

TABLE 1. Pharmacokinetic Microconstants for *d*Tc with a Two-compartment Open Model

Alpha	0.063
Beta	0.004
$k_{21}$	0.017

Values are given per min.

where  $K$ , the mean effective plasma *d*Tc concentration at 50 per cent paralysis during recovery from blockade, was  $0.537 \mu\text{g/ml}$ , and the power function,  $s$ , was 5.15. Solving this equation for 90 per cent paralysis (10 per cent of control twitch height) gives a plasma concentration ( $C_p$ ) of  $0.82 \mu\text{g/ml}$ . Ham and colleagues based their pharmacokinetic analysis of their *d*Tc concentration data on the three-compartment model of Gibaldi,<sup>3</sup> with adjustment of the apparent volume of distribution. From our studies, we have found that a two-compartment open model adequately characterizes the plasma concentration-time ( $t$ ) curve for *d*Tc; pooled results for 32 patients are shown in table 1. The curve for either single or multiple doses with a two-compartment model is described by:

$$C_{pN} = \left[ \frac{(k_{21} - \alpha) \cdot D}{(\beta - \alpha) \cdot V} \cdot e^{-\alpha t} + \frac{(k_{21} - \beta) \cdot D}{(\alpha - \beta) V} \cdot e^{-\beta t} \right] N \quad (2)$$

where  $V$  is the volume of the central compartment;  $N$  is the number of doses administered; and the dose ( $D$ ) is adjusted appropriately. Simulations were made for  $V$  at  $4 \text{ l/m}^2$  and the data in table 1, then equations 1 and 2 were combined to predict recovery to 90 per cent paralysis. In these calculations, least support is given to  $V$  of  $4 \text{ l/m}^2$ . Although it approximates the value for the apparent volume of the central compartment reported by Ham's group,<sup>1</sup> our studies suggest a higher volume, closer to  $6 \text{ l/m}^2$ .

Ninety per cent paralysis should occur 81 min following administration of *d*Tc,  $20 \text{ mg/m}^2$ . An in-

crement of  $5 \text{ mg/m}^2$  then should again recover another 70 min later. The equations predict that five doses of  $5 \text{ mg/m}^2$  would be needed in a two-hour period, with the first dose causing 90 per cent paralysis at 9 min. Incidentally, this model reproduces almost exactly the times to 90 per cent and 50 per cent paralysis following *d*Tc,  $8 \text{ mg/m}^2$ , reported by Walts and Dillon.<sup>4</sup> However, their *d*Tc cumulation ratios are larger than those predicted.

Constant-rate infusion dosage can be calculated from multiplication of the desired (90 per cent paralysis) plasma concentration with the plasma clearance rate. Our mean value for the latter is  $0.117 \text{ l/m}^2/\text{min}$ , giving a two-hour *d*Tc total of  $11.5 \text{ mg/m}^2$  infused, to which a loading dose in excess of  $5 \text{ mg/m}^2$  should be added.

It would appear that the time to spontaneous recovery of twitch tension can be predicted from either a two- or three-compartment model.

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## Positive End-expiratory Pressure (PEEP) Ventilation Suppresses the Increase of Shunting Caused by Dopamine Infusion

To the Editor:—Recently, Hemmer and Suter showed that intrapulmonary shunting ( $\dot{Q}_s/\dot{Q}_t$ ) is not increased by dopamine-infusion augmentation of cardiac index (CI) in patients who are also given positive end-expiratory pressure (PEEP).<sup>1</sup> However, a linear and positive correlation between CI and  $\dot{Q}_s/\dot{Q}_t$  has been previously documented in patients receiving dopamine,<sup>2</sup> in patients having a veno-arterial by-

pass with a membrane lung,<sup>3</sup> and more generally, in both man<sup>4</sup> and animals<sup>5</sup> with acute pulmonary diseases. In all these studies,  $\dot{Q}_s/\dot{Q}_t$  was initially increased markedly and the end-expiratory pressure was zero (ZEEP).

