

Hemodynamic effects of periodic G_z acceleration in meconium aspiration in pigs

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Adams, Jose A., Martin J. Mangino, Jorge Bassuk, and Marvin A. Sackner. Hemodynamic effects of periodic G_z acceleration in meconium aspiration in pigs. *J Appl Physiol* 89: 2447–2452, 2000.—The hemodynamic effects of periodic acceleration (pG_z), induced in the spinal axis with noninvasive motion ventilation (NIMV), were studied in a piglet model of pulmonary hypertension associated with meconium aspiration. Animals ($n = 12$) were anesthetized, paralyzed, intubated, and supported by conventional mechanical ventilation (CMV). Thirty minutes after tracheal instillation of meconium solution (6 ml/kg), either CMV ($n = 6$) was continued or NIMV ($n = 6$) was initiated. Changes in systemic and pulmonary hemodynamics and arterial blood gases were tracked for 2 h after aspiration. Thermodilution, cardiac output, and heart rate were not significantly different after meconium aspiration in the pG_z group relative to the CMV controls. Aortic pressure and systemic vascular resistance were significantly lower ($\sim 30\%$) after meconium aspiration in NIMV animals relative to CMV animals. Pulmonary arterial pressure and pulmonary vascular resistance were also significantly lower, by 100%, after aspiration of meconium in the NIMV animals compared with the CMV controls. Meconium aspiration significantly decreased total respiratory compliance by $\sim 50\%$ and increased total respiratory resistance by $\sim 100\%$ in both CMV and NIMV animals, but such alterations did not differ between the two groups. Both CMV and NIMV satisfactorily supported ventilation in these paralyzed animals. In conclusion, NIMV through pG_z in the spinal axis decreased systemic and pulmonary vascular resistance in piglets after meconium aspiration.

inertial forces; pulmonary hypertension; vasodilatation; arterial pulsation; cardiac output

NONINVASIVE MOTION VENTILATION (NIMV) is a novel method of ventilatory support that produces whole body periodic acceleration (pG_z) along the spinal axis in a sinusoidal head-to-foot motion (1). It causes paradoxical motion of the rib cage and abdomen during inspiration and expiration and operates at frequencies moderately above, and tidal volumes below, natural breathing. Ventilation is achieved by imparting of inertial forces of the abdominal viscera to the diaphragm during periodic accelerations and decelerations of the body in the spinal axis. In contrast to positive-pressure conventional mechanical ventilation (CMV), pG_z pro-

duces negative pleural pressures that are comparable to normal breathing (1). We previously reported that pG_z can effectively ventilate normal lungs and lungs affected by meconium aspiration injury in a paralyzed porcine model (1). The imposition of external pressure pulses to the cardiovascular system during the periodic oscillations of the motion platform was also observed in these studies.

Meconium aspiration syndrome (MAS) is a pulmonary disease in newborns that carries significant mortality and morbidity. This syndrome is associated with severe hypoxemia due to intrapulmonary shunt and pulmonary hypertension (12, 18, 21, 22). These effects have been attributed to the concentration of the meconium in the aspirate and not to the liquid vehicle per se (8). Animal models of meconium aspiration with attendant hemodynamic changes during conventional and high-frequency mechanical ventilation have been characterized (6, 9, 15, 21). Meconium aspiration increases pulmonary and systemic vascular resistance while cardiac output decreases. High-frequency ventilation generally has no significant effect on these parameters (6, 21) or potentiates the aspiration-induced increase in pulmonary vascular resistance, relative to conventional ventilation (2, 15). Recently, inhalation of nitric oxide, which relaxes pulmonary vascular smooth muscle, has been successful in lowering the pulmonary hypertension of MAS, with reduced intrapulmonary right-to-left shunting and increased arterial oxygenation in most studies (5, 9, 11, 12). Furthermore, other studies have shown that pulsatile flow stimulates endogenous production of endothelial cell-derived nitric oxide, which is encoded in the pulse amplitude and pulse frequency applied to the arterial wall (10, 17). These imposed cardiovascular forces are similar to those observed during NIMV. Therefore, it was hypothesized that NIMV produces cardiovascular changes during MAS that differ from CMV, possibly due to differences in ventilatory pressures or imposed forces to the cardiovascular structures.

