end-diastolic volume (LVEDV) during positive-pressure ventilation with PEEP. Ventilation with PEEP decreases CO when LVEDV is low, while at higher LVEDV, PEEP may increase CO by reducing left ventricular afterload.[2,3] In fact, Venus *et al.* noted an increase in CO in the group of hydrated swine during CMV with PEEP.[1]

As demonstrated by Venus *et al.*, the hemodynamic alterations occurring during PEEP activate compensatory hormonal mechanisms (ADH, epinephrine, norepinephrine, and renin) in an attempt to maintain MAP.[1] Since CO decreased more than MAP in the normovolemic group of swine during ventilation with CMV with PEEP, systemic vascular resistance (SVR) must have increased. Although these hormonal mechanisms along with activation of the sympathetic nervous system are effective in maintaining adequate circulation by increasing SVR during CMV with PEEP, it seems likely that they are at least in part responsible for the alteration in renal function (decreased urine flow and creatinine, free water, and osmolar clearance).[4] Therefore, sufficient hydration results in normalization of left ventricular end-diastolic volume and cardiovascular hemodynamics so that compensatory hormonal and neural responses are not activated and renal function remains unaltered. If LVEDV rather than $LVEDP_{TM}$ were kept constant after initiation of CMV with PEEP, would the same alteration of cardiovascular and renal function have occurred?

After all this, there is one final caveat. The study by Venus *et al.*, as well as most others assessing the effects of CMV with PEEP, was performed using animals with normal lungs and pulmonary vasculature. Since most patients ventilated with PEEP have significant pulmonary pathology, one must be careful judging the clinical applicability of this data.

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In reply:—Dr. Berry correctly points out that transmural left ventricular end-diastolic pressure ($LVEDP_{TM}$) is not an accurate measure of left ventricular end-diastolic volume (LVDV) in the face of controlled mechanical ventilation (CMV) and positive end-expiratory pressure (PEEP). With this we concur. The purpose of this study[1] was to confirm our clinical impression that aggressive hydration can obviate the changes in renal function that frequently accompanies the application of CMV + PEEP. By study design, the animals in the normovolemic group received an average of 25 ml/kg lactated Ringer's solution while the hydrated group received 65 ml/kg. Since the degree of hydration was the only difference between the two groups, we concluded that hydration would prevent activation of compensatory hormonal mechanism by maintaining normal cardiac output and perfusion pressure. We agree with Dr. Berry that in normovolemic animals the decrease in CO and BP was likely due to decreased venous return, which was not reflected in $LVEDP_{TM}$ measurement because of changes in left ventricular compliance. However, the observed improvement in CO in the hydrated group was presumably due to optimization of ventricular filling rather than decrease in afterload, since the latter mechanism is thought to operate only in conjunction with ventricular dysfunction.[2] Our swine exhibited improved CO during CMV + PEEP when they were hydrated with lactated Ringer's solution. Therefore, their ventricular function was normal.

Can these data obtained from animals with normal lungs be applied to the management of patients suffering from adult respiratory distress syndrome (ARDS) with noncompliant lungs? Although many animal models produce pulmonary dysfunction similar to the acute phase of ARDS, they invariably depress cardiac function, which clinically is not common.[3–5] For this reason, these models cannot be used for evaluation of hemodynamic effects of CMV + PEEP. In an animal study,[6] we observed that a decrease in lung compliance by acid aspiration failed to prevent or to significantly decrease the percentage fall in CO. Therefore, we think that the presence of normal lung in our animals did not affect the outcome. Recently, a new animal model for ARDS has been described.[7] N-

nitroso-N-methylurethane (NNNMU) produced histopathologic alteration closely resembling those seen in ARDS while preserving baseline cardiac output. We will wait for studies of hemodynamic effects of CMV + PEEP utilizing NNNMU lung injury model before casting the final vote.

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Benzocaine-induced Methemoglobinemia in Sprague-Dawley Rats

To the Editor:—A current experiment in our laboratory attempts to evaluate neurologic outcome following hypoxic-ischemic stress. Animals are intubated with PE 200 polyethylene tubing cut and tapered to tracheal size for 250- to 350-g male and female Sprague-Dawley rats. To facilitate intubation, catheters were lubricated with Americaine®, an ointment containing 20% benzocaine.

Several animals prepared in this manner were noted to have dark arterial blood in spite of $Pa_{O_2} > 100$ mmHg. In one instance, blood analyzed by a CO-oximeter® showed oxyhemoglobin as 74% and methemoglobin as 21.1%, while Pa_{O_2} was 125 mmHg.

We subsequently injected one rat subcutaneously with 0.1 ml Americaine®. By 10 min following injection, methemoglobin level increased from control of 0.8% to 28.5%.

It appears, therefore, that Sprague-Dawley rats, like newborn and infant humans[1,2] and dogs,[3] are deficient in reduced nicotinamide adenine dinucleotide-methemoglobin reductase.

We suggest that benzocaine-containing preparations not be used in rats.

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