What Hemmer and Suter document in their paper suggests that the relationship between CI and  $\dot{Q}_s/\dot{Q}_t$  no longer exists when end-expiratory pressure

is increased and  $\dot{Q}_s/\dot{Q}_t$  decreased. Snider and Zapol have also documented such an effect in a patient undergoing cardiopulmonary bypass. When the pulmonary blood flow decreased during venoarterial perfusion, the influence of CI on  $\dot{Q}_s/\dot{Q}_t$ , which was present at ZEEP, disappeared when PEEP was instituted.<sup>6</sup>

In order to confirm the effects of CI on shunting relative to PEEP levels, we compared the effects of dopamine infusion in six patients with septic shock whose lungs were mechanically ventilated at 15 cm H<sub>2</sub>O PEEP with previously published results describing nine patients who were given dopamine and whose lungs were ventilated at ZEEP. Unfortunately, both PEEP and ZEEP were not assessed in the same patients, but the nature of the disease (septic shock with pulmonary edema) and the initial values for shunting and CI were identical in the two groups.

Although CI augmentation by dopamine from  $2.9 \pm 0.9$  (SD) to  $4.1 \pm 1.2$  l/min/m<sup>2</sup> increased  $\dot{Q}_s/\dot{Q}_t$  from  $27 \pm 9$  to  $42 \pm 12$  per cent in the ZEEP group, the same increase in CI (from  $2.5 \pm 1.2$  to  $3.5 \pm 1.4$  l/min/m<sup>2</sup>) did not modify  $\dot{Q}_s/\dot{Q}_t$  in the PEEP group (fig. 1). The insensitivity of  $\dot{Q}_s/\dot{Q}_t$  to CI variations during PEEP fits well with the recruitment theory.<sup>3-5</sup> This theory suggests that augmentation of CI will not recruit low  $\dot{V}_A/\dot{Q}$  ratio zones and increase  $\dot{Q}_s/\dot{Q}_t$ , either because these zones have been eliminated by PEEP ventilation,<sup>7</sup> or because no change in distribution of vascular resistance between normal and abnormal zones has occurred. The geometric factors associated with high lung volumes tend to lower resistance in the extraalveolar vessels and tend to elevate resistance in the alveolar vessels that could become less sensitive to flow. Finally, lack of influence of CI on  $\dot{Q}_s/\dot{Q}_t$  during PEEP ventilation is of great practical importance for patients whose plasma volumes are increased by fluid infusion or vasoactive drugs that have been administered in order to improve hemodynamic tolerance to PEEP.<sup>1</sup> The protective effect of PEEP seems to indicate that these therapies can be administered safely, even in presence of pulmonary edema.

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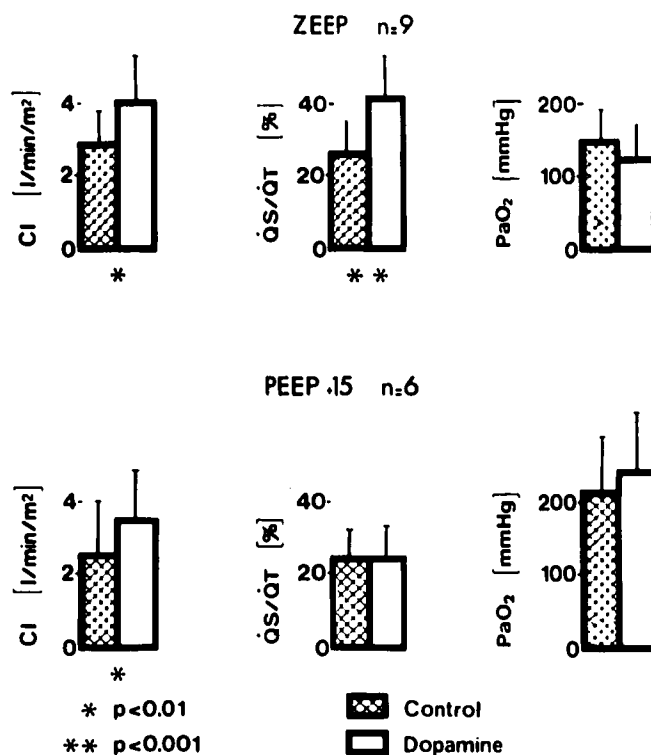


FIG. 1. Comparison of simultaneous variations of cardiac index (CI) and intrapulmonary shunting during ZEEP (top) and PEEP (bottom) ventilation, in 15 patients who had septic shock complicated by pulmonary edema. There were nine patients in the ZEEP group and six in the PEEP group. Explanation of abbreviations: ZEEP = zero end expiratory pressure; PEEP = positive end expiratory pressure; C = control; D = dopamine (10 µg/min/kg body weight) CI = cardiac index;  $\dot{Q}_s/\dot{Q}_t$  = shunt fraction ( $F_{IO_2}$ :1);  $P_{aO_2}$  = arterial partial pressure of oxygen ( $F_{IO_2}$ :1).

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