Commentaries on Viewpoint: Why do some patients stop breathing after taking narcotics? Ventilatory chemosensitivity as a predictor of opioid-induced respiratory depression

VIEWPOINT COMMENT ON VENTILATOR CHEMOSENSITIVITY AS A PREDICTOR OF OPIOID-INDUCED RESPIRATORY DEPRESSION

TO THE EDITOR: Patients who are underdose-induced ventilatory chemoreceptor depression respond variably to narcotics. This is illustrated in Potter and Moon’s (2) Fig. 1 in which great variability is shown of the hypercapnic ventilatory response (HCVR) test. In patients not undergoing pharmacological alterations (3, 4), there is great uniformity in hydrogen ion (H⁺) regulation. This might be explained by chemical stimulus being H⁺ and not carbon dioxide (CO₂).

Having tested their patients under partial anesthesia, increasing CO₂, Potter and Moon (2) have a mix of stimuli but only an insensitive CO₂ stimulus. Above the anaerobic threshold, H⁺ only drives ventilation. Patients may seriously underventilate and it does serious harm to patients when putting them under anesthesia. The reason for the variability is that the HCVR and the hypoxic ventilatory response (HVR) test of chemosensitivity may be insensitive and atypical when tested in nonphysiological ranges. This would be especially problematic if the patient has a background of heart or lung disease (4).

Normal patients are extremely sensitive to H⁺ ventilatory regulation. However, they are insensitive to CO₂ regulation over the entire range of chemical receptor control (3, 4). When arterial CO₂ competes with hypoxemia or as the stimulus provided by CO₂ gas, the CO₂ loses its power and arterial [H⁺] wins. We conclude that the arterial [H⁺] is the chemical controller rather than CO₂. See Fig. 4 in Ref. 3. This concept was in agreement with findings from other groups (1).

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COMMENTARY ON VIEWPOINT “WHY DO SOME PATIENTS STOP BREATHING AFTER TAKING NARCOTICS? VENTILATORY CHEMOSENSITIVITY AS A PREDICTOR OF OPIOID-INDUCED RESPIRATORY DEPRESSION”

TO THE EDITOR: We read with interest the Viewpoint from Potter and Moon (5) proposing that low chemoreceptor sensitivity may be a major contributor to opioid-induced apnea. We appreciate the focus on clinical incidents but believe that this might reflect only the tip of a very large iceberg. The number of drug overdose deaths in the United States continues to rise, with recreational opioid use contributing substantially to this increase (2). Especially intriguing is that 50% of incidents occur in low-risk patients, <60 yr old.

So, what could we be overlooking? Related to the authors’ hypothesis of low chemoreceptor sensitivity, we propose premature birth as a risk factor. Large-scale survival of very premature infants is a historically recent phenomenon and coincides with widespread surfactant use, beginning ~25 years ago. We recently found low chemoreceptor sensitivity in young adults born prematurely (1), evidenced by a blunted response to isocapnic, isobaric hypoxia. Complimentary studies in rats and premature infants suggest that this is caused by perinatal hyperoxia exposure, which impairs development of immature chemoreceptors (3, 4). Evaluating prematurity will be challenging. Many preterm-born adults appear clinically indistinguishable from term-born adults and birth status is typically lost from the medical record with the transition from pediatric to adult care primary care. However, given the large number of premature births (12% of live births), we hope our colleagues will deem it worthy to evaluate this in subsequent endeavors.

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TO THE EDITOR: Potter and Moon (4) discuss whether a noninvasive method of assessing opioid induced respiratory depression (OIRD) is primarily attributed to the lack of reliable predictors (5). Potter and Moon (5) proposed that the decrease in ventilator chemosensitivity may be a risk factor for OIRD. The alteration of chemosensitivity during opioid application is reflected by hypercapnic ventilatory response (HCVR), which can be associated with baseline HCVR (1), as a useful indicator for OIRD (5).

We agree that chemosensitivity likely correlates to OIRD susceptibility with respect to individuals but some reservations could remain when this statement is applied across a population. As the authors mentioned, HCVR baseline can vary 80-fold among 211 healthy people (5). Thus it is reasonable to speculate that the tolerance of chemosensitivity decline involved in OIRD can also change significantly from individual to individual. For example, the patients with obesity or chronic airflow obstruction are subject to a low chemosensitivity but can still demonstrate normal breathing. Their respiratory be-

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FURTHER CONSIDERATION OF VENTILATORY CHEMOSENSITIVITY AND OPIOID-INDUCED RESPIRATORY DEPRESSION

TO THE EDITOR: The high proportion of death caused by opioid-induced respiratory depression (OIRD) is primarily attributed to the lack of reliable predictors (5). Potter and Moon (5) proposed that the decrease in ventilator chemosensitivity may be a risk factor for OIRD. The alteration of chemosensitivity during opioid application is reflected by hypercapnic ventilatory response (HCVR), which can be associated with baseline HCVR (1), as a useful indicator for OIRD (5).

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Behavior is believed to be further regulated by respiratory control system (2).

In our view, the decrease of OIRD occurrence also depends on the identification of high-risk patients via reliable testing methods. For example, esophageal diaphragm electromyogram (EMGdi) can effectively assess neural respiratory drive (3) and distinguish between central and obstructive sleep apnea (4). Future studies should emphasize the necessity on the correlation between chemosensitivity and OIRD susceptibility as well as related potential mechanisms.

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**COMMENTARY ON VIEWPOINT “WHY DO SOME PATIENTS STOP BREATHING AFTER TAKING NARCOTICS? VENTILATORY CHEMOSENSITIVITY AS A PREDICTOR OF OPIOID-INDUCED RESPIRATORY DEPRESSION”**

**To the Editor:** We connect this question and the article by Potter and Moon (3) to the increasingly prevalent epidemics of obesity, metabolic syndrome, and type 2 diabetes. A common feature of advanced type 2 diabetes, associated with extremes of HbA1c and elevated fasting glucose levels, is neuropathy (1). Loss of sensation, particularly in limbs is common. O’Donnell et al. (2) showed that type 2 diabetes and its neuropathy may extend to the respiratory tract. They report diminished perception of inspiratory resistance in diabetics. It has also been reported that patients with type 2 diabetes exhibit diminished ventilatory responses to isocapnic hypoxia (4).

We have no data but raise the possibility of whether persons addicted to narcotics are more susceptible to overdose-induced respiratory depression when they have type 2 diabetes. A related question is the potential for increased risk of opioid-induced respiratory depression in persons with type 2 diabetes during surgery. Is neuropathy caused by type 2 diabetes associated with a greater respiratory depression when narcotic analgesics are used for preanesthetic medication, as supplements to other anesthetic agents, or as primary anesthetics?

Existing data should be gathered and analyzed to help answer these intriguing questions. Patient safety and public health may benefit from targeted research to elucidate the risks of opioid-induced respiratory depression in these vulnerable populations.

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