The Respiratory Effects of
Prostaglandin F2α in Anesthetized Cats

Max W. Talbott and Lloyd P. Gabel
Biological Research, American Chicle Division
Warner-Lambert Company, Morris Plains, New Jersey 07950

Abstract

Prostaglandin F2$_\alpha$ was administered to eight anesthetized cats. The respiratory response to the prostaglandin was assessed by mass spectrometric analysis of expired respiratory gases, pulmonary resistance monitoring and systemic blood pressure determination. Prostaglandin F2$_\alpha$ was found to elicit significant decreases in fractional expired carbon dioxide, alveolar carbon dioxide tension, VA/VT, alveolar ventilation, minute alveolar ventilation, tidal volume, oxygen consumption, carbon dioxide production, systemic blood pressure and heart rate. Significant increases were found in fractional expired oxygen, alveolar oxygen tension and pulmonary resistance. The effects of prostaglandin F2$_\alpha$ diminished within 10 min after administration.

Introduction

Various prostaglandins have been shown to affect respiration in anesthetized animals. Prostaglandin E_1 has been shown to increase respiratory rates in anesthetized dogs (5). Alveolar ventilation in anesthetized dogs was reportedly increased by administration of prostaglandin E_2 or prostaglandin A_1 (9). Administration of prostaglandin $F_2{}_\alpha$ (PGF2a) to anesthetized dogs caused decreased alveolar ventilation (11) while PGF2a has been reported to cause an increase in respiratory frequency in anesthetized cats (8). In other studies with anesthetized cats, PGF2a was found to increase bronchial resistance while decreasing systemic blood pressure (2).

With the increasing interest in the respiratory role of PGF2a, we initiated studies to determine respiratory function values in anesthetized cats treated with PGF2a. Parameters were measured by means of mass spectrometric respiratory gas analysis and pulmonary resistance calculation.

Materials and Methods

Eight cats of both sexes weighing between 2.2 kg and 6.0 kg were anesthetized by intraperitoneal injection of sodium pentobarbital (30 mg/kg) and tracheostomized. An L-shaped metal tracheal cannula was inserted and secured with sutures. An inlet/exhaust valve arrangement permitted the inhalation of ambient fresh air while routing the expired air to a mixing chamber. A sampling cannula (polyethylene tubing 1.22 mm o.d.) from the respiratory gas analysis apparatus was positioned in the tracheal cannula. A second sampling cannula was placed in the expired air mixing chamber.

To determine respiratory flow rate, tidal volume and transpulmonary pressure, a Fleisch Number 00 Pneumotachograph was inserted between the tracheal cannula and the inlet/exhaust valve system and connected to a Statham PM-5 pressure transducer. Transpulmonary pressure was determined by inserting a Reisch Number 20

cannula through the animal's chest wall at the seventh intercostal space and positioning one end of the cannula in the intrapleural cavity. The other end of the cannula was connected to a second PM-5 pressure transducer. A sidearm connection between the tracheal cannula and the second pressure transducer completed the system for determining transpulmonary pressure.

Signals from the flow rate pressure transducer were amplified and integrated to yield tidal volume values by a Beckman Type R Dynograph. The transpulmonary pressure transducer was also connected to the dynograph. Pulmonary resistance was calculated using the method of Amdur and Mead (1).

Analyses of respiratory gases were made with a Medspect MS-8 mass medical spectrometer (Scientific Research Instruments Corporation, Baltimore, MD). The spectrometer utilizes the tracheal-positioned sampling cannula to sample end-expired oxygen and carbon dioxide. The second cannula (positioned in the expired air mixing chamber) permitted determination of mean mixed-expired oxygen and carbon dioxide levels. Signals from the spectrometer were also recorded on the Dynograph. This allowed each gas analysis to be graphically recorded on an individual channel.

Arterial blood pressure was determined by cannulation of a femoral artery with saline-filled polyethylene tubing connected to a Statham P23AA pressure transducer and recorded on the Dynograph. Heart rate was determined by counting pulse deflections in the blood pressure tracing.

