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Vaporized Perfluorocarbon

Taking the "Liquid" out of Liquid Ventilation

ALTHOUGH only a relatively limited amount of oxygen is dissolved in water under natural conditions, aquatic creatures enjoy great success in extracting sufficient amounts to meet the metabolic demands of life. Mammals (even aquatic mammals) avoid this limitation by using atmospheric oxygen through specialized gas exchange mechanisms in the lung. However, the mammalian lung can also extract sufficient amounts of oxygen from liquids to support life—if it is the right liquid. Many recall from student days the dramatic demonstration that small mammals can be totally immersed for extended periods of time while breathing liquids in which sufficient amounts of respiratory gasses are dissolved.[1] Variations of this strategy have been applied with some success in the supportive therapy of acute lung injury (ALI) in both animals and humans. Two techniques have been applied: the lungs can be completely filled with fluid, which is moved to and fro by specialized equipment (total liquid ventilation), or partially filled with liquid, permitting gas ventilation *via* conventional ventilators (partial liquid ventilation). In this issue of ANESTHESIOLOGY, Bleyl *et al.*[2] introduce a new method of delivering liquid to the injured lung that may possess clinical advantages and that raises interesting questions regarding the mechanism of benefit. Indeed, their technique is not liquid ventilation at all, but rather a technique near and dear to anesthesiologists—the inhalation of a "vaporized" agent, in this case a perfluorocarbon.

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Perfluorocarbons have several potential medical applications based on their radio-opacity, low surface tension, and high capacity to dissolve respiratory gasses.[3] The two indications of greatest interest to the perioperative physician are as an intravascular transporter of oxygen and as the "liquid" used in liquid ventilation. In animal models of ALI, perfluorocarbons used in total or partial liquid ventilation strategies improve measures of gas exchange and pulmonary mechanics over the short term.[4,5] The initial clinical experience in patients ranging in age from neonates to adults has also been encouraging,[6-8] although randomized clinical trials demonstrating safety and efficacy are not yet available.

Exactly how the installation of perfluorocarbons into the airways acutely improves the gas-exchanging function of the injured lung remains a mystery. In many studies, they are administered in relatively large volumes (at least equal to the functional residual capacity). The fluid, which is preferentially distributed to the dependent lung, is thought to abolish the normal gas-fluid interface in the lung and "splint" the alveolae by hydrostatic pressure.[9] This action would thus treat the atelectasis characteristic of ALI which, conveniently, also tends to be distributed to the dependent lung. Respiratory gases would then diffuse *via* the fluid to the interface between liquid and inspired gas, perhaps aided by bulk transport of fluid provided by respiratory motion. These large volumes of liquid also encourage preferential gas ventilation gas of nondependent, less-injured areas of lung and increase the relative perfusion of these areas.[10] However, the bulk effects of large fluid volumes cannot be the whole story because other studies show that smaller doses of perfluorocarbon also can be beneficial.[11,12]

The work of Bleyl *et al.*[2] provides further evidence that perfluorocarbons may have benefit apart from effects secondary to large volumes of fluid. The authors exploit the fact that the perfluorocarbon studied (perfluorohexane) possesses a high vapor pressure at room temperature, similar to those of volatile anesthetics in clinical use. They used two standard anesthetic vaporizers connected in series to deliver approximately 18% perfluoro-

hexane to the lungs of sheep with oleic acid-induced ALI. Thirty minutes of administration produced significant improvements in several parameters of gas exchange and lung mechanics. Two features of the data are of particular interest. First, oxygenation parameters continued to improve *after* the administration of perfluorocarbon ceased, with sustained beneficial effects for up to 2 h. This sustained benefit generally has not been observed after liquid perfluorocarbon administration. Second, estimates of the actual amount of perfluorocarbon delivered to the lung, based on differences between inspired and expired concentrations, suggest that only a small amount of perfluorocarbon was actually retained in the lung, perhaps 2–3 ml/kg (much less that the functional residual capacity), and that uptake was largely complete by 10 min. Clearly, these beneficial effects cannot be attributed to large volumes of liquid in the airways.

