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Cardiogenic shock induced reduction in cellular O_2 delivery as a hallmark of acute H_2S intoxication

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One of the main mechanisms of hydrogen sulfide toxicity is thought to relate to the ability of H_2S/HS^- to block the activity of the mitochondrial electron transport chain, preventing the creation of a proton gradient across the mitochondrial membrane, and in turn impeding ATP regeneration in all cells (1, 2). The corollary of the impediment in ATP production is a reduction in cellular O_2 utilization, leading to a reduction in peripheral O_2 extraction and thus an increase in venous and tissular O_2 content (and partial pressure), akin to the well documented rise in venous PO2 (and paradoxical reddish color of tissues) during cyanide poisoning-induced cellular "anoxia" (3).

Fernandes et al. (4) have recently argued that this mechanism is difficult to reconcile with the data published by Brenner et al. (5) depicting a *drop*, instead of an *increase*, in "tissular" oxyhemoglobin during sulfide intoxication, i.e. in the setting of an inhibition of oxidative phosphorylation. However, we have found that H_2S intoxication dramatically decreases cardiac contractility and cardiac output (6), as soon as the concentration of free H_2S/HS^- reaches levels of about 3–5 microM, before signs of toxicity can be observed (6–8), leading to fatal pulseless electrical activity within minutes (9). No significant peripheral vasodilation was observed during sulfide induced circulatory failure (6). This striking and very rapid depression in cardiac contractility has been previously suggested to result from the blockade of LCa channels in cardiomyocytes (10, 11). The "poisoning" of the cardiomyocytes appears very early (6), possibly through non-ATP related mechanisms (10) at a time when the cytochrome C oxidase activity is not yet, or not dramatically, impeded in most tissues. As a consequence, a *decrease* in venous/peripheral O_2 saturation/content is not unexpected. To clarify this matter, we have recomputed (figure), from data previously obtained in 7 sedated rats (6), the relationship between cardiac output (determined from aortic or pulmonary blood flow), $\dot{V}O_2$ (determined by pulmonary gas exchange), the change in O_2 extraction (computed as $\dot{V}O_2$ /cardiac output ratio), during the first minutes of H_2S/HS^- infusion at a rate, which is fatal within 5–6 minutes (2 mg/kg/min) (6). Such a H_2S infusion produced a rapid decrease in cardiac output/O_2 delivery, which was proportionally much more severe and rapid than the reduction in O_2 consumption. As a result, O_2 extraction rises (figure), reflecting a larger fall in the rate of O_2 delivery than in the rate of cellular O_2 utilization. Incidentally, a similar *reduction* in tissular/venous O_2 saturation has also been documented during cyanide poisoning, wherein acute cardiac failure occurs (12).

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These data support the view that a rapid cardiogenic shock leading to a profound reduction in O_2 delivery to peripheral tissues is a one of the dreadful and early effects of H_2S intoxication. The proper identification of this cardiogenic shock, in a clinical setting of patients exposed to mitochondrial “poisons” presenting with circulatory failure and tissue hypoxia, has crucial therapeutic implications.

