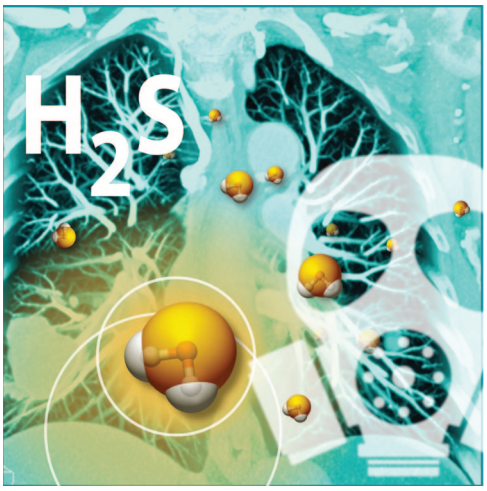
# Hydrogen Sulfide

## *A Hot Molecule*

HYDROGEN sulfide ($H_2S$) is a potentially toxic gas with an obnoxious smell. It is a common cause of gas–related fatalities and is notorious for its use to commit suicide. Despite these properties, scientists have readily embraced $H_2S$ ever since its discovery as the third gaseous signaling molecule after carbon monoxide and nitric oxide. Exogenously $H_2S$ or $H_2S$-donating compounds were reported to yield beneficial effects in numerous biologic systems. As such, $H_2S$ has been quickly targeted for its therapeutic potential in a variety of diseases.[1] However, concerns of toxicity remain. In particular, pulmonary toxicity is reported, underlining the need for a thorough analysis of this compound. In this issue of ANESTHESIOLOGY, Francis RC *et al.* shed light on this matter by comparing the route of administration of $H_2S$ in a murine model of ventilator-induced lung injury (VILI).[2] Although bolus injection of $H_2S$-donating compound sodium sulfide exerted a protective effect, inhalation of high doses of $H_2S$ was found to aggravate lung injury. The mechanism of sodium sulfide-induced protection included a favorable balance in the antioxidant levels by up-regulation of genes involved in this process.




***"... there is a continuing need for understanding mechanisms of toxicity of $H_2S$ before we can rejoice on potential clinical applications."***

Presumably, toxicity of $H_2S$ is because of inhibition of the respiratory complex in mitochondria, resulting in an inability of cells to use oxygen for oxidative metabolism. The authors hypothesize that because hypoxia (low arterial oxygen tension) is associated with pulmonary vasoconstriction and pulmonary edema, this may have been the mechanism underlying the detrimental effect of inhaling $H_2S$ in VILI. However, in their study there was no difference in arterial oxygenation between animals treated with a high dose of $H_2S$ compared with controls, while the fraction of inspired oxygen was unchanged. There may have been "functional hypoxia" after inhalation of $H_2S$, *i.e.*, an inability to use available oxygen, but to our knowledge, there is no known association between cytopathic hypoxia and pulmonary vasoconstriction. In addition, beneficial effects of $H_2S$ inhalation on lung injury have previously been found in another model of VILI.[3] Thereby, the question remains what the mechanism is of the observed toxicity of inhaled $H_2S$ in the present study.

The dose is likely to be of importance. The toxicity of $H_2S$ is correlated with its concentration and depends less upon the duration of exposure,[4] suggesting that $H_2S$ is rapidly eliminated, with concomitant low levels of free $H_2S$. This begs the questions as to what "physiologic" concentrations of $H_2S$ are. Measuring $H_2S$ concentrations is difficult, however, as the various techniques measure not only the biologic active form but also its intermediates. An explanation for discrepant results of routes of administration on toxicity could be that parenteral $H_2S$ is metabolized and exhaled within seconds, whereas continuous inhalation may expose the alveoli to high $H_2S$ concentrations. Also, the murine nasal cavity has an enormous surface area, thereby enabling deposition efficiency of inhaled $H_2S$ in the nose. Mechanical ventilation *via* a tracheotomy exposes the lungs to high $H_2S$ concentration as compared with spontaneously breathing animals. Of note is that only a high dose of $H_2S$ aggravated lung injury, whereas the low dose of inhaled $H_2S$ had no effect. This high dose nearly corresponds to a dose that has been shown to induce a "suspended animation like" state,[5] characterized by a reduction of oxygen consumption and a concomitant decrease in body temperature to ambient temperature. In their study, Francis RC *et al.*[2] notably kept body temperature constant. If $H_2S$ exerts protection against VILI *via* reducing energy expenditure, it can be hypothesized that eliminating oxygen utilization with the use of "hibernating" doses of $H_2S$, while preventing a drop in body temperature that lowers oxygen consumption, can be toxic.

*Illustration: A. Johnson.*

Accepted for publication July 18, 2011. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

 Anesthesiology 2011; 115:921–2

◆ This Editorial View accompanies the following article: Francis RC, Vaporidi K, Bloch KD, Ichinose F, Zapol WM: Protective and detrimental effects of sodium sulfide and hydrogen sulfide in murine ventilator-induced lung injury. ANESTHESIOLOGY 2011; 115:1012–21.

Alternatively, $H_2S$ may have differential effects on endothelial and epithelial cells. The work by Francis RC *et al.*[2] highlights that during VILI, injected sodium sulfide inhibited the expression of adhesion molecules needed for diapedesis and extravasation of neutrophils from the circulation into the alveoli. This may suggest a mechanism by which $H_2S$ exerts effects, which is less apparent in alveolar cells. Of note, chronic exposure to $H_2S$ induced bronchial epithelial hypertrophy.[6]

In conclusion, both beneficial as well as detrimental effects of $H_2S$ have been reported in various preclinical studies. Dose and route of administration are important factors related to $H_2S$ toxicity. The work by Francis RC *et al.*[2] contributes to the hypothesis that $H_2S$ might protect the lung from damage caused by the mechanical ventilator. However, there is a continuing need for understanding mechanisms of toxicity of $H_2S$ before we can rejoice on potential clinical applications.

**Hamid Aslami, M.Sc.,* Marcus J. Schultz, M.D., Ph.D.,† Nicole P. Juffermans, M.D, Ph.D.†** *Laboratory of Experimental Intensive Care and Anesthesiology, Academic Medical Center, Amsterdam, The Netherlands. h.aslami@amc.uva.nl. †Laboratory of Experimental Intensive Care and Anesthesiology, and Department of Intensive Care Medicine, Academic Medical Center.

## References

1. Aslami H, Schultz MJ, Juffermans NP: Potential applications of hydrogen sulfide-induced suspended animation. Curr Med Chem 2009; 16:1295–303
2. Francis RC, Vaporidi K, Bloch KD, Ichinose F, Zapol WM: Protective and detrimental effects of sodium sulfide and hydrogen sulfide in murine ventilator-induced lung injury. ANESTHESIOLOGY 2011; 115:1012–21
3. Faller S, Ryter SW, Choi AM, Loop T, Schmidt R, Hoetzel A: Inhaled hydrogen sulfide protects against ventilator-induced lung injury. ANESTHESIOLOGY 2010; 113:104–15
4. Guidotti TL: Hydrogen sulfide: Advances in understanding human toxicity. Int J Toxicol 2010; 29:569–81
5. Blackstone E, Morrison M, Roth MB: $H_2S$ induces a suspended animation-like state in mice. Science 2005; 308:518
6. Dorman DC, Struve MF, Gross EA, Brenneman KA: Respiratory tract toxicity of inhaled hydrogen sulfide in Fischer-344 rats, Sprague-Dawley rats, and B6C3F1 mice following subchronic (90-day) exposure. Toxicol Appl Pharmacol 2004; 198:29–39