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OPINION

Death by hypoxia: what were they thinking?

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Alabama recently had the dubious distinction of being the first state in the USA to put someone to death by inhalation of pure nitrogen through a face mask. Claiming the judicial killing of Kenneth Smith on January 25 was a 'textbook' execution is galling, considering what physiologists know about the effects of hypoxia on the body. Having been on death row for 33 years, Kenneth Smith was subjected to several attempts in November 2022 to kill him by lethal injection. Officials at Holman Correctional Facility in Atmore, Alabama, had tried for 1 h to insert a cannula into one his veins without success, even trying to insert a central line, but abandoned it <1 h before the death warrant was to expire at midnight. He was back on death row for another 2 years before someone had the idea of killing him with hypoxia. 'Alabama has done it, and now so can you', Mr Marshall, the State's Attorney General, said after the execution, with other states willing to take on this method of capital punishment (New York Times, 2024).

Notwithstanding my complete opposition to the death penalty, what were they thinking when considering death by hypoxia? Our bodies are equipped with specialized chemoreceptors (the carotid bodies, located at the bifurcation of the carotid arteries, and the aortic bodies, located in the aortic arch) that respond to reductions in blood oxygen. These chemoreceptors are also sensitive to increases in CO_2 and reductions in pH, as are the central chemoreceptors located on the ventral surface of the brainstem, but it is only the peripheral chemoreceptors that are able to respond to hypoxia and evoke the physiologically purposeful responses that aim to normalize blood O_2, increasing ventilation and constricting peripheral resistance vessels to ensure delivery of oxygenated blood to the vital organs, the heart and brain. Air hunger is the term often used to describe the dyspnoea associated with an inability to satisfy the drive to breathe (Banzett et al., 2021), and the increased work of breathing is observed as an increase in respiratory rate and depth, inward motion of the lower thorax, downward motion of the trachea, nasal flaring and activation of the accessory muscles of inspiration (the sternocleidomastoid and trapezius muscles); these clinical signs can be seen in acute respiratory distress syndrome, chronic obstructive pulmonary disease and asthma attacks (Santus et al., 2023). These signs can also be seen with increased chemical drive to breathe brought about by hypercapnia and/or hypoxia. It is known that an increase in arterial CO_2 is a stronger stimulus to breathe than a reduction in inspired O_2; marked dyspnoea is experienced with increases in arterial P_{CO_2} of only 10 mmHg, whereas reductions in arterial P_{CO_2} need to be much greater (40–50 mmHg; the normal partial pressure of O_2 is 160 mmHg) in the presence of normal CO_2 levels (Moosavi et al., 2003). Nevertheless, the perception of air hunger is similar to that experienced with normoxic hypercapnia, suggesting that it is the central drive to breathe that leads to the dyspnoea (Moosavi et al., 2003). Indeed, people who had been pharmacologically paralysed and artificially ventilated reported increasing air hunger as inspired CO_2 was progressively increased (the same experiment was not done for hypoxia), indicating that the increase in ventilatory movements was not responsible for the air hunger (Gandevia et al., 1993). Expansion of the thorax can alleviate the air hunger to some extent; rebreathing an asphyxic gas mixture at the breaking point of an end-expiratory apnoea relieves the urge to breathe (Fowler, 1954), and even taking a single breath of pure N_2 allows one to continue the apnoea for an extra 10 s or so (Seitz et al., 2013). But there is no doubt that breathing pure N_2 evokes air hunger, and this is evidenced by the increased work of breathing.

The signs of respiratory distress were recounted by witnesses to the death of Kenneth Smith, which by all accounts was a very slow execution (Hedgepeth, 2024). Strapped tightly to a gurney at the wrists, with his arms stretched out, and with a gas mask fixed to his face, at 7.57 pm, as the N_2 was administered through the mask, 'he began thrashing against the straps, his whole body and head violently jerking back and forth for several minutes [and] for around a minute, [he] began heaving and retching inside the mask.' By ∼8:00 pm, 'Smith's struggle against the restraints had lessened, though he continued to gasp for air. Each time he did so, his body lifted against the restraints. Smith's efforts to breathe continued for several minutes as his spiritual advisor Jeff Hood prayed nearby, tears streaming down his face. Around 8:07 pm, Smith made his last visible effort to breathe' (Hedgepeth, 2024).

Why choose nitrogen as a means of killing, particularly given that it had never been a documented method of capital punishment? A comparison of euthanasia of dogs through inhalation of pure N_2 with I.V. injection of pentobarbitone showed that loss of EEG activity occurred on average after 36 s (range 33–42 s, $n = 4$) following pentobarbitone injection, but after 959 s (285–2700 s; $n = 9$) following inhalation of pure N_2 in a sealed chamber; ECG activity was lost after 250 s (180–300 s) and 1435 s (660–3900 s) (Quine et al., 1988). Hence, even in this veterinary setting, in which animals were presedated, signs of brain death took 16 min with N_2 inhalation, with cardiac death occurring after 24 min. In a second study, these authors proceeded to induce euthanasia with N_2 inhalation in a larger group of cats ($n = 63$) and dogs ($n = 5$) without presedation and without EEG or ECG monitoring. The majority collapsed within 60 s (range 13–60 s) of the O_2 concentration falling to 10%, with respiratory arrest (associated with dilatation and fixation of the pupils) occurring within 120 s after collapse (Quine et al., 1988). Convulsions followed the collapse, with opisthotonos (arching of the back, extension of the forelimbs and flexion of the hindlimbs) occurring subsequently, occasionally accompanied by vocalizations; opisthotonus occurs towards the end of hypoxia-induced apnoea, immediately preceding hypoxic gasping (Davis et al., 1986).

Thus, this execution, the first in which nitrogen inhalation was used, was not

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humane at all. Respiratory signs of life disappeared after 10 min, and time of death was reported as 8:23 pm. Although consciousness would have been lost well before hypoxic gasping occurred (a small experimental study in humans instructed to hyperventilate with pure N_2 revealed 'clouding of consciousness' and impaired vision after 15 s; Ernsting, 1963), there is no doubt that the extreme hypoxia would have induced air hunger and stress, particularly if there was a leak in the mask that allowed atmospheric O_2 to enter.

Physiologists abide by rules to ensure that euthanasia of experimental animals is performed humanely; one would hope that the same treatment is extended to humans. I plead with physiologists in states of the USA that uphold the death penalty to speak to their legislators and insist that death by hypoxia is never used again.

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