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How do you study blue?

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Cyanosis is perhaps one of the most impressive signs one can note on physical examination. The ability of the human body to adapt to function satisfactorily—well in many cases—in the setting of an arterial oxygen saturation of under 80% is remarkable. Since cyanosis is oftentimes a secondary phenomenon of congenital heart disease and since congenital heart disease producing cyanosis will usually require cardiac surgery, it seems prudent to evaluate the impact of cardiopulmonary bypass on the heart that has been subject to low oxygen tension for a prolonged period. This is certainly not a new concept or subject of experimentation as there are many studies reported in the literature using different models of acute and chronic hypoxemia in an attempt at studying "blue." There are many variables in these studies, including the model used to produce hypoxemia, the age at which it commenced, the duration before experimental study, the consistency of the hypoxemia, the animal species, and the precise nature of the experimental design evaluating myocardial response to the setting of cardiac surgery. There is conflicting evidence regarding the impact of chronic cyanosis on outcome from cardiac surgery, although most agree that it does have a deleterious effect overall. On the surface it seems counterintuitive, but there is a growing body of evidence that oxygen itself might be an underlying toxin. Ideally, cyanosis should be evaluated in isolation absent any other factors. There are basically two general experimental models. One is to place an animal in a low oxygen tension environment for a prolonged period and then perform the studies. The other is to create a right-to-left shunt of significant magnitude as to produce low systemic oxygen saturations. Another issue in designing experimental models has to do with timing. Should the hypoxemia begin soon after birth, before maturation of the myocardium, or does it make any difference? How long should the animals remain hypoxic before study?

There are problems inherent in both general types of experimental models and with timing. It is very difficult to keep an animal in a low oxygen tension environment continuously from birth onward. These animals will need to nurse for the first few days or weeks of life, and it is unlikely that the mother can be safely kept in this environment. Bringing the animals out several times per day likely will negate the impact of the hypoxic environment for the replication of a clinically relevant state of cyanosis. Creating surgical shunts is a high-risk operation in newly born animals and introduces potential hemodynamic factors that might confound the experiments where the control animals have normal hearts. It is not completely clear what constitutes complete maturation of the myocardium and when it occurs in any one animal species. Furthermore, children with congenital heart disease—particularly cyanotic congenital heart disease—may not "mature" at the same time as children with normal hearts.

The study from Corno and associates[1] is another attempt at evaluating the impact of reoxygenation on the myocardium of chronically hypoxic Sprague-Dawley rats. They found evidence of deleterious effects of the reoxygenation process on myocardial function and metabolism. This experiment is fairly simple and straightforward. Animals are kept hypoxic continuously beginning at 5 weeks of life, even while the hearts are stabilized on the Langendorff preparation before seeing hyperoxic blood. These investigators have done a meticulous job of maintaining a strictly hypoxic environment for their experimental animals in an effort to eliminate any effect of even brief exposure to normoxia. Changes in systolic and diastolic function of the chronically hypoxic hearts occur precisely when exposed to hyperoxic

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perfusion. The obvious implication of oxygen-derived free radicals in the pathogenesis of findings is compelling.

Unfortunately, there are significant confounding variables present in their hypoxic group of animals: They were 5 weeks of age when first exposed to the hypoxic environment; a hypoxic environment is not exactly the same as a congenital cardiac lesion producing cyanosis; and the hypoxic animals were all starving. The authors appropriately point out examples of congenital heart lesions that do not produce cyanosis at birth only to occur later during infancy, that is, tetralogy of Fallot. The goal of a set of experiments, however, is to design an experimental model that mimics the clinical situation, not the reverse. There is excellent documentation of significantly less nutritional intake and weight loss of the hypoxic group of animals. Whereas children with cyanotic congenital heart disease may not gain weight well, they generally do not lose weight. Starvation may result in decreased ventricular function as evidenced both experimentally[2] and clinically in patients with anorexia nervosa.[3] Although the likelihood of starvation playing a major role in the changes noted with exposure to oxygen seems small, the marked difference between the two groups concerning weight and nutritional intake is compelling enough to raise questions.

Despite the shortcomings in experimental design, the authors provide thought-provoking information that will undoubtedly stimulate further research to find answers to questions left behind, the main one concerning the strategy for reoxygenating the chronically hypoxic myocardium. Eventually we have to re-establish normal arterial oxygen saturation in cyanotic patients, don't we? For now, I suppose one might attach a label to the big green canister: "Caution: the administration of oxygen MAY be hazardous to your health."

References

1. Corno AF, Milano G, Samaja M, Tozzi P, von Segesser LK. Chronic hypoxia: a model for cyanotic congenital heart defects. *J Thorac Cardiovasc Surg.* 2002;124:105-12.
2. Freund HR, Holroyde J. Cardiac function during protein malnutrition and refeeding in the isolated rat heart. *J Parenteral Enteral Nutrition.* 1986;10:470-3.
3. Moodie DS. Anorexia and the heart. Results of studies to assess effects. *Postgrad Med.* 1987;81:46-8.