you breathe it, it's toxic, and if you inject it, it's safe. I don't recall a recent investigation that has looked at whether, in fact, the addition of an injectable component did create an inherently safer approach to anesthesia. In fact, the famous Beecher-Todd Report suggested an inherent toxicity of the injectable addition. At any rate, as of today, it is difficult to support the addition of new or different drugs simply because they reduce anesthetic requirement.

Additionally, the Darwinians among us intuitively assume a purposeful role for the adrenergic nervous system. Having finally accomplished the difficult mental gymnastics to realize that any adrenergic agonist will be sympatholytic, I'm left with questions that I believe should be investigated before trials on human subjects are instituted. These include describing the distribution of cardiac output among and within organs and the adequacy of perfusion of the entire organism and its component parts. We should look at the organism's ability to respond to the inevitable challenges of blood loss, carbon dioxide excess, oxygen want, and biochemical alterations such as severe acidosis.

The previous report from this laboratory suggests that with the 1 MAC combination of that alpha2 agonist and isoflurane is associated with a 50% reduction of cardiac output and heart rate. Shouldn't we have some idea as to whether there is an equivalent reduction in metabolism? Are all vascular beds adequately perfused if surgery lasts for several hours? Are the brain, heart, or other vital structures deprived of a rightful share? What is the time dimension of the effect of these drugs? Can these effects be reversed or withdrawn at the completion of surgery? How do they relate to postoperative pain control? Is the bradycardia resulting from the alpha2 agonists a stable rhythm? Increases in pulse rate may be beneficial on occasion—is this prohibited by the sympatholysis?

The potential for a most interesting era in the development of anesthesia is raised by these studies and we will anxiously await and or seek additional information. The specialty is mature enough now to investigate this thoroughly and wisely. We must ask and try to answer all the questions along the way.

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References

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Understanding Images: Correlation Between Computerized Tomographic Scans of Lung Structure with Impaired Function in ARDS

CONVENTIONAL WISDOM REGARDS the adult respiratory distress syndrome as an acute, homogeneous, bilateral inflammatory lung disease in which widespread damage to pulmonary microvasculature causes diffuse pulmonary edema and produces symmetrical bilateral pulmonary infiltrates on the chest radiograph. Research over the past several years substantiates this as an accurate portrayal of ARDS in its milder and earlier stages.

In this issue of Anesthesiology, Dr. Luciano Gattoni and his colleagues in Milan have further enhanced our understanding of this early form of ARDS by correlating physiological measurements with images of the lung obtained by computerized tomography. The most important relationships they demonstrate are: 1) pulmonary artery pressure increases in concert with lung weight;
and 2) as the mass of non-inflated lung tissue increases, so do venous admixture and $V_{D}/V_T$, while PaO$_2$ decreases.

Without the CT scanner, no such correlations would have been possible, because we have no other means for measuring reliably at the bedside either lung weight or non-inflated lung tissue mass. Earlier inhalation and indicator dilution techniques that measured extravascular lung water were restricted, as x-rays are not, to assessing those areas within the reach of inhaled or perfused agents.

Gattinoni's work also provides us with quantitative proof of what had hitherto been deduced only from indirect evidence, such as helium dilution measurements of communicating lung gas volume. PEEP augments the recruitment of lung volume during ARDS by increasing low-density, presumably ventilated, lung regions at the expense of high-density, presumably non-ventilated (shunted) regions.

The correlation in early ARDS of increased pulmonary artery pressure (PAP) with increased lung weight as estimated by CT corroborates our current understanding of fluid and solute transport in injured lung. We can expect that increasing PAP in the presence of lung injury will cause the lung to gain weight by directly forcing plasma into the interstitial and alveolar spaces. However, at least in the early stages of ARDS, a gain in weight probably is not responsible for the increase in PAP. To support this hypothesis, we note that increased PAP is due to a reduced vascular cross-sectional area that is adequately accounted for by many other factors. These include hypoxic and mediator-induced vasoconstriction, thrombosis, and obliteration of pulmonary microvasculature. While many animal models of early acute lung injury with severe pulmonary edema do not demonstrate pulmonary hypertension (e.g., Erdmann et al.$^5$), there may be direct compression of the remaining vessels by coagulated interstitial edema fluid late in ARDS. Weight gain due to the latter will directly raise the PAP.

How far can computerized tomography take us in predicting pathophysiology? If the anatomic correlations of this study hold true, a chest CT scan in ARDS should enable estimation of the level of pulmonary artery pressure, venous admixture, $V_{D}/V_T$, and PaO$_2$. Indeed, given a group of patients with ARDS at an early and mild stage, similar to that studied here, I am confident such prediction would be possible and useful. However, these correlations would not exist for ARDS patients with major amounts of non-homogeneous lung disease. This would include patients with extensive unrecruitable lung consolidation, intravascular thrombosis, and ischemic necrosis or abscesses, as well as those with severe injury with cystic dilatation and emphysema. Such patients with ARDS have a high mortality rate and constitute a special challenge for developing better therapy.