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METHODS

Platform design. The motion platform was constructed around a linear displacement direct current motor (model 400, 12 volt; APS Dynamics, Carlsbad, CA). The motor is powered by a dual-mode power amplifier (model 144, APS Dynamics) connected to a sine-wave controller (model 140-072; NIMS, Miami Beach, FL). The controller allows for the control of the frequency of the table oscillation, the amplitude of the voltage reaching the motor and subsequent acceleration of the stroke, and the duty cycle of the motor. The motor is secured in the bottom and center of a frame constructed from treated pine lumber. The table platform is directly driven by the underlying motor and articulates across the frame on stainless steel tracks and nylon wheels. The unit has a maximum weight capacity of ~30 kg and operates at a frequency of 0.5–10 Hz at a force of 0.1–1.5 G.

Animal preparation. All animal studies were approved by the Institutional Animal Care and Use Committee and were in compliance with the Animal Welfare Act. Twelve juvenile pigs (9.5 ± 1.2 kg) were used in this study. The animals were initially anesthetized with ketamine (10 mg/kg im) and maintained in a surgical plane of anesthesia with intravenous pentobarbital sodium as needed. Anesthetic depth was determined by loss of spinal and corneal reflex and maintenance of a normal heart rate for newborn piglets (~150 beats/min). The total amount of pentobarbital administered in these experiments was at least 40 mg/kg iv. An airway was established by tracheotomy and insertion of a 4.0-mm endotracheal tube. Intravascular catheters were placed into the femoral artery to measure systemic blood pressure by connecting the fluid-filled catheter to a pressure transducer (Transpac, Abbott Critical Care Systems, North Chicago, IL). A Swan-Ganz thermodilution catheter was inserted into the pulmonary artery via the right jugular vein to obtain pulmonary arterial pressure and cardiac output. The position of the catheter was verified by pressure tracings and thermodilution curves. A right atrial catheter was placed via the left external jugular vein for administration of fluids and drugs and the measurement of right atrial pressure ($n = 4$). Systemic and pulmonary vascular resistance were estimated as mean blood pressure and mean pulmonary arterial pressure, respectively, divided by cardiac output. Arterial blood gases were measured at various intervals during the experiments by use of a blood gas analyzer (Radiometer model ABL 30). Pulmonary airflow and volume were measured with a pneumotachograph (Fleisch model 5751) connected to a differential pressure transducer (Validyne model MP-14-871). Total dynamic respiratory system compliance was computed as the ratio of the change in lung volume to the corresponding change in transpulmonary pressure (airway) at multiple points of zero flow. Both groups of animals (CMV and NIMV) were briefly placed on mechanical ventilation before aspiration and at the end of the experiment to obtain these measurements. The range of volumes tested was similar in both groups of animals. NIMV, with its attendant periodic acceleration, was achieved by supporting the animal on the oscillating motion platform in the supine position. The platform moved sinusoidally in a headward-to-footward direction, which allowed for the control of the both the frequency and the force of acceleration, which determines the ventilation of the piglet. During pG_z , platform acceleration was measured by using an accelerometer (NIMS, model 140-060). All animals were paralyzed with pancuronium bromide (0.1 mg/kg) and received a bias flow of 100% O_2 and continuous positive airway pressure of 5 cmH₂O to maintain oxygenation and functional residual capacity, respectively.

