COMMENTARY: SIMPLE GASES AND COMPLEX SINGLE VENTRICLES

David L. Wessel, MD

Management of patients born with hypoplastic left heart syndrome or other complex single ventricle anatomy continues to challenge the technical skills of surgeons and the innovation and vigilance of those involved in perioperative care. Although mortality substantially improved after the introduction of palliative techniques for patients with single ventricle physiology who require complex aortic arch reconstruction,[1-3] the national experience still suggests less than optimal outcomes for many patients.[4]

Postoperative management

Common teaching has held that postoperative mortality and hemodynamic lability are attributable to myocardial dysfunction and the physiologic burden imposed by a shunt-dependent pulmonary circulation in parallel with systemic blood flow. Current treatment strategies have emphasized factors that may affect the balance between pulmonary and systemic blood flow.[5] Immediately after a Norwood operation pulmonary vascular resistance (PVR) may be transiently elevated, but soon decreases. Once PVR falls, treatment is aimed at raising resistance to blood flow through the lungs and redirecting cardiac output to the systemic circulation. High inspired concentration of oxygen, hyperventilation, alkalosis, systemic vasoconstriction, and anemia may exacerbate pulmonary vasodilation and are avoided. Therapies designed to raise PVR and thereby direct aortic blood flow to the systemic circulation have entailed lowering the inspired oxygen fraction (Fio_2) or allowing the arterial carbon dioxide tension ($Paco_2$) to rise. Further measures, such as ventilation with hypoxic gas mixtures or added carbon dioxide, have been advocated by some centers and have been intermittently embraced and abandoned by others. Validation of the effectiveness of these techniques to balance the pulmonary and systemic circulations has been difficult. Direct measurement of cardiac output or pulmonary artery pressure is not easy in the neonate with a shunt and univentricular heart. For the ratio of pulmonary-to-systemic blood flow (Qp/Qs) to be estimated, superior vena cava (not right atrial) blood must be sampled and estimates made of pulmonary venous oxygenation. Absence of an appropriate animal model with direct measurement of single ventricle physiology has hindered progress in this field.

Animal models

In the August and September issues of the Journal, two articles[6, 7] describe the use of animal models of single ventricle physiology to test the effects of changing concentrations of simple gases, oxygen, hydrogen (pH), carbon dioxide, and nitric oxide on such important physiologic variables as Qp/Qs, systemic and venous oxygenation, and oxygen delivery. Development of these animal models provides an experimental basis for testing hypotheses pertinent to this area of congenital heart disease.

Riordan and associates[7] describe a model using piglets that have undergone ligation of the pulmonary artery and disruption of the tricuspid valve after a balloon atrial septostomy and placement of a 6 mm polytetrafluoroethylene graft from the aorta to the pulmonary artery. The pulmonary and systemic hemodynamics were measured directly in response to hypoxic and hyperoxic gas mixtures along with increased inspired carbon dioxide and addition of positive end-expiratory pressure. PVR increased as Fio_2 was progressively lowered from 1.0 to 0.21. PVR also increased with positive end-expiratory pressure. Most important, the authors demonstrate that systemic arterial oxygen saturation itself is not predictive of improved systemic blood flow or oxygen delivery. Mixed venous oxygen saturation interpreted in conjunction with systemic ar-

From the Department of Cardiology, Children's Hospital, Harvard Medical School, Boston, Mass.

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Address for reprints: David L. Wessel, M.D., Cardiac ICU Office, Farley 653, Department of Cardiology, Children's Hospital, 300 Longwood Ave., Boston, MA 02115.

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terial oxygen saturation is a more reliable predictor of Qp/Qs and optimal oxygen delivery. A Qp/Qs of 0.7 appeared to be the ideal ratio in this model.

Readers looking for therapeutic recipes based on this model will be disappointed. Surprisingly, the "best" Fio_2 was 0.5, not 0.21, and PVR did not rise substantially with inhaled carbon dioxide until the pH was less than 6.9. These data are not consistent with previously published animal work[8] or with postoperative studies in infants, in whom the pulmonary vasculature seems to be sensitive to modest changes in pH.[9] These differences probably relate to limitations of the model, because it is not entirely analogous to the neonate recovering from a Norwood operation. The model retains some features of two-ventricle physiology; the right ventricle fills and ejects a variable volume back through the tricuspid valve. Complex ventricular interaction may vary according to the amount of tricuspid regurgitation and the pressure developed in the right ventricle. Although the shunt diameter (6 mm) is large, it does not result in either a substantial rise in pulmonary artery pressure or any significant increase in Qp/Qs (maximal average Qp/Qs 1.2). Furthermore, it is not a model that incorporates any effects of cardiopulmonary bypass, which may have a dramatic impact on the sensitivity and reactivity of the pulmonary vasculature in the postoperative period.[10] In many ways the model more accurately reflects the physiologic condition observed in patients with pulmonary atresia and intact ventricular septum who are dependent on a patent ductus arteriosus. However, this work focuses on the importance of monitoring mixed venous oxygen saturation, arteriovenous oxygen difference, and on the concept that diminishing Qp/Qs is not always associated with improved oxygen delivery. This is ultimately the objective of our therapeutic maneuvers.

