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*Editorials*

# Dangers of high-frequency ventilation in hyaline membrane disease

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The journey of high frequency ventilation (HFV) as a laboratory curiosity in search of clinical applications is illustrated by the paper of Pfenninger and Gerber in the last issue of Intensive Care Medicine [1]. They describe their experience with a high frequency ventilation modality in human neonates with hyaline membrane disease (HMD) which we have found to cause extensive lung damage in an animal model of HMD. For a variety of sociopolitical and financial pressures which continue to evolve, research related to intensive care is frequently based on animal models in the US and in the human clinical population in Europe. Each type of research adds needed insights into our understanding of the pathophysiologic process we encounter in the ICU. In a most simplistic analysis, animal models allow us to control confounding variables, produce defined perturbations of the system, and define pathologic changes, all of which would be ethically impossible in human studies. Conversely, the bottom line for the importance or efficacy of most experimental variables rests with human studies which in some circumstances may be the only model appropriate for study. In most instances, significant animal toxicity markedly limits or precludes human experimental application of a drug or therapeutic intervention.

We have participated in studies utilizing the premature baboon with HMD to evaluate IPPV, high frequency ventilation and high frequency oscillation (HFO) respiratory support. The premature baboon delivered at 140 days of a normal 180 day gestation develops respiratory failure with a disease process which is clinically, radiographically and pathologically indistinguishable from HMD in humans. Furthermore, utilizing IPPV support when needed and continuous 100% oxygen, a disease process ensues over two weeks which is clinically, radiographically and pathologically consistent with bronchopulmonary dysplasia observed in human neonates [2, 3]. For these reasons, we believe that the premature baboon is an excellent animal model for the human disease process. We wish to highlight the potential for pulmonary complications with HFV which may be particularly relevant to those involved in or contemplating the use of HFV in human neonates.

We have evaluated the use of a high frequency flow interrupter (HFFI) type ventilator (Percussionair Inc., Sand Point, Idaho) when compared to standard IPPV (Bournes Inc., Riverside, Calif) or high frequency oscillation (Texas Research Co., San Antonio, Texas) [4–6]. While IPPV and the flow interrupter type ventilator had similar incidences of clinical and X-ray evidence of barotrauma, i.e. interstitial air, pneumothorax; the pathologic changes observed appeared to be more severe with the high frequency interrupter ventilator. Conversely with HFO barotrauma was essentially non-existent. The diffuse atelectasis of

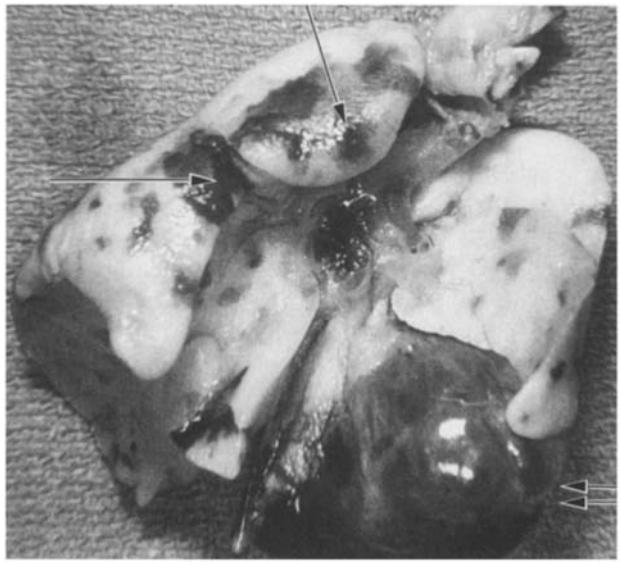

**Fig. 1.** The lungs from a premature baboon with hyaline membrane disease ventilated with a high frequency flow interrupter ventilator were perfused fixed while the lungs were held at a constant inflation pressure of 20 cm $H_2O$. Several pseudocysts can be seen (arrows). The massive pseudocyst in the left lower lobe (double arrows) extended over the diaphragm.

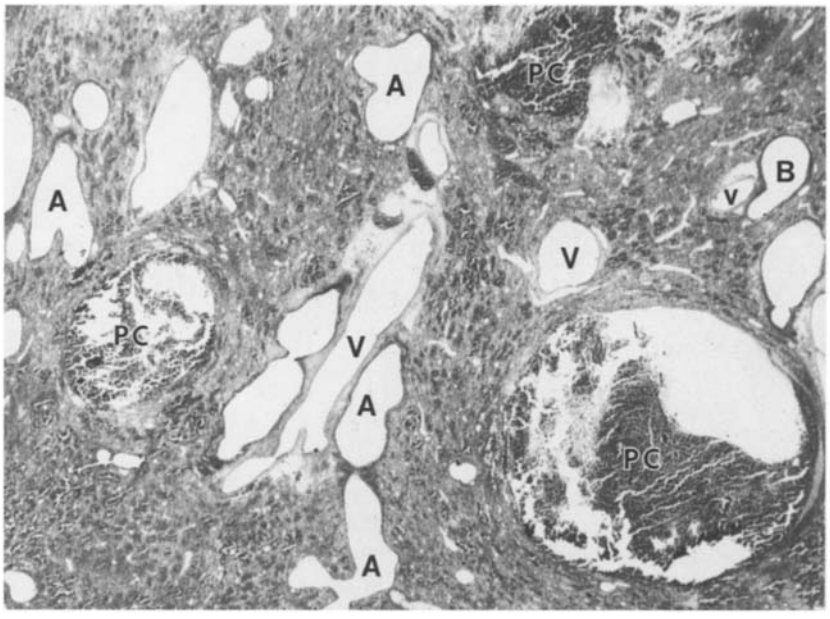


**Fig. 2.** A low power micrograph further details the pathologic findings. Several hemorrhage filled pseudocysts (PC) are seen. Airways (A) and pulmonary artery branches (V) are labelled. Hematoxylin and eosin; X15

HMD produces an extremely noncompliant alveolar bed such that the distal airways become the most compliant region. Thus as recognized by Hawker et al. [7] the "typical IPPV" pathology can be interpreted as overdistension of these distal airways in the presence of alveolar atelectasis. The HFFI and IPPV type ventilators can create disruption of the compliant conducting airways in the presence of a noncompliant alveolar space. We have termed these lesions as they appear on both cut section and low power photomicrographs "pseudocysts" (Fig. 1). The degree of dilation resulting from a "blow out" lesion of the airway look like small to moderate size cysts (Fig. 2). It is difficult to imagine that such severe and diffuse injury to the distal airways will not result in long term injury. It is important to stress that during the early clinical course by routine clinical, radiological and physiologic parameters, both the IPPV and HFFI animals were similar [4]. Thus human prematures treated with HFFI or possibly another type of jet ventilator might sustain serious lung damage which could not be immediately apparent unless acute pathologic specimens were obtained. As pointed out by Pfenninger and Gerber our use of the HFFI has involved different airway recruiting patterns, however, the same sighing techniques linked with HFO has not been associated with lung injury.

In summary we hope that the report by Pfenninger and Gerber of the technical difficulties with the use of a high frequency flow interrupter ventilator available for use in many parts of Europe, combined with our observations of its association with lung damage in the premature primate with HMD, will promote appropriate caution in any planned application of HFV to human subjects with HMD. It is likely that different types of high frequency ventilators will interact in substantially different ways with varying underlying lung pathology. Therefore extrapolation from either one ventilator to another, or one disease process to another is inappropriate without animal studies. On the positive side, based on our continuing animal studies, HFO offers the possibility of a significant advance in the treatment of HMD.

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