Experimental design. After an initial postsurgical stabilization period of 30 min, the animals were placed on a conventional pressure-limited ventilator (Bear Cub BP-200, Inter Med) with peak inspiratory pressures of 15–18 cmH₂O, positive end-expiratory pressure of 5 cmH₂O, frequency of 15–20 breaths/min, and inspired O_2 fraction of 1.0. The ventilatory settings were set to maintain arterial partial pressure of CO_2 (Pa_{CO_2}) in the range of 35–45 Torr. During the baseline period, intravascular pressures, cardiac output, arterial blood gases, and respiratory mechanics of breathing were measured. A solution of unfiltered human meconium, 25% by weight (6 ml/kg), was administered via a catheter placed at the carina through the endotracheal tube. Fifteen minutes after meconium instillation, the measurements were repeated. Piglets were randomized to either CMV ($n = 6$) or NIMV ($n = 6$) for 150 min after meconium aspiration. CMV settings were increased initially to a peak pressure of 25–30 cmH₂O to obtain adequate gas exchange based on the results of previous experiments and not modified further during the entire protocol. NIMV was performed at frequencies of 2.5–4 Hz and pG_z of ± 0.5 to $\pm 0.7 G_z$ and was maintained during the protocol. The NIMV settings were established from previous experiments and typically resulted in a normal range for blood gas parameters. One hundred percent O_2 was administered to both groups during the 150-min postaspiration period. Intravascular pressures, cardiac outputs, and arterial blood gases were measured at baseline, 15 min after meconium aspiration, and at 30, 60, 90, 120, and 150 min thereafter. Total dynamic respiratory system compliance and resistance were measured after baseline and 150 min after meconium aspiration in both groups while on mechanical ventilation. Data from a physiological recorder (model 7, Grass Equipment) were digitized and recorded using RespiTrace PT (NIMS), and the digital data were analyzed using RespiEvents software (NIMS).

Statistical analysis. All data that followed a Gaussian distribution frequency were analyzed by one-way ANOVA with Dunnett's correction for multiple comparisons or the unpaired *t*-test. Data in Fig. 1 were normalized to percent change from baseline because many baseline changes covaried with changes induced by the experiment. These data were then analyzed by the Kruskal-Wallis test. Data are expressed as means \pm SD, and statistical significance was set at $P < 0.05$.

RESULTS

All animals survived the MAS protocol to 180 min. There were no significant differences in arterial blood gases before meconium instillation between the two groups. Fifteen minutes after meconium instillation, Pa_{CO_2} increased and arterial partial pressure of O_2 (Pa_{O_2}) decreased (Table 1). Pa_{CO_2} , Pa_{O_2} , HCO_3^- , and pH remained relatively constant thereafter in animals ventilated with either NIMV or CMV. The motion platform was set to frequencies between 2.5 and 4 Hz at pG_z of about ± 0.4 – $0.7 G_z$, which, in turn, produced pulse pressures of 3–40 mmHg.

After meconium installation, all animals experienced at least 50% decrease in total respiratory dynamic compliance and a greater than doubling in total respiratory resistance. There were no significant differences in respiratory mechanics between piglets in the CMV and the NIMV groups at baseline or after meconium aspiration (Fig. 1). Peak inspiratory pres-

Table 1. Arterial blood gases

	BL	Mec	15	30	60	90	120	150
pH								
CMV	7.35 ± 0.05	7.19 ± 0.07	7.39 ± 0.18	7.51 ± 0.11	7.38 ± 0.17	7.45 ± 0.10	7.46 ± 0.08	7.48 ± 0.02
pG _z	7.42 ± 0.07	7.23 ± 0.08	7.41 ± 0.12	7.44 ± 0.11	7.45 ± 0.08	7.45 ± 0.10	7.43 ± 0.13	7.40 ± 0.17
PCO ₂ , Torr								
CMV	41.8 ± 5.5	67.7 ± 29.5*	40.0 ± 18.7	26.7 ± 10.0	43.7 ± 28.0	33.0 ± 10.5	32.5 ± 6.3	32.0 ± 3.03
pG _z	39.9 ± 4.8	60.9 ± 9.2*	33.4 ± 7.4	32.6 ± 9.9	32.6 ± 8.3	33.2 ± 9.8	35.2 ± 13.1	36.5 ± 13.9
PO ₂ , Torr								
CMV	360 ± 91	128 ± 147*	243 ± 132	281 ± 131	235 ± 130	222 ± 111	266 ± 84	286 ± 98
pG _z	393 ± 108	148 ± 84*	236 ± 122	220 ± 130	164 ± 155	164 ± 162	162 ± 155	144 ± 140
HCO ₃ , meq/dl								
CMV	22.5 ± 1.2	25.7 ± 5.1	22.5 ± 2.6	20.5 ± 3.3	22.9 ± 3.6	22.1 ± 1.7	22.4 ± 0.6	23.6 ± 2.0
pG _z	25 ± 3.2	24.6 ± 2.2	21.0 ± 3.7	21.4 ± 3.3	22.4 ± 1.8	22.3 ± 2.4	22.2 ± 2.7	21.5 ± 3.2