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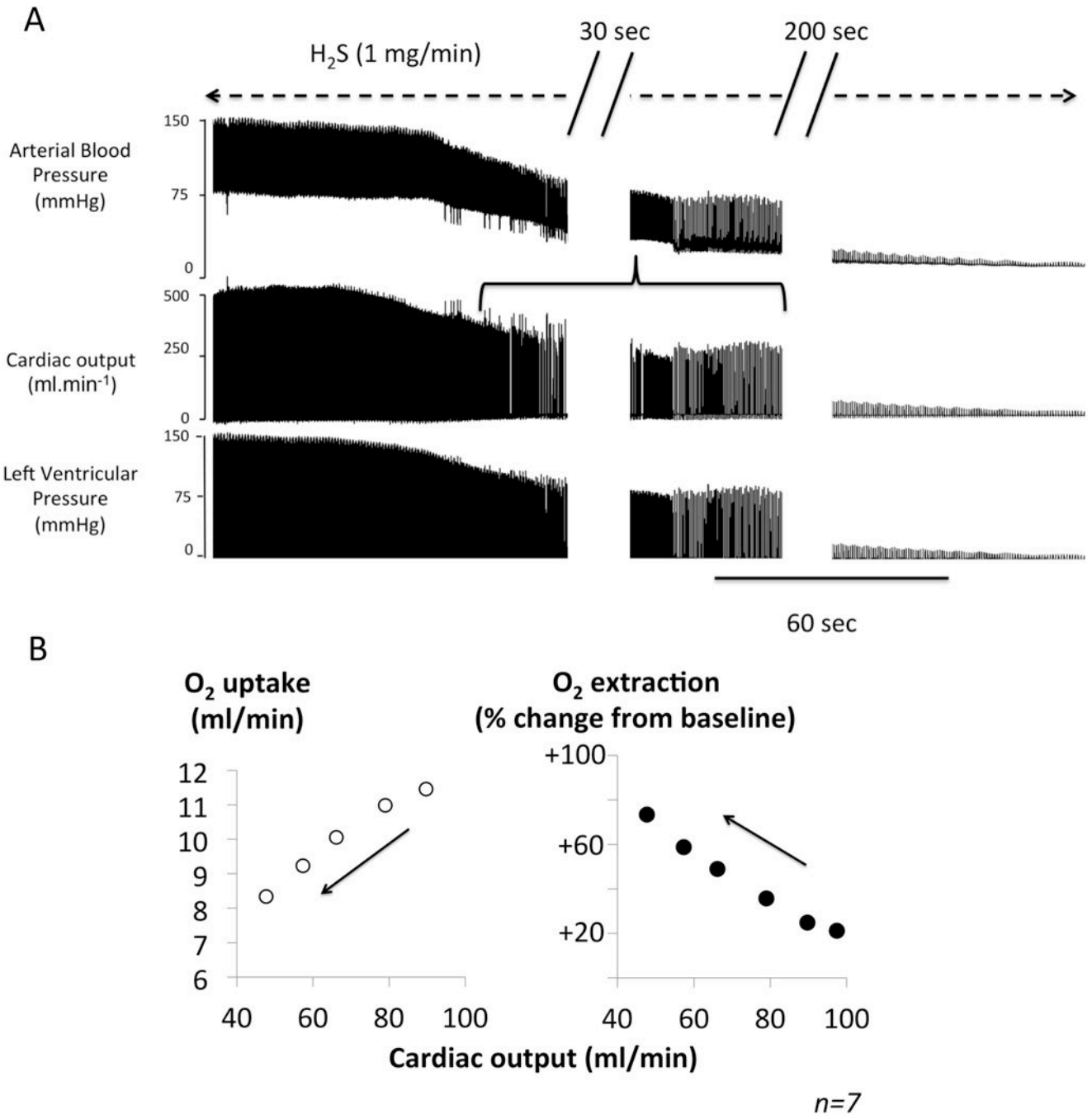

Figure.

Panel A. Original recording of the changes in arterial blood pressure, cardiac output and the left ventricular pressure, during H_2S infusion in a 500 g rat receiving a solution of sulfide made from NaHS (1 mg/min). There was a rapid decrease in cardiac output, arterial pressure and left ventricular pressure, which led to asystole, within 5 minutes. The horizontal bracket shows the period at which of cardiac output was determined for the computations shown in B. **Panel B.** $\dot{V}O_2$ (left panel) and the change in O_2 extraction as % from baseline (Right panel) as a function of cardiac output. 10 second-averaged data obtained from 7 rats during

the first minutes of an infusion of H2S at toxic levels (2 mg/min) are shown. Cardiac output dropped dramatically, while oxygen extraction increases reflecting a proportionally higher fall in O_2 delivery than in O_2 utilization. Note that PaO_2 and thus the arterial O_2 content was prevented to decrease by mechanical ventilation throughout the period of infusion.