therapy is not indicated for individuals who have echocardiographic evidence of RV dysfunction without hypotension or shock. Dr. Kreit may even have overestimated the mortality in this group of patients, as his Table 1 includes two studies in which there is no indication that hypotensive patients were excluded. When these studies are not considered, the average mortality falls from the quoted 9.3% for the four studies in the Table 1, to 4.5% for the remaining two studies. Additionally, Dr. Kreit does not comment on the 10-year retrospective study by Vieillard-Baron et al. in which 32 subjects with massive PE and echocardiographic RV dysfunction without frank shock had only a 3% mortality.

Dr. Kreit suggests that hypotensive patients have a higher mortality and quotes the 14% mortality in 43 such patients in a large registry. However, in the study by Grifoni et al. included in Table 1, 19 patients were prospectively identified who had echocardiographic evidence of RV dysfunction and hypotension without shock. The mortality in this group was only 5%, identical to that in the normotensive patients in the study. Furthermore, in the study by Vieillard-Baron et al. in 32 patients with echocardiographic RV dysfunction and hypotension requiring vasopressor support but without metabolic acidosis, the mortality rate was 3% and no different than the in group without hypotension. In sharp contrast, 34 patients who were hypotensive with a metabolic acidosis despite intravascular volume expansion and vasopressor support had a 59% mortality rate. Although not randomized, it is notable that the mortality in these 34 patients was the same in the 14 patients receiving thrombolytics (57%) as in the 20 patients receiving only heparin (60%).

It is important to be fully aware of several limitations in the study by Jerjes-Sanchez et al., which Dr. Kreit cites, the only randomized prospective study to claim a survival advantage in patients in shock receiving thrombolytic and heparin therapy rather than heparin alone. The groups differed substantially with respect to the time from onset of symptoms of PE to onset of shock. The patients randomized to streptokinase presented quickly and directly to the study hospital, while those randomized to heparin were all transferred to the study hospital after sudden deterioration on heparin at another institution. This suggests a different pathophysiology between the groups, such as recurrent PE prior to randomization in the heparin only group. The patients in this study were very unusual. The patients were much younger than in the previous studies with PE (mean age, 51 years and 47 years in the two groups, respectively) and had extremely high estimated pulmonary artery systolic pressure (97 mm Hg and 94 mm Hg, respectively). Angina was reported in all patients, and three of the four patients who died and underwent autopsy had grossly visible RV infarctions. Finally, the termination of the study after enrollment of only 8 of the intended 40 patients is problematic for two reasons. First, the small sample size lowers the confidence in the p value. That is, if a ninth patient had been enrolled and had a different outcome from the previous eight patients, the p value would be markedly higher. Second, the analysis of the data “as it accumulated” rather than at the intended end point of 40 patients requires the application of “sequential methods” to the statistical analysis in order for it to be valid. It is far from clear that this was done.

It appears that what Dr. Dalan stated in an editorial in 2002 remains true today: “Despite > 3 decades of experience with thrombolytic agents, their role in the treatment of PE remains uncertain and controversial.” In making treatment decisions on individual patients with PE, however, the physician must bear in mind that the sharp rise in mortality from PE may not occur until patients are vasopressor dependent and exhibit a metabolic acidosis. Even in this latter group, solid evidence that thrombolysis confer a survival advantage is lacking.

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Interpretation of Transpulmonary Thermodilution Curves

To the Editor:

Michaeld recently reported a possible artifact that appeared to mimic the biphasic thermodilution display of temperature vs time of an intracardiac right-to-left shunt after injection of cold indicator via a femoral vein catheter and temperature measurement using a thermistor placed via the femoral artery. It was thus stated to be similar to transpulmonary thermodilution curves observed with this technique in the presence of right-to-left intracardiac shunts with early temperature change from rapid transit of indicator through the shunt followed later by temper-
To the Editor:

I thank Dr. Cole for focusing on a figure I recently published in CHEST (August 2004). However, I totally disagree with his comments. Dr. Cole claims that the time interval between the two peaks of the so-called camel transpulmonary thermodilution curve (with two humps) that was presented in my article is “much too short” to mimic a right-to-left intracardiac shunt.

When the camel curve is due to a right-to-left intracardiac shunt, the time interval between the two peaks represents the blood transit time between the right and left atrium through the pulmonary circulation. When the camel curve is due to a cross-talk phenomenon, the time interval between the two peaks is necessarily longer (and not shorter!), since it represents the blood transit time between the femoral vein (cold indicator injection) and the femoral artery (a longer distance means a longer time interval).

Moreover and more importantly, in both cases the time interval between the two peaks is highly dependent on cardiac output and, for instance, will be three times shorter in a patient with a cardiac output of 9 L/min than in a patient with a cardiac output of 3 L/min. Therefore, I still believe that the “eyeball” inspection of a transpulmonary thermodilution curve does not allow the discrimination between a cross-talk phenomenon and a right-to-left intracardiac shunt. The camel curve represented in my article is now depicted in Figure 1 with a different time scale and really looks like a camel curve due to a right-to-left intracardiac shunt.

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REFERENCES

Effects of Leukotriene Receptor Antagonists on Vascular Endothelial Growth Factor Levels in Asthma

To the Editor:

Kanazawa et al1 have reported an interesting reduction in airway permeability with pranlukast that correlated with a reduction in airway vascular endothelial growth factor (VEGF) levels. However, no such reduction in VEGF levels was observed in steroid-treated asthmatics. In contrast, a clinical study2 has shown a further benefit in symptoms and lung function in the combination of leukotriene receptor antagonists and inhaled steroids. It is therefore perhaps surprising that no further reduction in airway VEGF occurred with pranlukast added to the steroid-treated patients.

Other questions remain. What is the mechanism of the reduction in measured airway VEGF level in asthma? Is there a VEGF receptor up-regulation in the airway or an increase in sflt binding free VEGF? Could this reduction be secondary to cellular changes in the airway epithelium, a known source of VEGF? Are there other significant sources of VEGF in asthma?

One limitation of the VEGF enzyme-linked immunosorbent assay is its inability to measure the more cell-associated VEGF isoforms (VEGF_{165} and VEGF_{206}) that still have bioactivity. Analysis of their expression would increase understanding of the changes in VEGF bioactivity in asthma.

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