Reddy and colleagues[6] address the limitations of the late postnatal animal model by creating an in utero model of single ventricle physiology. A Damus-Kaye-Stansel procedure was performed in fetal lambs and a systemic–pulmonary artery shunt was created. The fetus was then allowed to develop and be delivered spontaneously at term. After birth, the pulmonary and systemic hemodynamic response to interventions were measured directly, both before and after the lamb was supported by cardiopulmonary bypass and deep hypothermic circulatory arrest. The results support the clinical practice of manipulating PVR by altering the alveolar concentration of simple gases. Hypoxic gas mixtures and respiratory acidosis were potent pulmonary vasoconstrictors that redirected cardiac output away from the pulmonary bed and into the systemic circulation. Nitric oxide and high Fio_2 were pulmonary vasodilators. In this model, the respiratory acidosis derived from breathing 5% carbon dioxide (carbon dioxide tension 55 mm Hg, pH 7.25) imposed marked changes in pulmonary vascular resistance and Qp/Qs.

The work by Reddy and associates[6] represents remarkable technical accomplishment. It provides a physiologically relevant animal model of single ventricle physiology that can account for the transitional physiology of the newborn infant and the effects of cardiopulmonary bypass. Again, the model is not strictly characteristic of single ventricle anatomy or physiology. Although there is common mixing of systemic and pulmonary venous blood, both right and left ventricles freely eject into the aorta where mixing occurs and from which the shunt-dependent pulmonary circulation is derived. Inasmuch as the animal displays low, not high, PVR, it is not the most relevant physiologic model to investigate pulmonary vasodilators. However, if after fetal surgery and birth the animal model can be maintained for some weeks and develop more of the pathologic features of elevated PVR, then it will provide an even more important investigational tool to study the influence of vasodilators on PVR before and after cardiopulmonary bypass.

Manipulating gases

Studies of Reddy and coworkers along with Riordan and associates corroborate the clinical practice of manipulating simple alveolar gases to achieve optimal balance between pulmonary and systemic vascular resistance in patients with complex single ventricles. Alveolar hypoxia, respiratory acidosis, and positive end-expiratory pressure raise PVR and can be used to advantage to optimize oxygen delivery. Oxygen and nitric oxide relax the constricted pulmonary vasculature and may augment pulmonary blood flow. The appropriate use of animal models of single ventricle physiology will allow us to pose and accurately test hypotheses. A number of relevant questions come to mind. Is there any hemodynamic advantage in allowing carbon dioxide to be inspired while maintaining a high minute ventilation strategy? Is the simpler alternative, to diminish the minute ventilation and allow $Paco_2$ to rise, equally effective? Both animal and human infant studies after cardiopulmonary bypass indicate

that it is pH and not $Paco_2$ that is the primary determinant of pulmonary vascular resistance.[9] Animal models will permit more precise testing of this principle in the setting of single ventricle physiology. The models also allow investigators to explore how vasoconstricting factors influence PVR after cardiopulmonary bypass and what treatment is most effective?

Toxicity

We must be cognizant that like any therapeutic agent, all of these simple gases have dose-related toxicities. High Fio_2 has well-defined pulmonary toxicity that may appear in a matter of days or even hours after exposure. The use of low Fio_2 (below room air concentrations) to raise PVR transiently and stabilize patients is both counterintuitive and relatively uncommon therapy in clinical medicine. Whether iatrogenically induced or as part of a pathologic process, alveolar hypoxia can be life threatening when aggravated by unexpected hypoventilation. A mechanically ventilated and sedated patient receiving an Fio_2 less than 0.21 has little safety margin for dangerous hypoxemia even in the most intensively monitored environments. Also, recall that excellent animal models of long-term pulmonary hypertension are produced by relatively brief exposure to hypoxic gas. A newborn infant breathing hypoxic gas mixtures in the preoperative period of stabilization may have a favorable response by raising PVR and diminishing pulmonary blood flow. However, if this treatment is prolonged during preparation for reconstructive or transplantation surgery, the caretakers may be frustrated by subsequent elevation in PVR that persists during and after weaning from cardiopulmonary bypass.

In centers where neonates are allowed to awaken and breath spontaneously during the immediate postoperative period, pulmonary blood flow may become excessive and will further stimulate hyperventilation and respiratory alkalosis. Adding carbon dioxide to the inspired gas may indeed reverse this trend toward respiratory alkalosis and stabilize the relative balance of the pulmonary and systemic circulations if the forces that drive minute ventilation are suppressed with agents for sedation or analgesia. However, the metabolic cost of carbon dioxide breathing in an awakening child given little analgesia, may discourage widespread application of this technique until the physiologic advantage over conventional means of controlling alveolar ventilation and $Paco_2$ has been demonstrated. This is especially true in unsedated, preoperative patients, in whom factors controlling respiration during carbon dioxide breathing may permit minimal change of $Paco_2$ but substantially increase the respiratory rate and work of breathing. Inhaled nitric oxide may also have toxicitities, especially when used at higher doses. Methemoglobinemia, pulmonary toxicity related to nitrogen dioxide exposure, and formation of peroxynitrite in the lung require further investigation.

The simplicity of these ubiquitous gases is deceiving when applied to complex pathophysiologic conditions of infants with single ventricles. The development of animal models can enhance our ability to investigate important questions and will focus attention on more appropriate variables to monitor in the postoperative period.

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