Values are means ± SD; *n* = 6 per group. Effects of meconium aspiration (Mec) on arterial pH and blood gas values in animals on conventional mechanical ventilation (CMV) and noninvasive motion ventilation achieved by means of periodic acceleration in the *z*-plane (pG_z). HCO₃, bicarbonate. Numbered columns after Mec indicate the time in minutes after the aspiration of meconium solution. **P* < 0.01 baseline (BL) vs. Mec.

ures ranged from 25 to 30 cmH₂O after meconium instillation in animals on CMV, with mean airway pressures in the range of 9–13 cmH₂O. In contrast, peak airway pressures did not exceed 9 cmH₂O in the NIMV group after meconium aspiration, which was 4 cmH₂O above the continuous positive airway pressure level established for these animals, owing to the mechanical resistance of the breathing circuit.

The effects of meconium aspiration and NIMV on systemic and pulmonary hemodynamics are shown in Fig. 2 and Table 2. Cardiac output and heart rate were not significantly different in animals after meconium aspiration relative to before aspiration and between the two groups of animals (CMV vs. NIMV). Mean

aortic blood pressure was significantly lower after the instillation of meconium in animals experiencing pG_z relative to animals on CMV. Accordingly, systemic vascular resistance was significantly lower in the NIMV animals after meconium instillation, owing to the significantly lower mean arterial blood pressures relative to the CMV animals (Fig. 2). Both mean pulmonary arterial pressure and pulmonary vascular resistance were significantly lower after meconium instillation in the NIMV than the CMV piglets (Fig. 2). In piglets on CMV, both pulmonary arterial pressure and pulmonary vascular resistance were significantly elevated after meconium aspiration, relative to the values observed before aspiration. However, in the animals on NIMV that experienced pG_z, significant increases were not observed after meconium aspiration, and the pulmonary arterial pressure and vascular resistance actually trended below preaspiration levels (Fig. 2). Right atrial pressures (*n* = 4) in this study ranged from 5 to 10 mmHg and appeared unaffected by meconium aspiration or the mode of ventilation.

DISCUSSION

This study demonstrated that NIMV, utilized as a means of ventilatory support in a piglet model of MAS, had significant effects on central hemodynamics. After meconium aspiration, pulmonary arterial pressure, pulmonary vascular resistance, aortic blood pressure, and systemic vascular resistance were significantly lower during NIMV (pG_z) than during CMV by 102%, 95%, 23%, and 58%, respectively. Cardiac output, heart rate, and right atrial filling pressure were not different either after meconium aspiration or between groups (CMV vs. NIMV). Total respiratory compliance significantly declined after meconium aspiration and was not affected by pG_z. Finally, both CMV and NIMV maintained adequate ventilation after meconium aspiration.

