

■ Do Decreases in Hemoglobin Impair Cognitive Function and Memory? Weiskopf *et al.* (page 1646)

Although erythrocytes are transfused to prevent or treat inadequate oxygen delivery resulting from insufficient hemoglobin concentration, specific indications for transfusion have yet to be defined. Weiskopf *et al.* used nine healthy, paid volunteers to assess whether acute decrease of hemoglobin concentration to 5 g/dl would affect cerebral function.

Reaction time tests were given in sessions before the test day to familiarize patients with the procedures and to minimize postbaseline improvements in performance caused by practice effects. On the test day, using local anesthesia, two peripheral venous cannulae were inserted in each participant. Subjects used hand-held controllers to complete baseline neurobehavioral and memory tests before the removal of any blood. Tests were repeated 10–15 min after producing isovolemic anemia by removing blood into collection bags, to hemoglobin concentrations of 7, 6, and 5 g/dl. The subjects' platelet rich plasma and 5% human serum albumen were infused intravenously at the same time that blood was withdrawn. Subjects also completed the same test procedures (including insertion of venous cannulae) given at the same time of day on separate "control study" days.

Acute reduction of hemoglobin concentration to 7 g/dl did not produce changes in reaction times or error rates, compared with data at baseline hemoglobin concentration of 14 g/dl. Subjects' reaction time for horizontal addition and digit-symbol substitution test increased at a hemoglobin concentration of 6 g/dl, but error rate did not. At a hemoglobin concentration of 5 g/dl, immediate and delayed memory was degraded. All decrements in memory and reaction time were reversed with restoration of hemoglobin to 7 g/dl. After transfusion the next morning of all autologous erythrocytes, test results again were at baseline levels. Despite its small sample size and the fact that volunteers were not blinded to the study day, the model described here could prove useful to test the effectiveness of erythrocytes, oxygen therapeutics, or other treatments for acute anemia.

■ Is Sildenafil Indicated in Treatment of Pulmonary Hypertension? Weimann *et al.* (page 1702) and Bigatello *et al.* (page 1827)

Two articles in this issue of ANESTHESIOLOGY point to increasing evidence that sildenafil may offer promise as a

treatment for pulmonary hypertension. The first article details a study of the pulmonary and systemic vasodilator properties of sildenafil in an awake ovine model. The second article is a case report of a woman with severe hypoxemia caused by pulmonary hypertension, in whom sildenafil was used in association with inhaled nitric oxide (NO) to reverse pulmonary hypertension and venous blood shunting through a patent foramen ovale.

After baseline hemodynamic measurements, Weimann *et al.* induced pulmonary hypertension in Suffolk lambs by intravenous infusion of U46619. In one protocol, five lambs were administered 12.5, 25, and 50 mg sildenafil *via* nasogastric tubes at 15-min intervals, and the hemodynamic measurements were again obtained. In the second protocol, the team studied the effects of sildenafil and zaprinast administration on pulmonary vasodilation produced by inhaled NO (2.5, 10, and 40 ppm) during U46619-induced pulmonary hypertension. In the third set of experiments, five lambs were administered an intravenous dose of the NO synthase inhibitor L-NAME after pulmonary vasodilation induced by 50 mg sildenafil.

Results of the first set of experiments revealed that cumulative doses of sildenafil decreased the pulmonary artery pressure and pulmonary vascular resistance in a dose-response fashion. Systemic arterial pressure decreased 12%, but only after administration of the maximum cumulative sildenafil dose. Neither sildenafil nor zaprinast, a second phosphodiesterase 5 (PDE5) inhibitor, augmented the ability of inhaled NO to promote pulmonary vasodilation. However, zaprinast prolonged the duration of pulmonary vasodilation after NO inhalation was discontinued. Finally, in the third protocol, infusion of L-NAME abolished the pulmonary vasodilation induced by sildenafil. The researchers conclude that at low doses sildenafil, the new PDE5 inhibitor, approved to treat erectile dysfunction, is a selective pulmonary vasodilator in awake lambs in whom pulmonary hypertension has been induced with U46619. This vasodilation appears to be mediated by augmentation of the endogenous NO cyclic guanosine monophosphate (cGMP) signal transduction system.

The second article details the case of a 52-yr-old woman with severe interstitial pulmonary fibrosis, Crohn disease, and previous pulmonary thromboembolism in whom acute respiratory failure developed while being evaluated for a living-related-donor lung transplant. An indocyanine dilution study also showed a pattern of early dye recirculation compatible with a right-

to-left intracardiac shunt. Familiar with the use of sildenafil and other PDE5 inhibitors in investigational protocols of inhaled NO in patients with acute respiratory distress syndrome, Bigatello *et al.* elected to administer inhaled NO in conjunction with oral sildenafil and obtained consent to do so. Sildenafil, 25 mg, was administered *via* a nasogastric tube after the pulmonary artery (PA) pressure returned to baseline values after the use of inhaled 5 ppm NO. Thirty minutes later, administration of inhaled NO was resumed and further decreased PA pressure to 40 mmHg. At that point, a subsequent indocyanine dilution study showed a marked reduction of the right-to-left intracardiac shunt. The patient's partial pressure of arterial oxygen ( $Pa_{O_2}$ ) increased by 76% with NO alone, by 40% with sildenafil alone, and by 112% with a combination of the two. Inhaled NO was continued and

a second dose of sildenafil was administered 12 h later. However, the patient continued to deteriorate because of a worsening lung infection and progression of parenchymal infiltrates. Ten days later, she was removed from the transplant list and died. Despite her death, the case has important implications because of the demonstrated enhanced action of NO by administration of small doses of sildenafil. The authors caution that these findings should not be extrapolated to patients with hypoxemia from intrapulmonary shunting, in whom sildenafil might increase shunting and worsen  $Pa_{O_2}$ . In addition, use of sildenafil would be absolutely contraindicated in patients with ongoing administration of systemic nitrovasodilators, such as nitroglycerin and sodium nitroprusside.

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