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CRITICAL CARE

COMMENTARY

# Of mice and men (and sheep, swine etc.): The intriguing hemodynamic and metabolic effects of hydrogen sulfide ($H_2S$)

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**Abstract**

Whether the hydrogen sulfide ($H_2S$)-induced metabolic depression observed in awake rodents exists in larger species is controversial. Therefore, Derwall and colleagues exposed anesthetized and ventilated sheep to incremental $H_2S$ concentrations by means of an extracorporeal membrane oxygenator. $H_2S$ caused pulmonary vasoconstriction and metabolic acidosis at the highest concentration studied. Oxygen uptake and carbon dioxide production remained in the physiological range. The authors concluded that, beyond the effect of temperature, $H_2S$ hardly modifies metabolism at all. Since the highest $H_2S$ concentration caused toxic side effects (possibly due to an inhibition of mitochondrial respiration), the therapeutic use of inhaled $H_2S$ should be cautioned.

In the previous issue of *Critical Care*, Derwall and colleagues [1] reported on the effects of gaseous hydrogen sulfide ($H_2S$) (100 to 300 parts per million) in healthy, anesthetized, and mechanically ventilated sheep. To avoid any airway irritation, the authors used an elegant approach to circumvent inhaling $H_2S$ (that is, administration via an extracorporeal, veno-arterial membrane oxygenator). The major findings were that (a) whole body oxygen uptake ($VO_2$), carbon dioxide production ($VCO_2$), and cardiac output remained within the physiological range but that (b) $H_2S$ caused pulmonary vasoconstriction, which was (c) associated with a fall in blood pressure and metabolic acidosis at the highest doses administered.

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In a landmark paper, Blackstone and colleagues [2] demonstrated that, in awake, spontaneously breathing mice, inhaling $H_2S$ induced a hibernation-like metabolic state characterized by reduced energy expenditure and hypothermia. Subsequently, Volpato and colleagues [3] reported that this metabolic depression was associated with bradycardia and reduced cardiac output but that blood pressure and stroke volume remained unaffected. Consequently, given the exciting prospect of pharmacologically reducing energy expenditure to protect against ischemia ('suspended animation' [2]) by application of a gaseous drug, the effects of inhaled $H_2S$ were investigated in various models. In fact, inhaled $H_2S$ protected rodents against otherwise lethal hypoxia [4] and hemorrhage [5] and attenuated murine kidney and lung injury [6-8]. Equivocal data, however, are available from large animals: inhaled $H_2S$ failed to show any metabolic effect in sheep or swine [9,10], and the intravenous $H_2S$ donor sodium sulfide ($Na_2S$) was reported either to reduce energy expenditure [11] or to have no effect at all [12].

What do we learn from the study by Derwall and colleagues [1]? The authors confirm previous data in the same species [9] that even a fivefold-higher concentration of inhaled $H_2S$ did not depress energy expenditure. Since the authors maintained the body temperature, they speculate that in larger species $H_2S$ can hardly affect metabolism at all beyond the effect of temperature per se (the 'Q10 effect': the fall of $VO_2$ and $VCO_2$ associated with a 10°C decrease), in particular when metabolism is already depressed. In fact, in anesthetized and mechanically ventilated mice subjected to deliberate hypothermia, inhaled $H_2S$ had no further metabolic and circulatory effects [13]. Moreover, in larger adult animals, non-shivering thermogenesis is negligible and thus cannot be influenced such as in small animals (for example, mice) with a metabolic rate that is 15- to 20-fold higher than that of humans [9]. Finally, any $Na_2S$-related therapeutic effect in larger animals was independent of body temperature [14-16].

What is the future of $H_2S$ in critical care medicine? The vascular effects of $H_2S$ are still controversial: Derwall and colleagues [1] found a dose-dependent pulmonary vasoconstriction, which at first glance agrees with the hypoxia-sensing properties attributed to $H_2S$ [17]. However, the mixed venous oxygen partial pressure ($PO_2$) was 50 to 55 mm Hg (that is, clearly above the range that induced hypoxic vasoconstriction of isolated pulmonary arteries of cows [17]). In addition, the pulmonary vascular vasomotor response to $H_2S$ *in vitro* showed marked interspecies differences, so that any effect in the critically ill patient is difficult to anticipate [17]. The systemic vasomotor effect of $H_2S$ is equally intriguing: endogenous $H_2S$ is a physiological vasodilator and thus assumes major importance in the control of blood pressure [18]. Derwall and colleagues [1] report that the highest $H_2S$ concentration caused marked systemic vasodilation, whereas other authors [11,16] found that $Na_2S$ reduced the noradrenaline doses required to achieve hemodynamic targets during reperfusion after porcine aortic balloon occlusion.

The appropriate $H_2S$ dose is also unknown: in the previous large animal studies, a 25-fold range of intravenous $Na_2S$ infusion rates was used [11,12,14-16], and, as in the present investigation, higher infusion rates over longer periods of time impaired pulmonary gas exchange [11,12]. The significant metabolic acidosis affiliated with the highest $H_2S$ concentration deserves particular attention, but unfortunately the authors did not further elucidate this finding. It is tempting to speculate that inhibition of mitochodondrial respiration with subsequent reduction of aerobic capacity caused this metabolic acidosis: $H_2S$ is a well-established inhibitor of the cytochrome C oxidase, and the subtle increase in the respiratory quotient that can be derived from the mean $VO_2$ and $VCO_2$ values before and after exposure to 300 parts per million $H_2S$, respectively, replicates data reported on the effects of $H_2S$ inhalation in exercising humans [19]. Finally, as the authors themselves acknowledge, the fate of exogenous $H_2S$ remains unclear: they found, in the efferent blood of the extracorporeal membrane lung, sulfide levels that were associated with near-complete inhibition of the respiratory chain *in vitro* [13]. The arterial blood concentrations, however, were in the same range as measured during $Na_2S$ infusion in swine, in which $Na_2S$ protected against myocardial [16] and renal [17] ischemia/reperfusion injury.

In conclusion, Derwall and colleagues performed an elegant ovine study to test whether a pharmacological (that is, $H_2S$-induced) metabolic depression can be achieved in large animals. While the authors did not find any gross modifications of energy expenditure, they observed several intriguing hemodynamic and acid-base effects, which confirm the complex actions of this 'third gaseous mediator'.

**Abbreviations**

$H_2S$, hydrogen sulfide; $Na_2S$, sodium sulfide; $VCO_2$, carbon dioxide production; $VO_2$, oxygen uptake.

**Competing interests**

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