therefore, the increase in PAP was due probably to pulmonary vascular damage, which in turn was due either directly to viral replication within the endothelial cell, or indirectly, to activation of complement by viral-immune complexes.[27]

The clinical relevance of these findings should be considered both in terms of the pulmonary responses to anesthesia, as well as in terms of the viral infection model. Similarities of human and ovine responses to anesthesia include the increased shunting, $\dot{V}_A/\dot{Q}$ inequality, and FRC reduction typically seen with inhaled anesthetics.[1,2,8] In addition, the enhanced intrapulmonary shunt/FRC relationship is analogous to the pattern seen in anesthetized young smokers.[2] Smokers showed shunt development at an anesthesia FRC above their awake closing capacity, whereas nonsmokers developed shunt only if FRC was below closing capacity.

A potentially important difference between sheep and human studies, however, was the use of a preexisting tracheostomy. This enabled placement of the endotracheal tube with local and topical anesthetic in awake sheep, presumably with normal awake chest wall and lung volume reflexes. This could have limited or modified reflex lung volume responses to intubation, such as those seen by Bickler *et al.*[9]

Despite these potential animal model differences, our findings were consistent with the clinical reports by McGill *et al.*,[3] who showed atelectasis in pediatric patients anesthetized during acute viral respiratory infection. In contrast, the findings of Tait and Knight,[4] who suggest that viral upper respiratory tract infection prior to inhalation anesthesia does not lead to an increased incidence of pulmonary complications, may not be strictly comparable with our sheep study. Their findings were based on mask-breathing subjects with no evidence of lower airway or alveolar disease, whereas our sheep almost certainly had an acute pulmonary parenchymal infection. We therefore suggest that lower *versus* upper respiratory tract infection may be an important reason for the difference in the conclusions of McGill *et al.*[3] and Tait and Knight.[4] Another important difference may have been the use by McGill *et al.* of an endotracheal tube in their patients. Although the precise nature of the pulmonary response to tracheal intubation has not yet been determined, the findings of Bickler *et al.* suggest that intubation elicits a potent airway reflex that results in enhanced FRC reduction and impaired oxygenation.

Increased airway reactivity due to viral infection may therefore be an important factor in the severity of shunting induced by anesthesia and tracheal intubation. It is noteworthy that airway reactivity is frequently enhanced after viral respiratory infection, for as long as 6 weeks after recovery from the acute symptoms.[28] Presumptive evidence that a vagus reflex is involved was derived from pretreatment with aerosolized atropine, which significantly reduced the airway reactivity to histamine. Buckner *et al.*[29] studied guinea pig infection with PI-3 virus and found enhanced responses to electrical stimulation of the vagus, whereas surgical vagotomy suppressed the response to histamine. Fryer et al.[30] recently showed that this hyperresponsiveness may be due to inhibition of vagal (M_2) autoreceptors by viral neuraminidase. In addition, studies of guinea pig infection with parainfluenza type-1 (Sendai) virus suggest that the change in airway reactivity during viral infection may also involve impairment or depletion of neutral endopeptidase in tracheal epithelium, resulting in increased levels of endogenous bronchoactive tachykinins, such as substance P.[31]

Finally, our experimental design did not address the question of how long elective general anesthesia with tracheal intubation should be delayed after viral respiratory infection. We speculate that this would depend on the severity of tracheobronchial epithelial damage, the severity of parenchymal inflammation, any bacterial superinfection, and the presence of preexisting lung disease. Recovery of normal O_2 saturation will probably precede recovery of normal airway reactivity, which in turn may correlate better with recovery from breathlessness during exercise. The most important outcome variable for the pulmonary response to anesthesia during viral infection may be preexisting lung disease, since this would reduce the pulmonary reserve for airway reactivity and FRC reduction.

In conclusion, our observations indicate that acute viral respiratory infection may add significantly to the pulmonary effects of anesthesia. These effects may be clinically important in certain patients, especially those with preexisting functional impairments, such as those induced by smoking in adults, cystic fibrosis and neonatal respiratory distress in children, and asthmatics in all age groups.

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