of TNG in our protocol are consistent with data that vasodilators are most effective when baseline vascular resistance is high.[2,5]

The hypothesis that right and not left ventricular performance limited cardiac output in our protocol was confirmed by the effects of sodium nitroprusside (SNP) in our study. SNP is more potent than TNG as a systemic arterial vasodilator and should therefore result in a greater increase in cardiac output when left ventricular performance limits cardiac output. In our study, SNP produced only a 14% increase in cardiac output and did not affect pulmonary artery pressure or resistance at doses that produced similar decreases in systemic arterial pressure compared with TNG. The different hemodynamic effects of these two drugs in our study are explained by their relative potencies as pulmonary and systemic vasodilators in a model where pulmonary vascular resistance limits cardiac output.

The cardiopulmonary effects of TNG in humans will depend upon the patient population selected. When TNG is administered to patients with adult respiratory distress syndrome in whom cardiac output is not limited by pulmonary vascular resistance, the result will be arterial hypoxemia, and, if the patient is hypovolemic, decreased cardiac output and hypotension may occur. In contrast, when TNG is administered to patients with severe pulmonary hypertension in whom cardiac output is limited by right heart afterload, an increase in cardiac output may occur[6]; the effects on arterial oxygenation will depend upon the degree to which hypoxic pulmonary vasoconstriction was maintaining arterial oxygenation. Further studies are required to determine the risks and benefits of TNG therapy in selected subsets of patients with adult respiratory distress syndrome.

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The Hemodynamic Effects of Positive End-expiratory Pressure

To the Editor:—Although Venus *et al.* have presented an explanation of the data from their study on the effect of hydration on renal function during ventilation with positive end-expiratory pressure (PEEP), I feel that several aspects require additional comment.[1] The study protocol was designed to compare renal function during PEEP in two groups of animals that differed only in the degree of hydration as measured by transmural left ventricular end-diastolic pressure ($LVEDP_{TM}$). After the addition of PEEP to controlled mechanical ventilation (CMV), $LVEDP_{TM}$ remained at 5 ± 1 mmHg in the normovolemic animals and at 10 ± 1 mmHg in the hydrated group as a result of infusion of lactated Ringer's solution. In spite of no change in $LVEDP_{TM}$ in the normovolemic group during ventilation with PEEP, there was a 35% decrease in cardiac output (CO) and a 20% decrease in mean arterial pressure (MAP). If ventricular contractility was not affected, the above results suggest that, although $LVEDP_{TM}$ was unchanged after instituting PEEP, there was a decrease in left ventricular compliance resulting in a decreased left ventricular preload. In reviews of their own data as well as that of other investigators, Robotham *et al.* have presented evidence that left ventricular compliance is altered during ventilation with CMV with PEEP while contractility remains unchanged.[2,3] Therefore, $LVEDP_{TM}$ is not an accurate measure of left ventricular

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-