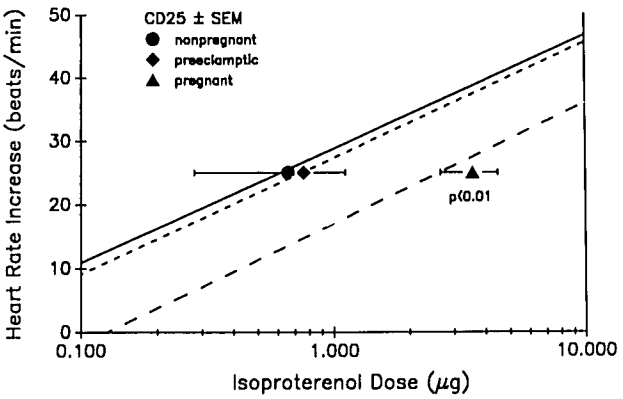

FIG. 1. The chronotropic response to isoproterenol in pre-eclamptic pregnant, healthy pregnant, and nonpregnant women. Mean regression lines were interpolated from individual dose-response curves. Data for healthy pregnant and nonpregnant women were obtained previously. The CD25 in pre-eclamptic patients (0.8 μg) was significantly less than the CD25 in healthy pregnant patients (2.6 μg) but did not differ from the CD25 in healthy nonpregnant patients (0.7 μg). The slopes of the mean regression lines did not differ significantly.

fetal heart rate (FHR) tracings were normal (FHR >120 and <160 beats per min with normal long-term variability, 5–10 beats per min short-term variability, and no decelerations). While participants rested quietly in a supine position with left uterine displacement, we continuously infused 0.9% saline. We recorded BP every minute and continuously recorded maternal heart rate (MHR), FHR, and uterine contractions.

After recording baseline measurements, we administered incremental bolus iv injections of isoproterenol (0, 0.1, 0.25, 0.5, 1, and 2 μg) until the MHR increased 25 beats per min above baseline (CD25) for ≥ 15 s. We waited until 5 min after the MHR had returned to baseline before injecting the next dose. As in our previous study, all drugs were prepared and administered by the same two authors (BLL and CAD). An obstetrician (MJD) analyzed the FHR tracings for signs of fetal distress (short-term FHR variability ≤ 5 beats per min, > 1 late deceleration, or a change in baseline FHR to ≤ 120 or ≥ 160 beats/min).

We estimated each patient's CD25 by log interpolating between the neighboring isoproterenol doses. We compared the group geometric mean CD25 with CD25 values previously obtained for healthy term pregnant and nonpregnant women using Student's *t* test with Bonferroni correction.[1] One-way ANOVA for repeated measures and Dunnett's test determined the significance of BP changes following the isoproterenol doses that surrounded the CD25. $P < 0.05$ indicated significance.

The mean CD25 in preeclamptic patients (0.8 μg with a coefficient of variation of 102%) differed significantly from the CD25 previously determined for healthy term pregnant patients (3.6 μg with a coefficient of variation of 51%) ($P < 0.01$) but did not differ from the CD25 previously determined for healthy nonpregnant women (0.7 μg with a coefficient of variation of 130%) (fig. 1). Systolic and diastolic BP and FHR patterns did not change.

The fivefold difference in the chronotropic responsiveness of pre-eclamptic and healthy pregnant women may complicate efforts to design a chronotropic epidural anesthesia test dose that is both safe and effective in all parturients. Isoproterenol 5 μg safely and effectively indicates iv injection in healthy pregnant women.[3] However, isoproterenol 5 μg, which is 1.4 times the CD25 for healthy term pregnant women, is 6.25 times the CD25 for pre-eclamptic term pregnant women. Isoproterenol 5 μg is more likely to cause hypotension or exaggerated tachycardia in a pre-eclamptic woman than in a healthy pregnant woman.

Of course, isoproterenol cannot yet be used in an epidural anesthesia test dose even in healthy term pregnant women, for insufficient animal neurotoxicology data exist.

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Propofol Causes Cardiovascular Depression. I.

To the Editor:—In the otherwise exhaustive and excellent review of the new iv anesthetic propofol, Sebel and Lowdon[1] confused at least this reader about the cardiovascular effects of the drug. As one of the FDAs consultants, particularly on the cardiovascular effects of propofol, I have had the opportunity to review both the company's studies and the published literature in some detail. In my opinion, all of the studies that have looked at the effect of propofol on cardiovascular dynamics in a variety of populations have demonstrated that propofol produces cardiovascular depression that is very similar to that of the iv barbiturates (thiopental and methohexital). When differences have been demonstrated, propofol has almost universally been more depressant to the cardiovascular system than are the iv barbiturate-induction agents. Although Sebel and Lowdon note that cardiac output and arterial pressure were significantly and markedly decreased in a number of studies, several of their statements, I believe, may be misleading.