The cephalic vein was catheterized for drug administration. The drug dosage was dissolved in 1 cc of physiological saline and injected over a 30 sec period, followed by a rapid flushing of the cannula with 1 cc of saline.

Prostaglandin F2α (20 μg/kg) was injected into the animals no sooner than 30 min after the completion of surgical preparation. Measurements of end-expired oxygen, end-expired carbon dioxide, mean mixed-expired oxygen, mean mixed-expired carbon dioxide, respiratory flow rate, tidal volume and transpulmonary pressure were made before and at 1, 3, 5, 10, 15 and 30 min past the end of PGF2α injection.

Calculations

The following formulas were utilized in determining the various functional respiratory parameters. Symbols and gas equations conform to Comroe et al (3).

PB   Atmospheric pressure (mm Hg)
PBO2   Partial pressure of oxygen in ambient air (mm Hg)
PBN2   Partial pressure of nitrogen in ambient air (mm Hg)
MEPO2   Mean mixed-expired oxygen (mm Hg)
MEPCO2   Mean mixed-expired carbon dioxide (mm Hg)
AAO2   End-expired oxygen (mm Hg)
AACO2   End-expired carbon dioxide (mm Hg)
VT   Per breath tidal volume
f   Respiratory rate per min

vr   Tidal volume flow rate (cc/sec)

TPP   Transpulmonary pressure (cm $H_2O/l/sec$)

PBC   PB corrected for water vapor pressure

Fractional inspired nitrogen (FIN2):

$$\frac{PBN2}{PB}$$

Fractional inspired oxygen (FIO2):

$$\frac{PBO2}{PB}$$

Fractional expired oxygen (FEO2):

$$\frac{PBC(MEPO2)}{PB}$$

Fractional expired carbon dioxide (FECO2):

$$\frac{PBC(MEPCO2)}{PB}$$

Alveolar oxygen tension in mm Hg (PALVO2):

$$[FIO2\ (PBC) - PALVCO2]\ [FIO2 + \frac{1-FIO2}{R}]$$

Alveolar carbon dioxide tension in mm Hg (PALVCO2):

$$PBC(AACO2)$$

Oxygen consumption cc per breath (VO2):

$$VT - \frac{[FIO2(1-FECO2) - FEO2]}{(1 - FIO2)}$$

Carbon dioxide production cc per breath (VCO2):

$$VT - \frac{FECO2(1-FIO2)}{(1-FIO2)}$$

Respiratory quotient (R):

$$\frac{VCO2}{VO2}$$

Per breath alveolar ventilation in cc (VA):

$$PBC - \frac{R}{PACO2}\ VT$$

Percent alveolar ventilation (VA/VT):

$$VA/VT$$

Minute alveolar ventilation in cc (VA):

$$f(VA)$$

Pulmonary resistance cm $H_2O/l/sec$

$$\frac{TPP}{vr}$$

Results

Respiratory function values obtained before and after PGF2a administration are summarized in Table 1. After one minute (following the end of drug injection) significant decreases were noted in fractional expired carbon dioxide, alveolar carbon dioxide tension, VA/VT, alveolar ventilation, minute alveolar ventilation, tidal volume, oxygen consumption, carbon dioxide production, systemic blood pressure, and heart rate. These decreases were observed to remain constant through the ten minute post injection point. Gradual return of the respiratory parameters toward the pre-injection levels occurred between the 10 min and 30 min post injection points. Similarly, the fractional expired oxygen, alveolar oxygen tension and pulmonary resistance were seen to increase significantly at the one minute post injection point and remain elevated to the ten minute post injection point. After ten minutes these values began to decrease toward control levels. Respiratory rate and respiratory quotient values did not change significantly following PGF2a administration.

Discussion

Other workers have reported that administration of PGF2a to anesthetized animals precipitates respiratory impairment. The respiratory dysfunction was characterized by an increase of airways resistance, a decrease in alveolar ventilation, and a drop in systemic blood pressure (9, 11).

