EVLW in several animal models. Such an increase was seen by the TPT method but not by the CT. Had the authors controlled for the effects of lipopolysaccharide on EVLW alone, we may have been better able to determine the sensitivity of the two methods for detecting changes in EVLW with changes in V/Q matching and perfusion after lipopolysaccharide administration. As the authors have so eloquently pointed out, understanding the limitations of any device and having as thorough an understanding as possible of the effects changes in physiology have on its accuracy and interpretation are vital for meaningful clinical application. We cannot agree more, and yet, it is doubtful that this study defines the limitations of TPT determinations of EVLW in acute lung injury when pulmonary perfusion is changed. In fact, another equally valid conclusion would be that the TPT method is at least equivalent if not superior to the CT method in this model.

The accompanying editorial appropriately calls into question our current method of introducing medical devices to the market without rigorous scrutiny of efficacy. But TPT has been compared with both the accepted standard gravimetric and dual dilution techniques in a variety of disease states and has performed well. Furthermore, EVLWTPT is the best pulmonary-specific index of disease severity and predictor of outcome available to us. Very importantly, EVLWTPT-guided management of hemodynamics has been shown to decrease mortality in acute lung injury. We believe that the foundation for clinical use of EVLWTPT has been established by these studies. We would, therefore, like to join with the authors of the current study and the accompanying editorial and now call for large prospective interventional investigations to examine the benefit.

Charles R. Phillips, M.D., Azriel Perel, M.D. *Oregon Health and Sciences University, Portland, Oregon. phillipc@ohsu.edu

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In Reply:

We appreciate the interest of Drs. Phillips and Perel in our recent article. However, they seem to have focused on whether there exists a numeric equivalence between extravascular lung water (EVLW) measured by computed tomography tissue volume and the transpulmonary thermodilution method (EVLWTPT). Any such equivalence between these values is as much coincidence as anything else, because it has been shown by Kirov et al. that a species-specific correction is required to calibrate the EVLWTPT measurement to accurately reflect gravimetric EVLW. We used the unmodified values from the PiCCO® device (Pulsion Medical Systems, Munich, Germany) because no validated canine correction factors are available. However, because this correction is linear, we believed that the changes in EVLWTPT would be reasonable to follow, and, as we described, the changes in each of these measures after lipopolysaccharide administration were very different. Our goal, however, was not to perform yet another validation of EVLWTPT but to gain insight into the pathophysiologic mechanisms that might impact the reliability of the measured EVLWTPT. Phillips and Perel apparently agree that the EVLWTPT increased after lipopolysaccharide while EVLW measured by computed tomography did not. Even if lipopolysaccharide administration caused an increase in the actual EVLW in the short time between administration and imaging, they offer no explanation as to why this was not evident on whole lung computed tomography imaging, which despite their objections is widely accepted as a sensitive and specific measure of lung mass. On the basis of the changing perfusion distribution observed, we interpreted this divergence of the two measurements to reflect an acute change in the perfused thermal mass, resulting in an artifactual increase in the EVLWTPT.

Nonetheless, we share the enthusiasm of Phillips and Perel in the value of a bedside measurement of lung edema and look forward to careful studies examining its optimal use and effect on outcomes. We hope, however, that the data we

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presented will assist practitioners in the thoughtful interpretation of the information this monitor provides.

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References


In Reply:
We thank Dr. Russell for his careful reading of our article.1 As highlighted by Russell, perioperative anaphylaxis remains a clinical diagnosis that is not always obvious. The Ring and Messmer four-step grading scale adapted for perioperative immediate reactions helps to stratify the severity and guides therapy for the ongoing clinical reaction.1 Common key points are highlighted in the various current clinical guidelines that recommend careful titration of epinephrine boluses according to the hemodynamic response during cardiovascular collapse (grade III reactions).2–6 Recommendations in the United States propose an initial dose of 100–300 µg intravenously, advise close monitoring because fatal overdoses of epinephrine have been reported, and suggest that an intravenous infusion of epinephrine (1–4 µg/min) may prevent the need to repeat epinephrine bolus administration.3,4 French guidelines recommend a 100–200 µg intravenous bolus epinephrine and state that intravenous infusion at a dose (0.05–0.1 µg · kg⁻¹ · min⁻¹) might be used in place of repeated bolus administration.2 Scandinavian recommendations state that a continuous infusion (0.05–0.1 µg · kg⁻¹ · min⁻¹) is advantageous in patients in need of repetitive doses of epinephrine (initial intravenous doses 100 µg), whereas British guidelines also state that an intravenous infusion should be considered in patients requiring repeated bolus dosing (initial intravenous boluses of 50 µg).5,6

The Dose of Epinephrine to Treat Anaphylaxis

To the Editor:
The article reviewing anaphylaxis and anesthesia1 is a useful timely reminder of a serious problem that may arise with any of us during anesthesia. I agree that the basic treatment should focus on intravenous (IV) epinephrine and expansion of intravascular volume. However, there is one aspect of this treatment that is misleading. The early administration of epinephrine is emphasized and the dose adjusted to the hemodynamic response, but for severe reactions a single IV bolus and infusion is suboptimal, because it may be slow to achieve the desired effect. Basic pharmacology teaches that the dose–effect relationship of a drug is log-linear and so the titration should be done in a logarithmic fashion. This is most easily done by doubling the amount of epinephrine in each progressive dose until the desired effect is achieved. Commencing with 100 µg IV epinephrine and administering a dose every 2 min as suggested, if the doubling is used, a 3-mg dose of epinephrine, if required, is reached in 8 min. If a 3 mg IV dose is required, the 200 µg epinephrine bolus and 4 µg/min infusion would take over 10 h! When an anaphylaxis occurs, it is not always obvious whether it is a grade III or IV reaction. Early progressive titration of the IV epinephrine will achieve an optimal dosing in the shortest time.

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Plotting the logarithm of the dose that fits a dose–response curve is a mathematical description of the receptor-occupancy theory that allows us to study the competition of a ligand (such as epinephrine) for receptor binding and allows the comparison of receptor agonists in terms of efficiency (E_max) and potency (EC_50). The shape of the dose–response curve corresponds to drug binding to its receptor, and the slope of the curve identifies the range of doses useful for achieving a clinical effect. With such a design, we previously provided dose (epinephrine)–response (mean arterial pressure) relationships and showed that the EC_50 of epinephrine in a rat model of anaphylactic shock was 10 µg/kg.7 Pulmonary edema and episodes of ventricular arrhythmia occurred at the highest doses of epinephrine in this rat model. However, most importantly, the magnitude of a pharmacologic drug response and the clinical use of a drug should be distinguished. Epinephrine has a relatively narrow therapeutic index,8 with pulmonary edema, ventricular dysrhythmias, and poor outcomes, including myocardial and cerebral infarctions or deaths (and in recent years Tako-Tsubo cardiomyopathy), associated with its use after excessive dosing during anaphylaxis.9,10 Finally, none of the current clinical guidelines recommend that “the titration of epinephrine should be per-