What, then, can explain these dramatic effects? The authors speculate that perfluorocarbon vapor condenses in the lung and forms a thin film that lines the alveolae, acting like natural surfactant to reduce surface tension at the gas–liquid interface and stabilize alveolar structure. The observed increases in respiratory system compliance after treatment would be consistent with this hypothesis. In comparison with liquid administration, the vapor should be relatively evenly distributed to ventilated lung units, facilitating its effects. Deficiencies in surfactant function certainly can play a major role in the pathogenesis of acute lung injury, but other factors must be involved. Although perfluorocarbons possess good spreading characteristics over aqueous surfaces with relatively low surface tension, the surface active properties of natural surfactant required for normal lung mechanics are considerably more complex. Furthermore, it is not clear how vaporized perfluorocarbon would access and expand the atelectatic lung regions that are presumably present in this ALI model, unless *via* blood-borne transport of absorbed agent that would somehow reach (and create) a gas–liquid interface. It is possible that perfluorocarbon may improve the functioning of native surfactant by improving its distribution, stimulating its production, or some direct physiochemical interaction, actions that might be consistent with prolonged benefit. For example, perfluorocarbon enhances the beneficial effects of exogenous surfactant in animal models of acute lung injury[13] and stimulates surfactant phospholipid production.[14] In addition to effects on surface tension, partial liquid ventilation with perfluorocarbon also may affect lung inflammatory responses, such as lung neutrophil accumulation, known to be of importance in the pathogenesis of ALI.[15,16] All of these potential mechanisms are amenable to experimental study. For example, imaging studies could take advantage of the radioopacity of perfluorocarbon and examine its distribution, as well as its effects on lung atelectasis in ALI.

Beyond these interesting mechanistic questions, this technique may have practical advantages. The installation of relatively large amounts of liquid into the trachea poses several technical challenges and may be associated with complications such as transient hypoxia during instillation, pneumothoraces, and liquithoraces.[7,8] Presumably, the use of vapor, a technique already familiar to anesthesiologists, should avoid many of these problems. Although the perfluorocarbons are believed to be relatively inert and have been systemically administered to humans in many clinical trials, using a minimal dose titrated to maximal effect would seem prudent, and vaporization would seem to be a very practical method to accomplish this goal. Finally, the sustained benefit observed after vaporization may suggest that this mode of administration simply works better, perhaps because of more uniform distribution compared with the administration of liquid, although this would need to be confirmed by direct comparisons. Obviously, many questions need to be answered before this technique is applied clinically, such as whether it is beneficial in other types of lung injury, the effects of prolonged administration, and the optimal perfluorocarbon for use (*e.g.*, the vapor pressure of some perfluorocarbons may not be suitable). However, the potential for the benefits of "liquid" ventilation without the potential drawbacks associated with a liquid-filled lung (a condition that, after all, the larynx is designed to prevent) may hold considerable promise.

David O. Warner, M.D.
Professor of Anesthesiology
Mayo Medical School
Mayo Clinic
Rochester, Minnesota 55905
warner.david@mayo.edu

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Airway Exchange Catheters

Simple Concept, Potentially Great Danger

AIRWAY exchange catheters (AEC) can be used to increase the safety of changing endotracheal tubes (ETTs).[1-3] An AEC is a long, small ID, hollow, semirigid catheter that is inserted through an *in situ* ETT before tracheal extubation. After the ETT is withdrawn over the AEC, the AEC serves as a conduit to administer oxygen manually, by insufflation, or by jet ventilation and as a stylet for repeated intubation. Because the repeated intubation rate is as high as 19% in extubated patients in the surgical ICU,[4-6] the airway management options provided by an AEC are extremely important and are well recognized by the American Society of Anesthesiologists.[7] Many types of AECs have been used[3]; however, the most widely used are the multiple-sized, appropriately adapted, centimeter-depth-marked, commercial variety made by Cook Critical Care (Bloomington, IN), Sheridan Catheter Corporation (Argyle, NY), and CardioMed Supplies (Gormley, Ontario, Canada).

This issue of ANESTHESIOLOGY includes a case report[8] that reminds us that although the concept of using an AEC is simple, failure to strictly adhere to a few simple principles and clinical details can result in life-threatening complications. These complications can be divided into two broad categories: (1) barotrauma resulting from air entry exceeding air exit (*e.g.*, as in the case report in this issue) and (2) failure to successfully pass the new ETT over the AEC.

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