The changes in pulmonary mechanics, gas exchange, and hemodynamics with MAS during CMV in the present study are similar to those described by others (6, 8, 15, 21). Several investigators have established

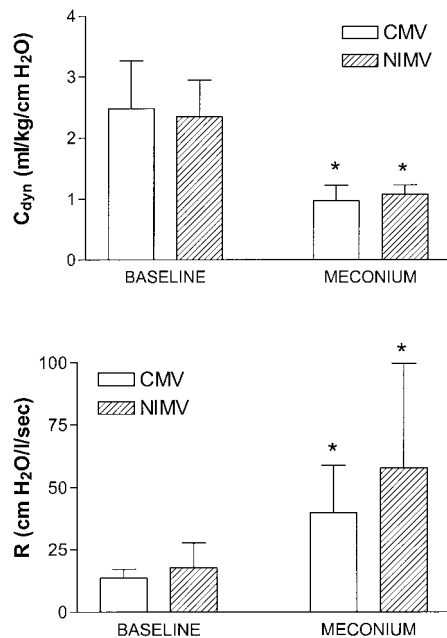


Fig. 1. Effects of meconium aspiration on pulmonary dynamic compliance (C_{dyn}) and resistance (R) in animals ventilated with conventional mechanical ventilation (CMV) and noninvasive motion ventilation (NIMV). Data were obtained before aspiration (baseline) and 180 min after meconium aspiration (meconium). Values are expressed as means ± SD *n* = 12. **P* < 0.05 relative to baseline.

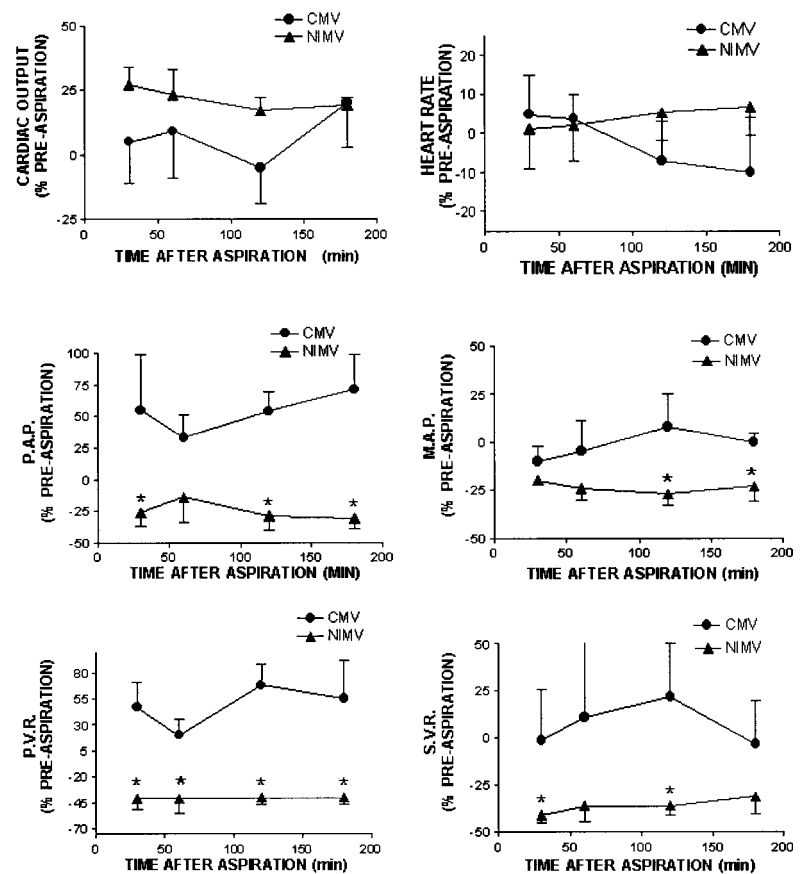


Fig. 2. Hemodynamic parameters measured at baseline and at various times after meconium aspiration. All animals started the experiment on CMV. PAP, pulmonary artery pressure; MAP, mean arterial pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance. Values are means \pm SD and represent the percent change from control (before aspiration); $n = 12$. * $P < 0.05$ relative to the corresponding values between NIMV and CMV at that time.

efficacy of high-frequency jet ventilation in meconium aspiration (9, 18, 21). Some studies have demonstrated improvements in blood oxygenation with similar or lower mean airway pressures but higher pulmonary arterial pressures compared with CMV (2, 15, 21). During meconium aspiration with NIMV in this study, gas exchange was maintained, and pulmonary arterial pressure and resistance not only did not rise, but also fell significantly below preaspiration values.