For instance, the statement that, "The cardiovascular effects of pro-

pofol are manifested as systemic hypotension resulting from a reduction in systemic vascular resistance. Cardiac output is not consistently affected," is definitely misleading. In most of the studies where cardiac output was "not consistently affected," there was significant respiratory acidosis. In particular, the study of Claeys *et al.*,[2] which Sebel and Lowdon repeatedly refer to, was conducted during spontaneous ventilation during propofol infusion with significant respiratory acidosis. Even the potent inhalation anesthetics show minimal cardiovascular effects when patients are allowed to breathe spontaneously and develop respiratory acidosis.[3-5] Stephan *et al.*[6] demonstrated after induction with 2 mg/kg propofol, 0.1 mg/kg pancuronium, and tracheal intubation that hypercarbia (Pa_{CO_2} = 50 mmHg) resulted in no depression of cardiac output, while normocarbia (Pa_{CO_2} = 40 mmHg) and hypocarbia (Pa_{CO_2} = 30 mmHg) produced significant decreases in cardiac output. Thus, if patient's lungs are ventilated during propofol anesthesia (and as Sebel and Lowdon point out, the drug is a potent respiratory depressant), then the usual cardiovascular response in almost all studies has been a decrease in cardiac output.

They also state that in the studies from Prys-Roberts' group,[7,8] "cardiac output decreased but the decrease was significant in only two studies and only during steady-state anesthesia before surgical stimulation." In all of the Prys-Roberts' studies, surgical stimulation resulted in an increase in arterial pressure, but with either no change in the significantly decreased cardiac output or further decrease. Although Sebel and Lowdon do not comment on the effect of propofol on cardiac output and stroke volume in the study by Larsen *et al.*[9] this group also showed major effects on cardiac output produced by propofol anesthesia. Again, I think they are misleading when they compare the study of Claeys *et al.*[2] to that by Larsen *et al.*,[9] both as far as the patient population is concerned and the conditions of the study.

It is important when a drug is introduced that the practitioner be well aware of the cardiovascular effects. In the case of propofol, if anything, the cardiovascular effects are more pronounced than those of the usual iv anesthetics we are accustomed to using and in patients with cardiovascular compromise, the drug must be carefully titrated to effect.

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Propofol Causes Cardiovascular Depression. II.

To the Editor:—We disagree with the description of cardiovascular effects of propofol recently summarized by Sebel and Lowdon.[1] While there is no doubt that propofol causes a significant decrease in arterial blood pressure by focusing on the results reported by Monk *et al.*,[2] Coates *et al.*,[3] and Claeys *et al.*,[4] the authors seem to accept the conclusion that the observed decrease in arterial blood pressure following administration of propofol is caused by a decrease in systemic vascular resistance without changes in cardiac output or stroke volume.

In fact, the reported effects of propofol on the cardiovascular system are conflicting. Some authors describe a decrease in systemic vascular resistance with no change in cardiac output,[4] whereas others report a decrease in cardiac output with an unchanged systemic vascular resistance.[5-7] Furthermore, a negative inotropic action has been demonstrated in humans[5,8] and in dogs.[9] The observed decrease in systemic vascular resistance in the experiments by Claeys *et al.*[4] and Monk *et al.*[2] may not necessarily reflect an effect of propofol but may be the result of a concomitant increase in Pa_{CO_2} in their patients.[7] Cullen *et al.*[10] have shown that an increase in Pa_{CO_2} causes an increase in cardiac output, stroke volume, and a decrease in systemic vascular resistance.[10]

Finally, we are concerned with the authors statement that, "the combination of propofol and opioids may constitute safer anesthesia practice." Although such therapy may blunt the sympathetic response to laryngoscopy and tracheal intubation, it will also enhance cardiovascular depression and lead to even greater hypotension.[5,8] This potentiation may in part be explained by the higher plasma propofol concentrations that occur if propofol is used together with opioids.[11] Furthermore, bradycardia as seen in some patients[12] after the administration of propofol is more likely to develop with the additional cholinergic action of opioids.

In conclusion, we think that the cardiovascular effects of propofol are profound, unpredictable in their severity, and not easily treated