Selective Pulmonary Vasodilation by Inhaled Prostacyclin in a Newborn with Congenital Heart Disease and Cardiopulmonary Bypass

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INCREASED pulmonary vascular resistance is common in patients with congenital heart disease¹ and may be further exacerbated by open heart surgery and cardiopulmonary bypass (CPB).² Successful management of pulmonary hypertension subsequent to CPB has been limited, because the intravenous administration of substances that decrease pulmonary artery pressure also decrease systemic arterial pressure³,⁴ and may adversely affect pulmonary gas exchange.⁵

Inhaled nitric oxide has been shown to reduce pulmonary hypertension after CPB in newborns and children.⁶,⁷ Unfortunately, nitric oxide is not generally available, its safe administration is technically demanding and expensive, and its use may be limited by its side effects.

Alternatively, it has been shown that aerosolized prostacyclin (PG₁₂), similar to nitric oxide, has the potential to elicit selective pulmonary vasodilation both in animals¹⁰ and humans¹¹ and to improve right ventricular function by reduction of increased pulmonary artery pressure.¹² In contrast to inhaled nitric oxide, no data are available on the effects of inhaled PG₁₂ on cardiopulmonary function in newborns presenting with severe pulmonary hypertension aggravated by cardiac surgery and CPB. In the current report, we describe the successful intra- and postoperative use of aerosolized PG₁₂ in a newborn with congenital heart disease and severe pulmonary hypertension.

Case Report

A 3.9-kg male newborn presented with hypoxemia and cardiovascular collapse immediately after birth and was transferred to our institution on day 4 of life. Cardiac catheterization revealed unobstructed total anomalous pulmonary venous connection of the supracardiac type. The child was hemodynamically unstable, and emergent surgical repair was undertaken.

Anesthesia was induced with 0.15 mg fentanyl (Janssen, Neuss, Germany) and 1 mg pancuronium (Organon-Teknika, Eppelheim, Germany) and maintained by bolus injections of fentanyl and pancuronium. Other drugs administered at time of induction included dobutamine (5–8 μg·kg⁻¹·min⁻¹; Dobutrex, Lilly Deutschland, Bad Homburg, Germany) and alprostadil (50 ng·kg⁻¹·min⁻¹; Minprogen Prola, Upjohn, Heppenheim, Germany).

Mechanical ventilation was performed (ID 3.5 mm, VYGON, Ecouen, France) using a Siemens Servo 900 D ventilator (Elema, Sweden).
Ventilation parameters were \( F_{\text{r}} \), 1.0, minute volume 2.0 l/min, respiratory rate 41 breaths/min, PEEP 2 cmH\(_2\)O, maximal airway pressure 20 cmH\(_2\)O, and I:E ratio 0.43:0.57. Monitoring included electrocardiogram, pulse oximetry, temperature (rectal, esophageal), invasive blood pressure \( via \) cannulation of the left femoral artery (22-G cannula, Arrow Deutschland, Erding, Germany), central venous pressure \( via \) the right anonymous vein (4-French, 2-lumen, Arrow Deutschland, Erding, Germany), and arterial blood gases (Blood Gas System 288, Ciba Corning Diagnostic, Medfield, MA).

Surgery consisted of median sternotomy, installation of CPB, total cardiopulmonary arrest, anastomosis of the pulmonary venous confluence to the left atrium, closure of the aortoventral defect, and ligation of the connection vein. During that time, a distended truncus pulmonalis and a minimally working right ventricle were noticed. CPB was terminated during infusion of enoximone (10 \( \mu \)g: kg\(^{-1}\)·min\(^{-1}\); Perfan, Marion Merrell Dow, Rüsselsheim, Germany) and alprostadil (150 ng: kg\(^{-1}\)·min\(^{-1}\)) into the pulmonary artery. Five minutes later (fig. 1), systolic arterial pressure (SAP) was 70 mmHg and sistolic pulmonary artery pressure (SPAP) was 60 mmHg.

