LETTERS TO THE EDITOR

What Causes the Microvascular Permeability Change in High Altitude Pulmonary Edema?

The mechanism of high altitude pulmonary edema (HAPE), remains an enigma. Dr. N.C. Staub in a recent review (Staub, 1978) has characterized this form of noncardiogenic edema as a form of "permeability edema" because the edema fluid in this condition is proteinaceous, implying an increased fluid and protein flux. The mechanism proposed for this alteration in microvascular permeability entails a kind of physical injury related to the increased linear velocity of flow consequent upon greater restriction of pulmonary vascular bed for a given level of cardiac output. Although detrimental effects of very high linear velocities on vascular endothelium are well known, the available volume of data on pulmonary vascular hemodynamics during acute as well as chronic hypoxia in various species does not lend credence to this hypothesis.

The pulmonary vascular beds of bovines and equines have been characterized as hyperreactive to both acute and chronic hypoxia (Will et al., 1977). Upon exposure to high altitude (HA), the mean pulmonary artery pressure and the calculated pulmonary vascular resistance (PVR) rise significantly in both species. In equines (Bisgard et al., 1975) this rise in PVR is also accompanied by a rise in cardiac output, whereas in bovines (Ruiy et al., 1973) the cardiac output is maintained at prehypoxic levels although stroke volume is reduced. In neither of these species does one ever observe pulmonary edema. If Staub’s hypothesis would hold, it would mean that the domestic pony upon exposure to HA would have the most severe damage to pulmonary vascular endothelial integrity, especially because of the increased linear velocity due to increased cardiac output in the presence of a significantly elevated PVR, and would inevitably develop HAPE. The mere fact that the domestic pony never develops HAPE despite elevated cardiac output at HA is contrary to the hypothesis that physical injury to the pulmonary vascular endothelium in cases of HAPE occurs because of the inertial stress (direct impact of blood against vascular endothelium), the shear stress (frictional force at the branch points) caused by rapid changes in flow profile, or a combination of both.

One is therefore posed with the dilemma: what other mechanisms of increasing microvascular permeability may be involved? Several investigators favor chemical mediators. The situation becomes further complicated by the fact that the exact chemical mediator(s) involved in causing hypoxic pulmonary vasoconstriction remain unidentified.

tified at the present time. It is likely that the same mediator might be involved in both instances. Sheep may not be the best animal model to investigate the problem because of the minimal responsiveness of their pulmonary vascular bed to acute as well as chronic hypoxia (Will et al., 1977).

Based on the current state of knowledge, HAPE would appear to be a complex pathophysiological phenomenon rather than a single increase in linear velocity of blood flow damaging the pulmonary vascular endothelial integrity and resulting in HAPE.

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Reply to the Above Letter

In “disproving” my hypothesis implicating increased linear blood flow velocity (shear stress) as the underlying mechanism of injury leading to increased pulmonary microvascular permeability (Staub, 1978), Dr. Manohar reveals a misunderstanding of the difference between even (uniform) and uneven (pulmonary arterial obstruction) (Manohar, 1978). He recites data about cattle and ponies to the effect that alveolar hypoxia leads to increased pulmonary vascular resistance, but does not lead to pulmonary edema. I agree completely.

Contrary to his belief, however, sea level adult sheep also show a healthy increase in pulmonary vascular resistance during hypoxia. But they do not get high altitude edema either; nor can we demonstrate any increase in fluid filtration, protein permeability, or lung water (Bland et al., 1976). In sheep, the evidence clearly indicates that hypoxia constrains all of the pulmonary arterial resistance vessels more or less evenly. Thus, there is no increased linear velocity of blood flow (increased shear stress). We presume cattle and ponies behave in a similar fashion.

Apparently only sinful, gin-soaked man (as the
poem goes) has a variable smooth muscle coating to his pulmonary resistance vessels (Viswanathan et al., 1969; Reid, 1968), so that his pulmonary vasoconstriction in hypoxia is uneven.

Although Dr. Manohar’s reasoning is faulty, his belief that the basic injury in high altitude edema is chemically mediated is widely shared. In fact, we included a discussion of some likely biochemical mediators in our extensive paper detailing the effects of uneven pulmonary artery obstruction on lung fluid balance (Ohkuda et al., 1978) which immediately followed my Brief Review.

Since that publication, we have systematically depleted sheep of various of the likely mediators of lung injury. These include fibrinogen (Binder et al., in press), platelets (Binder and Staub, 1978), and neutrophils (Flick et al., 1979). Depletion of fibrinogen or platelets does not affect the increased permeability occurring after uneven pulmonary artery obstruction. Leukopenia, however, does markedly attenuate the response. This is an exciting finding even though it may be incompatible with the shear stress hypothesis as originally stated. But I do not mind having my hypothesis modified or even disproven. That is what hypotheses are for. In fact, the shear stress hypothesis is still very much alive. For example, injury to neutrophils by inertial impaction in the lung microcirculation or increased neutrophil adherence to endothelium slightly injured by the increased shear stress may be critical events. These things remain to be tested.

Dr. Manohar’s final statement that high altitude pulmonary edema “would appear to be a complex pathophysiological phenomenon” is a truism that does nothing to advance our knowledge. I would have preferred that he offer a new idea.

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