The respiratory and blood pressure effects of PGF2a have been linked to the substance's action on smooth muscle. Bronchoconstriction results from bronchial smooth muscle contraction. Response of vascular smooth muscle is specific to the location of the vessel and can result in either constriction or dilation. The effects of PGF2a on smooth muscle are thought to be direct and without neuronal mediation (4).

Although the exact mechanism of action of PGF2a at the cellular level is not known, a great deal of data indicate that the effects are the result of an influence on cellular cyclic AMP. Depending on the tissue in question PGF2a can either increase or decrease the cyclic AMP level (4).

The data derived from our study would indicate that PGF2a acts as a bronchoconstricting agent eliciting a generalized contraction of the bronchial smooth muscle. The reduction of airway caliber is accompanied by a reduction of tidal volume with a concomitant decrease in both VA/VT and alveolar ventilation. The reduction in minute alveolar ventilation is due to reduced per breath alveolar ventilation, since respiration rate was unaltered. Additionally, the measurements of alveolar gas exchange (fractional expired oxygen, fractional expired carbon dioxide, alveolar oxygen tension, and alveolar carbon dioxide tension) suggest a reduction in the number of alveoli being ventilated. This reduction in total alveolar surface results in an overventilation of those alveoli with patent airways. With a decreased alveolar air demand (a lessened number of functional alveoli as a consequence of constricted airways) the composition of expired and alveolar air is found to be altered. Less oxygen is being extracted from inspired air and less

TABLE 1. *The effects of Prostaglandin F2a in anesthetized cats.a*

	Control	1 min	3 min	5 min	10 min	15 min	30 min
FEO_2	0.170±0.003	0.182±0.007*	0.181±0.004	0.179±0.004*	0.174±0.006	0.175±0.006*	0.174±0.003
$FECO_2$	0.034±0.002	0.023±0.006*	0.022±0.005*	0.026±0.005*	0.028±0.006	0.030±0.005	0.032±0.003*
PAO_2	116.9±3.0	127.9±6.9*	125.2±6.2*	139.3±15.3*	117.1±7.3	121.5±4.5	120.4±2.3*
$PACO_2$	33.0±2.3	24.4±4.4*	26.8±5.7*	29.1±4.5*	31.2±3.6	31.1±3.9	32.3±3.8
VA/VT	77.8±1.7	72.7±4.6	70.1±2.4*	67.2±4.2*	67.7±5.1*	72.6±4.1	74.6±2.0
Alv Vent	30.6±1.9	19.5±2.7**	21.3±1.8*	21.7±1.5*	21.3±2.1**	24.1±2.3*	26.6±1.9*
Min Vent	690±82.6	397±64.6*	475±63.0*	448±32.5*	458±56.2*	540±85.9*	640±88.6
Tidal Vol	39.1±1.9	26.3±2.9*	30.3±2.2*	32.5±1.6*	31.3±1.6*	33.0±2.1*	35.5±2.1*
Resistance	4.44±0.57	8.22±1.53*	9.78±1.62*	7.77±1.32*	7.35±1.26*	7.59±1.32*	6.78±1.11*
Resp Rate	22±2	21±1	22±2	22±2	22±1	22±2	24±2
Blood Press	146±5.0	114±5.8*	124±3.9*	131±4.2*	136±4.0*	140±4.2*	141±5.3*
Heart Rate	216±10.2	148±7.2*	148±3.4**	165±4.0**	193±10.8**	202±11.7*	208±10.8*
Resp Quot	0.80±0.06	0.90±0.08	0.96±0.08	0.92±0.08	0.91±0.09	0.95±0.10	0.92±0.10
O_2 Consump	2.31±0.19	0.96±0.23**	1.14±0.23**	1.26±0.26**	1.62±0.27*	1.53±0.29*	1.77±0.28*
CO_2 Product	1.86±0.17	0.87±0.12**	1.08±0.17**	1.17±0.17*	1.47±0.29*	1.44±0.22**	1.62±0.17*

aData expressed as the means of eight determinations. Readings are shown ± S.E.; significance calculated by paired t-test. Levels of significance are expressed by the following: *p<0.05 and **p<0.01.