NIMV resulted in significantly lower lung volumes and transpulmonary pressures during aspiration, relative to CMV (1). Because lung volumes and pleural pressures influence pulmonary vascular resistance and systemic cardiovascular parameters, the hemodynamic

changes during NIMV in this study could have resulted from the lower lung volumes associated with NIMV. Therefore, it seems possible that at least some of the cardiovascular changes associated with NIMV after meconium aspiration may be attributable to lower lung volumes and reduced pleural pressures inherent with this novel mode of ventilation. However, lung volumes alone cannot explain all the observed differences in hemodynamics between CMV and NIMV. Although lung volumes differed between the two groups, this factor is not the primary determinant of pulmonary vascular dilatation, even though the converse may be relevant. Lower lung volumes with NIMV, relative to the CMV controls, may be expected to attenuate any

Table 2. Hemodynamics and meconium aspiration: effects of pG_z

	CMV					pG_z				
	CO, l/min	BP, mmHg	PAP, mmHg	PVR, RU	SVR, RU	CO, l/min	BP, mmHg	PAP, mmHg	PVR, RU	SVR, RU
BL	1.2 \pm 0.3	76 \pm 5	15 \pm 5	17 \pm 2	67 \pm 13	1.2 \pm 0.3	79 \pm 18	11 \pm 6	9 \pm 6	66 \pm 28
Mec	1.8 \pm .08	98 \pm 21	31 \pm 4	20 \pm 9	58 \pm 18	1.62 \pm 0.5	82 \pm 19	26 \pm 8	11 \pm 8	54 \pm 23
15	0.9 \pm 0.1	74 \pm 21	23 \pm 9	25 \pm 7	82 \pm 8	1.6 \pm 0.4	66 \pm 8	7 \pm 3	7 \pm 3	44 \pm 19
30	0.93 \pm 0.2	78 \pm 22	20 \pm 3	23 \pm 8	89 \pm 22	1.6 \pm 0.6	65 \pm 13	6 \pm 2	5 \pm 4	48 \pm 27
60	0.93 \pm 0.1	87 \pm 22	23 \pm 3	24 \pm 4	95 \pm 43	1.5 \pm 0.5	70 \pm 6	7 \pm 2	5 \pm 4	52 \pm 22
90	0.83 \pm 0.1	84 \pm 26	23 \pm 2	28 \pm 5	102 \pm 31	1.5 \pm 0.4	62 \pm 11	7 \pm 2	5 \pm 4	45 \pm 18
120	1.1 \pm 0.4	73 \pm 17	21 \pm 2	20 \pm 9	75 \pm 30	1.5 \pm 0.4	67 \pm 8	8 \pm 4	6 \pm 3	49 \pm 19
150	1.1 \pm 0.4	84 \pm 19	25 \pm 4	25 \pm 10	85 \pm 40	1.4 \pm 0.2	62 \pm 15	7 \pm 4	5 \pm 3	45 \pm 18

Values are means \pm SE. CO, cardiac output; BP, blood pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; RU, resistance units.

aspiration-induced increase in pulmonary vascular resistance but not result in the lower pulmonary vascular resistance (below preaspiration levels) that were observed in this study (Fig. 2). Similar to the pulmonary circulation, systemic vascular resistance was lower than preaspiration values in NIMV animals. Also, it is generally held that lung volumes and pleural pressures influence vascular resistance by physical compression of the vessel cross-sectional area, thereby changing vascular resistance, venous return, and cardiac output. Mitigating all of these forces in the CMV animals after aspiration would have only abolished the increases in pulmonary arterial resistance but would not have dropped the values below baseline preaspiration levels. Also, blood pressure tended to fall and cardiac output tended to increase in animals experiencing pG_z . This suggests that pG_z caused vasodilatation, resulting in both the observed drop in aortic pressure and a reflex increase in cardiac output (Fig. 2). Thus other factors besides lower lung volumes are required to explain the pulmonary and systemic vasodilatation that was observed in these studies. These data are consistent with the generation of vasoactive mediators during meconium aspiration in the NIMV group. The possibility that lower lung volumes cause pulmonary vasodilatation by the direct release of vasoactive mediators, however, cannot be ruled out.

