were measured by radioimmunoassay (Amersham RPA525; Amersham International Ltd., Little Chalfont, U.K.). Arterial cGMP concentrations and the mean pulmonary arterial-systemic arterial pressure ratios, recorded with and without INO, are shown in Fig. 1.

Our results show that although the cGMP concentrations increased with the commencement of INO, levels appeared to fall below baseline when attempts were made to wean the patient from INO during the first 6 days of its administration. After 6 days of INO therapy, discontinuation of the INO was no longer associated with a fall in cGMP concentrations; this coincided with clinical resolution of the pulmonary hypertension, suggesting that spontaneous recovery of endogenous NO production had occurred. The patient was extubated 1 day later and was discharged home after 4 more days.

We believe that these results support the hypothesis that exogenous INO suppresses endogenous NO production after cardiopulmonary bypass when known reversible endothelial damage has occurred.⁴ Exogenous NO has been shown to suppress endogenous NO production in the rat cerebellum by inhibiting nitric oxide synthetase, the rate-limiting enzyme of NO production.⁵ Our findings indicate that similar changes may be occurring in the pulmonary endothelium. An alternative explanation could be that the falling concentrations of cGMP are the result of disease of the pulmonary endothelium, which is ongoing and was itself the initial cause of the pulmonary hypertension.

In conclusion, exogenous INO may suppress endogenous NO production by the pulmonary endothelium during the early course of its administration. This has a number of important clinical implications. First, regular

reverse dose-response studies should be conducted to allow the patient to be gradually weaned from INO as clinical improvement and endothelial recovery progress, because rebound pulmonary hypertension may occur if INO treatment is discontinued abruptly. Second, patients already receiving INO who require transfer to tertiary centers may require the INO administration to be continued during the transport. Finally, although prophylactic INO administration may be considered in patients at high risk, its administration may lengthen the time required for mechanical ventilation.

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EVANS BLUE AND GENTIAN VIOLET: ALTERNATIVES TO METHYLENE BLUE AS A SURGICAL MARKER DYE

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Dyes, such as methylene blue, are used during vascular surgery to aid in the visualization and orientation of the blood vessel. Although methylene blue dye is believed to

be innocuous, we¹ recently demonstrated that extravascular application of 1% methylene blue impairs both endothelium-dependent and endothelium-independent vasorelaxation. The present study investigated Evans blue and gentian violet as alternative surgical marker dyes to methylene blue.

Human saphenous veins were cut into 2 to 4 mm rings, carefully swabbed with 0.5% Evans blue, 1.0% gentian violet, or Krebs buffer, and incubated in 20 ml of buffer at 25°C for 45 minutes. The vascular rings were then suspended in 10 ml tissue baths containing Krebs buffer, and dose-response curves to acetylcholine, isoproterenol, verapamil, and sodium nitroprusside were performed as previously described.¹

Vascular rings were assayed in duplicate and averaged

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Fig. 1. The effect of Evans blue (EB) exposure on vasodilator activity in saphenous veins. Control ring preparations were swabbed with Krebs buffer. Responses are expressed as a percentage of phenylephrine (10^{-5} mol/L).

to yield a single n value. All statistical analyses were performed with the n values representing the number of patients. Differences were assayed by a one-way analysis of variance followed by a Bonferroni t test for multiple comparisons. All data are presented as the mean $\pm$ standard error of the mean. Only differences with a p value < 0.05 were deemed as statistically significant.

Potassium chloride (70 mmol/L) produced a contraction of 1.45 ± 0.36 gm in control rings, which was not significantly different from that observed in rings subjected to Evans blue (1.92 ± 0.48 gm) or gentian violet (1.81 ± 0.40 gm). Phenylephrine (10^{-5} mol/L) also produced a comparable constriction (1.73 ± 0.52 gm), which was unaffected by exposure to either Evans blue or gentian violet-treated tissue.

Acetylcholine, which assessed endothelium-dependent responses, produced a dose-dependent vasodilation with the nadir at $-54\% \pm 11\%$, which was unaffected by exposure to Evans blue (Fig. 1, A). Sodium nitroprusside was used to assess endothelium-independent vasodilation. As seen in Fig. 1, B, 100% relaxation was achieved in response to sodium nitroprusside in control vein segments and segments exposed to Evans blue. Verapamil was used to assess calcium-mediated responses. As seen in Fig. 1, C, no significant differences were noted between control vessels and those treated with Evans blue. Fig. 1, D, shows

Fig. 2. The effect of gentian violet (GV) exposure on vasodilator activity in saphenous veins. Control ring preparations were swabbed with Krebs buffer. Responses are expressed as a percentage of phenylephrine (10^{-5} mol/L). * $p < 0.05$.

that the vasodilatory responses to isoproterenol mediated through β_2 -adrenergic receptors was unaffected by Evans blue treatment.