Within the following minutes, right ventricular contraction further deteriorated, as judged by direct visual inspection. Because therapy had resulted in no improvement of cardiopulmonary function, the decision was made to administer epoprostenol, an analog of PGI\(_2\) via the tracheal route. For this purpose, a jet nebulizer (servo Nebulizer 945, Siemens, Erlangen, Germany) was connected to a Siemens 900 D ventilator. The nebulizer chamber (Cirrus, Intersurgical, Twickenham, United Kingdom) was adapted directly to the endotracheal tube. Thereafter, 500 \( \mu \)g epoprostenol (Fliolan, Wellcome, London, United Kingdom) were dissolved in 50 ml glycine buffer (pH 10.5) resulting in a PGI\(_2\) concentration of 10 \( \mu \)g/ml. Six milliters of this solution was filled into the nebulizer chamber, and the nebulizer was started operating at its low-flow mode. In this mode, the nebulizer delivers a peak inspiratory flow of 7 l/min, thereby adding notably to the minute volume applied to the patient. Therefore, the minute volume delivered by the ventilator was reduced from 2.2 to 0.9 l/min. Within the following 15 min, SPAP decreased from 60 to 50 mmHg, and SAP increased from 70 to 75 mmHg (fig. 1). Blood gas analysis revealed a P\(_{aCO_2}\) of 345 mmHg, and P\(_{aO_2}\) of 19 mmHg indicated severe hyperventilation. Therefore, the nebulizer was turned off after 15 min.

Within the following 10 min, SPAP increased again to 60 mmHg, and P\(_{aCO_2}\) decreased to 123 mmHg. Therefore, the nebulizer was turned on again; ventilator volume, however, was set to 0.3 l/min, resulting in P\(_{aCO_2}\) of 28 mmHg and peak airway pressure of 22 cmH\(_2\)O. Similar to the first trial, an increase of the SAP-to-SPAP gradient and of P\(_{aCO_2}\) were observed (fig. 1). Despite this improvement, the cardiopulmonary situation remained critical, and it was decided to close the chest using a large Gore-tex-patch to avoid further compromising right ventricular function.

Surgery lasted for 320 min, with a CPB time of 150 min and cardiopulmonary arrest of 59 min. Transfusions included 500 ml packed erythrocytes, 150 ml platelets, and 320 ml fresh frozen plasma. The patient was transferred to the pediatric intensive care unit using a transportable ventilator to allow continuous PGI\(_2\) administration. PGI\(_2\) was continuously aerosolized for 13 h, and SAP-to-SPAP gradient increased to 44 mmHg (fig. 2). Thereafter, PGI\(_2\) was discontinued. Within the following 30 min, however, an increase of SPAP from 33 to 44 mmHg and a decrease of P\(_{aCO_2}\) from 259 to 65 mmHg were observed. At this time, nitric oxide was available and was administered at a concentration of 40 ppm. This caused SPAP to decrease again to a level similar to that observed during aerosolization of PGI\(_2\). Within the next few days, the patient's condition continuously improved. Administration of nitric oxide was stopped on the 4th day, and the chest was definitely closed. Separation from mechanical ventilation was started on the 5th postoperative day, and exubation was performed 11 days later.

Fig. 1. Cardiopulmonary effects of inhaled PGI2 in the post cardiopulmonary bypass period (for further explanation, see text). BGA = blood gas analysis; CPB = cardiopulmonary bypass; PGI2 = prostacyclin; SAP = systolic arterial pressure; SPAP = systolic pulmonary artery pressure.

Anesthesiology, V 82, No 6, Jun 1995
Discussion

To our knowledge, this is the first case to demonstrate that inhalation of PGI₂ is effective in reducing an increased pulmonary artery pressure in a newborn with congenital heart disease and CPB without impairing systemic blood pressure or gas exchange. Although selective pulmonary vasodilatation has been described for inhaled nitric oxide (and was confirmed in our patient), the advantages of inhaled PGI₂ are its general availability and that administration is comparatively easy.

Several factors independent of PGI₂ may have influenced pulmonary artery pressure in our patient. Because of the severity of the condition of the newborn, enoximone and PGE₁ have been administered in the perioperative phase to reduce pulmonary artery pressure. Both drugs were continuously infused for more than 45 min before the onset of PGI₂ aerosolization, and no changes of dosage have been performed. Therefore, it seems unlikely that the reduction of SPAP in the post-CPB phase was a pharmacologic effect of enoximone or PGE₁.