In the Gattinoni et al.$^1$ study, despite a 44% venous admixture at PEEP 5 cm H$_2$O, only six of 22 patients died. Pontoppidan et al.$^3$ would classify these patients as having mild ARDS in an early stage of lung disease (mean 4 days of tracheal intubation). In contrast, Maunder et al.$^4$ reported a CT study of 13 patients with more advanced and severe lung disease (mean 8 days of tracheal intubation; three survivors). The lung lesions were non-homogeneous and many of the regions of consolidation were posterior.

Notable in the present study is a marked posterior distribution of regions of high density shown in the authors' figure 1. Why do lung lesions in ARDS usually develop a posterior distribution? Is it merely the effect of gravity causing airway and interstitial fluid to migrate to dependent lung regions, thereby filling airspaces with fluid and promoting consolidation? Future CT scan studies in ARDS will focus on these questions, and help us improve therapy.

Further work must be done to better explain one of Gattinoni's more mysterious and unexpected findings: increasing PEEP decreased estimated lung weight. Does increasing PEEP reduce the lung water—unlikely, considering evidence from many laboratory studies—or does PEEP reduce the lung's blood volume? Since only three CT sections were examined in each study, perhaps PEEP "chased" the edema to an unexamined section.

In addition to these beautiful studies focusing on the effects of high-density, non-ventilated lung regions, this group$^6$ has published another recent article$^4$ that makes correlations of normally aerated CT density lung regions with lung compliance during ARDS. I recommend it highly as an informative companion article.

It should come as no surprise to physicians in the western world that anatomic information improves medical practice. Medicine was revolutionized by the anatomic studies of Leonardo, Vesalius, and Fabricius in northern Italy during the Renaissance. Now their descendants have produced new knowledge correlating anatomy with physiology in acute lung disease.

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References

Immunological Basis of Anesthetic-induced Hepatotoxicity

Present evidence indicates halothane-induced hepatotoxicity can be considered as two entities in clinical practice. One, a mild form of toxicity, is seen shortly after anesthesia and can be reproduced in animals regardless of the mechanism of toxicity (chemotoxic or ischemia-hypoxia) or animal species. In the other form of hepatotoxicity, a delayed, severe, and often lethal clinical toxicity is observed. This form may be due to an allergic response producing a fulminant type of hepatotoxicity. The rapidity of the disease, its association with repeated administrations, and the difficulty in reproducing it in animals suggests an immune mediated mechanism.1

The idea that a hypersensitivity response may result in halothane-associated liver injury is not new. Studies have been initiated at various times through the years only to be blurred by the lack of a "complete picture." The inability to produce in animals a form of the disease involving an immune mechanism and/or the inability to demonstrate conclusively the role of the immune system in liver injury have been two reasons why a more definitive cause-effect relationship has not been established.2-5

How, then, have current studies improved the understanding of the role of the immune system in halothane-induced liver injury? In part, the application of newer, more sensitive technology that clearly demonstrates production of antibodies and the detection of liver antigens in these cases provides great insight. The importance of recent findings, such as those investigated by Christ et al. and reported in this issue of ANESTHESIOLOGY,6 suggests that hepatotoxicity following all volatile halogenated anesthetics may be linked by a common mechanism. Unquestionably, the incidence of hepatic injury following enflurane and isoflurane anesthesia is less than that reported following halothane, but it must be accepted that these volatile anesthetics can produce rare liver injury, albeit at a much lower incidence. The report by Christ et al. (National Institute of Health) as to the potential for a metabolic basis of hepatotoxicity following enflurane anesthesia via production of covalently bound liver antigens recognized by antibodies generated from patients with halothane hepatitis is significant. As clearly stated in their studies, the principal reason that isoflurane did not produce detectable liver antigens might be solely related to the level of biotransformation in their particular animal preparation. But, in fact, isoflurane, enflurane, and halothane all have the potential for producing acetylated intermediates that can alter liver proteins rendering them immunogenic. For example, such reactive metabolic intermediates of halothane could include, among others, either a trifluoroacetate halide from the oxidative pathway, free radicals, or carbene intermediates from reductive pathways.7

How does this work differ from earlier studies? Basically, very little. However, many of the earlier techniques used were of insufficient sensitivity, and variation in results from laboratory to laboratory were often contradictory.2-4 Many researchers tried to "clear the picture" by studies in antigenically sensitized animals; negative results frequently led to termination of studies.

At the time of many early investigations, little was known about the bioactivation of halothane along with