Ventilation with NIMV after meconium aspiration is as effective as CMV or high-frequency ventilation with respect to gas exchange. However, NIMV provides the added beneficial effects of reduction of pulmonary vascular resistance and mean airway pressures. This may have beneficial effects during meconium aspiration and other pulmonary diseases associated with reduced compliance (6, 20, 21).

The vasodilatory effects of pG_z were unmasked during meconium instillation that caused marked pulmonary hypertension (Fig. 2). Significant or sustained decreases in pulmonary arterial pressure and pulmonary vascular resistance were not observed in normal animals immediately after the onset of pG_z (1). These observations further support the hypothesis that vasoactive agents are generated during NIMV and unmask vasodilatory effects in the face of meconium-induced pulmonary artery precontraction.

Vasodilatation associated with NIMV and its attendant pG_z might have been due to inhibition of released vasoconstrictor substances during aspiration, disinhibition of a vasodilator, introduction of different vasodilating substances (pharmacological antagonism), or combinations of these possibilities. Vasoconstrictor substances found during meconium aspiration include endothelin-1, thromboxane A_2 , prostaglandin $F_{2\alpha}$, 20-hydroxyeicosatetraenoic acid, and others. Likely vasodilator substances include nitric oxide, PGI_2 , and endothelium-derived hyperpolarizing factor, among others (3, 4, 7, 10, 13, 14, 19).

Nitric oxide is released from vascular endothelial cells in response to changes in shear stress and frequency of pulsation (4, 10, 17). Rat donor aorta perfused with physiological buffer *ex vivo* produced max-

imal relaxation of endothelial denuded rabbit aortic rings at frequencies of 4–6 Hz and a constant pulse amplitude of 2 mmHg. These effects were abrogated with the nitric oxide synthetase inhibitor N^{ω} -nitro-L-arginine methyl ester, suggesting that frequency-induced vasorelaxation was due to release of nitric oxide by the donor vessel. During NIMV in this study, arterial pulse frequencies were 2.5–4 Hz at pulse amplitudes of 2–8 mmHg, measured by a catheter in the axis of flow. These frequencies and amplitudes are similar to data in isolated vessels (10) and suggest a similar release of nitric oxide during NIMV with attendant vasorelaxation. Other flow-released mediators include prostacyclin, nitric oxide-dependent release of endothelium-derived hyperpolarizing factor, and adenosine, which are released in response to both the frequency and amplitude of pulsatile flow (3, 16, 17, 19). Also, physiological levels of blood flow inhibit endothelial release of endothelin-1, a potent vasoconstrictor, whereas reduced blood flow with consequent low shear stress stimulates endothelin-1 release (13). In addition to flow shear stress, endothelin-1 may be modulated by other mechanisms during aspiration. Pulmonary vasoconstriction during MAS has been attributed to meconium *per se* and is dose related (8). Increased endothelin-1 is also detected in the circulation after meconium aspiration (14), and pG_z may interfere with the production of meconium-stimulated endothelin-1 via shear stress mechanisms, thus blunting the pressor response. The release of these vasoactive mediators by blood flow-generated shear stress have been described for physiological patterns, duration, and magnitudes of flow and may apply differently during pG_z .

The present study demonstrates that significant cardiovascular effects of pG_z take place when NIMV is utilized to provide ventilatory support to piglets undergoing experimental meconium aspiration. There is a significant reduction in pulmonary vascular resistance. This finding contrasts with elevated values of pulmonary vascular resistance present with CMV in the present study and in reports by others, as well as pulmonary hypertension associated with MAS during treatment with high-frequency jet ventilation. Further investigations need to focus on the mechanism for pulmonary vasodilatation attendant with NIMV and pG_z .

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M. A. Sackner is the chief executive officer of Non-Invasive Monitoring Systems and owns 52% of the shares.

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