This view is supported by the fact that a decrease of SPAP (from 60 to 50 mmHg) was observed within a few minutes after the onset of aerosolization of PGI₂. The termination of PGI₂ inhalation reproducibly resulted in a reduction of the SAP-to-SPAP gradient (figs. 1 and 2), which could be reversed by PGI₂ aerosol (operating room) or inhalation of nitric oxide (intensive care unit).

There was no measurement of pulmonary blood flow, and we cannot be certain what the natural history of post-CPB pulmonary hypertension was without prostacyclin treatment for this patient. Although the small increase in SPAP from 50 to 60 mmHg when the aerosol therapy was discontinued is supportive of the efficacy of this agent, it is well known that there is a transient overshoot in pulmonary artery pressure when almost any vasodilator is abruptly discontinued. Therefore, in this child, we may be overestimating the extent of the underlying pulmonary hypertension during the discontinuation of prostacyclin at 13 h.

Because no degradation products of epoprostenol (e.g., 6-keto PGF₁₆) have been measured, we cannot exclude the possibility that part of the observed reduction of SPAP was due to systemic resorption of inhaled PGI₂. Yet, this possibility seems unlikely because systemic administration of PGI₂ elicits systemic hypotension and may impair pulmonary gas exchange.⁴–⁶ Systemic arterial pressure, however, remained unchanged in our patient, whereas gas exchange was improved with PGI₂ aerosol. As a possible mechanism of pulmonary selectivity of inhaled PGI₂, it may be proposed that inhaled PGI₂, after inhalation and deposition within the bronchoalveolar tree, diffuses to its target vessels in the pulmonary vasculature resulting in local vasodilation. Part of the highly concentrated, local PGI₂ then is absorbed by the systemic circulation. At the same time, however, it is considerably diluted by the large intravascular compartment, which probably makes its concentration in the systemic circulation insufficient.

PGI₂ concentration in the tracheal fluid approximated 1.6 µg/ml, which was about one-half of the concentration in the bronchoalveolar lavage fluid. Therefore, the clearance of PGI₂ from the tracheal fluid was rapid enough to maintain a therapeutic concentration in the alveolar compartment, which probably explains the good clinical response in our patient.

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its concentration fall below that necessary to cause systemic side effects.

PGI₂ was put into the nebulizer chamber at a concentration of 10 μg/ml. Because 6 ml was sufficient for approximately 5 h, it can be calculated that 12 μg PGI₂ left the nebulizer chamber per hour. Taking into account a rate of disappearance of fluid from the nebulizer chamber of approximately 1.2 ml/h and the newborn's weight, the amount of PGI₂ aerosolized per minute approximated 51 ng·kg⁻¹·min⁻¹. This dose is large compared to intravenous doses. However, because only a small fraction (less than 5%) of an aerosol is deposited in the alveoli of the lung during mechanical ventilation, the effective dose administered to our patient was much less than 51 ng·kg⁻¹·min⁻¹ (probably in the range of 2.5 ng·kg⁻¹·min⁻¹), explaining the absence of effects on central hemodynamics and gas exchange.

Possible side effects of PGI₂ include inhibition of platelet aggregation, thereby increasing the risk of intra- and postoperative bleeding. In our patient, significant bleeding was not observed.

Several technical problems were encountered during aerosolization. First, the Siemens 945 nebulizer delivers a peak inspiratory flow of as much as 7 l/min, even if operating in the low-flow mode. As a consequence, the nebulizer contributes considerably to the total minute volume. In the current case, hyperventilation and an increase of airway pressures during PGI₂ aerosol could be avoided only by reducing the minute volume delivered by the ventilator to minimum (0.3 l/min). With this setting, a critical reduction of body temperatures might occur in small children and newborns during long-term aerosolization, because a device to heat the gas delivered to the nebulizer is not available.