442   Indiana Academy of Science

carbon dioxide is being released into exhaled air so that the oxygen component of expired air is increased. Similarly, the oxygen tension of the ventilated alveoli is found to be increased due to the nearly maximal ventilation of the remaining open alveoli while the alveolar carbon dioxide tension is reduced.

With the presumed reduction of total oxygen absorbing (and carbon dioxide liberating) alveolar surface, the oxygen consumption and carbon dioxide production of the animals dropped significantly. The decreases in both parameters were proportional so that no resulting significant change was noted in the respiratory quotient.

The deleterious pulmonary actions induced by the administration of PGF2a were accompanied by a precipitous drop in systemic blood pressure and bradycardia. These reductions remained throughout the length of the post drug observation time. Two possible mechanisms operating singularly or in combination may be responsible for the observed cardiovascular effects.

Injection of PGF2a in anesthetized dogs has been shown to increase pulmonary arterial pressure (6). Similarly an increase in right ventricular pressure was noted in anesthetized cats upon PGF2a administration (2). With the description of lobar artery contraction in anesthetized dogs subjected to PGF2a administration (6), it would appear that the congestion resulting from constriction of the pulmonary arteries would precipitate a systemic blood pressure drop and heart rate decline.

A second possible mechanism for the systemic blood pressure reduction involves peripheral vasodilation. A report states that PGF2a has shown vasodilator qualities in specific instances (2). With extensive vasodilation a fall in systemic blood pressure of the magnitude observed could occur.

Conclusion

Based on the data derived from respiratory gas analysis and pulmonary resistance calculation, it would appear that PGF2a acts as a bronchoconstricting agent. Administration of PGF2a induced within one minute significant bronchoconstriction in the anesthetized cat. Accompanying the bronchoconstriction was a significant depression in systemic blood pressure and bradycardia. These reactions to PGF2a began to gradually diminish 10 min after prostaglandin administration.

Literature Cited

1. Amdur, M. D., and J. Mead. 1958. Mechanics of respiration in unanesthetized guinea pigs. Am. J. Physiol. 192:364-368.

2. Anggard, E., and S. Bergstrom. 1963. Biological effects of an unsaturated trihydroxy acid (PGF2a) from normal swine lung. Acta Physiol. Scand. 58:1-12.

3. Comroe, J. H., et al. 1950. Standardization of definitions and symbols in respiratory physiology. Fed. Proc. 9:602-605.

4. Fanburg, B. L. 1973. Prostaglandins and the lung. Amer. Rev. Resp. Dis. 108:482-489.

5. HIROSE, T, and S. I. SAID. 1971. Respiratory effects of prostaglandins A_1, E_1, and $F_{2\alpha}$. Clin. Res. **19**:512.

6. HYMAN, A. L. 1969. The active responses of pulmonary veins in intact dogs to prostaglandins F_2 *alpha* and E_1. J. Pharmacol. Exp. Ther. **165**:267-273.

7. MAXWELL, G. M. 1967. The effect of prostaglandin E_1 upon the general and coronary haemodynamics and metabolism of the intact dog. Brit. J. Pharmacol. Chemother. **31**:162-168.

8. McQUEEN, D. S. 1974. The effects of some prostaglandins on respiration in anesthetized cats. Brit. J. Pharmacol. **50**:559-568.

9. NAKANO, J., R. B. McCLOY, and A. V. PRANCAN. 1973. Circulatory and pulmonary airway responses to different mixtures of prostaglandins E_2 and $F_{2\alpha}$ in dogs. Eur. J. Pharmacol. **24**:61-66.

10. SAID, S. I. 1968. Some respiratory effects of prostaglandins E_2 and $F_{2\alpha}$. In: *Prostaglandin symposium of the Worcester Foundation for Experimental Biology.* ed., Ramwell, P. W., and J. E. Shaw, pp. 267-277. Wiley, New York.

11. SAID, S. I., O. MUREN, and B. J. KIRBY. 1968. Some respiratory effects of prostaglandins E_2 and $F_{2\alpha}$. Clin. Res. **16**:90.