Gentian violet treatment did not affect the vasodilatory responses to acetylcholine (Fig. 2, A), verapamil (Fig. 2, C), or isoproterenol (Fig. 2, D). However, gentian violet inhibited the vasodilatory response to sodium nitroprusside, as seen in panel B of Fig. 2.

The present study demonstrates that Evans blue does not impair either endothelium-dependent or endothelium-independent vasodilation. Alternatively, gentian violet impaired only the endothelial response to sodium nitroprusside, and this degree of impairment was greater than that previously reported with the use of methylene blue dye.¹

Methylene blue dye has several actions that could adversely affect vascular reactivity, including inhibition of soluble guanylate cyclase² and production of superoxide.³

The pharmacologic actions of Evans blue and gentian violet have not been studied extensively and thus remain relatively poorly understood. Gentian violet is best known as a topical antimicrobial agent that irreversibly binds microbial deoxyribonucleic acid and directly inhibits replication.⁴ Evans blue is a biologic stain whose pharmacologic effects have not been extensively studied, but it is

commonly used as a diagnostic agent for the determination of plasma volume.⁵

The reason for inhibition of the sodium nitroprusside response by gentian violet is unclear. Gentian violet is metabolized to a reactive intermediate or free radical that could act at the vascular smooth muscle to inhibit the response. However, this is unlikely inasmuch as this mechanism would also interfere with the acetylcholine-mediated vasodilation. A more plausible explanation would be the formation of a reactive intermediate that interacts directly with the sodium nitroprusside molecule.

In conclusion, although methylene blue has been used as a marker dye, our studies suggest that it is inappropriate for marking vascular grafts. Evans blue did not adversely affect vasodilation to any agent and thus could be used as an alternative to methylene blue without fear of affecting graft reactivity. Gentian violet also appears to be a better alternate to methylene blue. However, we did observe a decrease in endothelium-independent vasodilation, a factor that should be considered when this agent is used.

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EROSION OF INLET CANNULA OF LEFT VENTRICULAR ASSIST DEVICE MANIFESTED AS INNOCUOUS BLEEDING IN STABLE PATIENT: LESSONS LEARNED IN PREVENTION OF CATASTROPHIC CONSEQUENCES

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We present the case of a patient who underwent implantation of a left ventricular assist device (LVAD) as a bridge to transplantation and subsequently had disruption of the Dacron inflow graft of the pump. Surgical investigation at the development of expanding hematoma and drive line bleeding resulted in entrainment of air into the pump, massive air embolus, and subsequent death of the patient. We believe that this case demonstrates the need for angiographic definition of bleeding associated with a completely implanted LVAD before surgical exploration, as well as specific surgical strategies to avoid air embolus.

A 64-year-old man was admitted to our institution with

a history of progressive cardiac failure. He had had aortic valve replacement with a porcine prosthesis and implantation of a pacemaker 7 years before this admission. An extensive evaluation indicated end-stage dilated cardiomyopathy. The patient was activated on the waiting list for cardiac transplantation. Despite a regimen of dopamine, dobutamine, amrinone, and intravenous diuretics, the patient had progressive symptoms of cardiac failure. An intraaortic balloon pump was inserted, with only marginal improvement in hemodynamics. Despite this aggressive conventional management, the patient had progressive deterioration and thus underwent preperitoneal implantation^{1,2} of the Thermo Cardiosystems Incorporated (TCI) Heartmate LVAD (Woburn, Mass.) 2 months after admission. The initial postoperative course was uneventful except for transient failure of the right side of the heart, responsive to dopamine, during the first postoperative week and thoracentesis on two occasions in the early postoperative course for recurrent left pleural effusion with drainage on each occasion of approximately 1 L of serous fluid. On postoperative day 32 the patient was evaluated on an emergency basis for brisk bleeding around the drive line site, and physical examination confirmed an expanding collection of fluid within the preperitoneal implantation pocket. The patient was promptly taken to the operating room for suspected bleeding within the preperitoneal pocket. The preperito-

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