Furthermore, the nebulizer output may be too high in babies weighing less than 4 kg, and a modification of the set-up (e.g., the introduction of an outlet valve at the tube) would be required when treatment with PGI₂ aerosol is considered. Finally, endotracheal suction had to be performed frequently in our patient. This may be explained by the amount of fluid nebulized throughout the duration of therapy. Because intratracheal PGI₂ may cause an irritation of the airways, we cannot exclude, however, that part of the hypersecretion observed was due to a direct irritant effect of PGI₂ on the bronchial system.

In summary, the current case suggests that intratracheal administration of PGI₂ may decrease a critically high and otherwise untreatable pulmonary artery pressure in newborns without causing systemic hypotension or deterioration of gas exchange. Further studies to establish dose-response relationships and to define potential toxic effects of inhaled PGI₂ are being performed in our laboratory.

References

Dissection of the Posterior Pharynx Resulting in Acute Airway Obstruction

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TRAUMA to the structures within the nose, nasopharynx, and posterior pharynx is a potential complication from nasal intubation.1-5 We report a case in which insertion of a nasal “trumpet” airway resulted in dissection of the retropharyngeal space, causing acute airway obstruction.

Case Report

A 46-yr-old male patient with a history of a gunshot wound to the spine with subsequent paraplegia 18 yr before the current admission was admitted from a chronic nursing care facility for surgical management of sacral/perineal decubiti. Oral tracheal intubation, anesthesia, and surgery were uneventful. At the conclusion of the case, the anesthetic agents were discontinued, neuromuscular blockade was reversed, and the trachea was extubated. After extubation, the patient responded to loud verbal stimuli with a deep breath and transient eye-opening. However, the patient became somnolent with very shallow respirations in the absence of repeated stimuli. A nasal airway (Concord/Portex, SIMS, Keene, NH) was placed, resulting in transient improvement in alertness and respiratory rate (approximately 12 breaths/min), and the patient was transported to the postanesthesia care unit (PACU). Within 5 min of PACU arrival, the patient’s oxygen saturation (SpO2) had decreased to 88% with a simultaneous decrease in mental status to obtundation. Evaluation by the PACU staff demonstrated that chin-lift was required to maintain airway patency, and SpO2 increased to 100% with FIO2 at 1.0.

Fifteen minutes after PACU admission, SpO2 again decreased to 80%, and despite chin-lift and verbal stimulation, the respiratory rate remained low with minimal air movement by auscultation. Bag-valve-mask-assisted ventilation with 100% O2 was initiated to improve oxygenation and ventilation. The decreased mental status and hyperventilation did not improve with 0.4 mg of intravenous naloxone and continued bag-valve-mask ventilation. Peripheral nerve stimulation demonstrated intact train-of-four without fade and sustained tetany. However, because the blood gas revealed a pH of 6.97, PaCO2 of 111 mmHg, and a PaO2 of 157 mmHg, the decision was made to reintubate the trachea.

During direct laryngoscopy, a bullous lesion was noted in the posterior pharynx that obstructed the majority of the pharyngeal space. Palpation of this lesion demonstrated it to be an air-filled sac within the submucosal tissue. A quick survey of the neck and upper chest failed to demonstrate any subcutaneous emphysema. Because clinical suspicion included a pharyngeal dissection, suction was connected to the nasal airway with subsequent reduction and disappearance of the bullous lesion. Once the airway obstruction was reduced, the nasal airway was removed and the trachea was reintubated orally, with rapid improvement in clinical condition.

Examination by an otolaryngologist demonstrated that the nasal airway had dissected into the retropharyngeal position, with a small (1.5 cm diameter) residual submucosal bulla. The trachea was left intubated overnight and was extubated the next morning without incident. No antibiotics were given. Subsequent examination by the otolaryngology service demonstrated no scarring or other chronic airway difficulty.

Discussion

Nasal airways (so-called “trumpets”) are airway adjuncts commonly used in PACUs and in intensive care units. They are especially useful in patients with airway obstruction or emergent airway protection. We have encountered a case of retropharyngeal suction due to a bag-valve-mask, and the risks of this condition are disturbing. We were unable to find a similar posterior pharyngeal laceration.

Dissection of the pharynx can also occur well anterior to the larynx, with the trachea remaining intact.1-5 In the case of tissue laceration, the posterior neck is at risk of upper airway obstruction. The pharynx is divided into an upper and lower portion.