OPIOID-INDUCED RESPIRATORY depression (OIRD) is a serious public health and patient safety concern. In 2010, drug overdose was the leading cause of injury death in the United States (32), with 75% of these deaths involving opioid analgesics (2, 10). The problem is not limited to outpatients: severe respiratory depression and death occur even in hospitals using closed-loop administration devices [patient controlled analgesia (PCA)] and continuous pulse oximetry (13, 18). This phenomenon has drawn the attention of the Joint Commission, which recently issued a Sentinel Alert (29). The incidence of postoperative OIRD is estimated to be 0.5–2% (4, 7, 31) but may be higher in certain patient populations and is almost certainly under recognized and under reported (6, 18, 27). There is clearly a need for greater understanding of risk factors for OIRD and development of monitoring techniques that can accurately and reliably detect respiratory depression.

Prediction of patients at risk for OIRD is difficult and tends to be inaccurate. Some associations have been identified, including advanced age, American Society of Anesthesiologists (ASA) status ≥3, chronic opioid use, obesity, obstructive sleep apnea (OSA), chronic pulmonary disease, and coadministration of sedative drugs (3, 28, 30). However, although these factors are statistically associated with OIRD, they are often poorly predictive in individual patients. Moreover, OIRD occurs unpredictably in patients who are not considered “high risk.” For example, in 102 consecutive opioid-related respiratory events at Duke Hospital, 50% occurred in patients younger than 60 years. There must therefore be additional potent factors that remain to be identified. An overlooked factor in the development of OIRD may be an individual’s baseline respiratory chemoreceptor responsiveness and the degree to which it is suppressed by opioids and possibly sleep.

Opioid receptors are found throughout the respiratory control centers of the brain stem, carotid bodies, vagus nerve, and walls of the airways. Exogenous administration of opioids causes a dose-dependent decrease in sensitivity to hypoxia and hypercapnia via inhibition of central and peripheral chemoreceptor activity. Both hypoxia and hypercapnia induce hyper-ventilation, and formal techniques for the assessment of both effects [hypoxic ventilatory response (HVR) and hypercapnic ventilatory response (HCVR)] in humans were described over 50 years ago. Although HVR (dependent on peripheral chemoreceptors) is influenced by PCO2, and HCVR (dependent on both peripheral and central chemoreceptors) by PO2, a technique to measure both has been developed (5).
In subpopulations of patients with morbid obesity and chronic airflow obstruction who develop hypercapnia, it has been suggested that the cause may be innate low ventilatory responsiveness (1, 12). It is logical therefore that low chemosensitivity may also explain susceptibility to OIRD in individuals without recognizable risk factors and may be the major risk factor for OIRD.

Ventilatory responsiveness as a risk factor for OIRD was first proposed in 1960 (11). Unfortunately a test of this hypothesis is only available from three small studies. The first, a study of 8 healthy men in which the ventilatory response to CO2 was measured before and after infusions of morphine and fentanyl, appeared not to show any systematic relationship between baseline CO2 responsiveness and opioid-induced respiratory depression as measured by changes in resting end-tidal Pco2, although HCVR after each drug was indeed correlated with the baseline measurement (21). The same researchers conducted a follow-up study involving 17 healthy adult patients presenting for elective surgery, in which the ventilatory response to CO2 was measured before and within 90 min after morphine 0.15 mg/kg delivered intramuscularly. The author concluded incorrectly that comparison of the slope of the HCVR curve before and after morphine did not suggest a greater susceptibility to morphine-induced respiratory depression in individuals with a low baseline response, because the postdrug slope was clearly correlated with the baseline (24).

In a later study conducted by the same group, the ventilatory response to CO2 was measured before and after establishing steady-state meperidine infusion in 10 healthy subjects (22). The effect of baseline ventilatory chemosensitivity on the degree of meperidine-induced respiratory depression was not reported, but a subsequent linear bivariable reanalysis of the individual reported data points shows a highly significant association between both plasma meperidine (P = 0.0021) and baseline HCVR slope (P < 0.0001) and HCVR after meperidine administration (Fig. 1). These results suggest that an individual’s baseline CO2 sensitivity predicts the magnitude of opioid-induced respiratory depression.

It is important to note that the above-mentioned studies were conducted before the development of new techniques for measuring ventilatory chemosensitivity. Duffin’s modification of the classic Read rebreathing technique allows for measurement of basal ventilation and ventilatory recruitment threshold in addition to sensitivity (5), in which the additional parameters may be important for the prediction of OIRD.

The effect of sleep state on the hypercapnic and hypoxic ventilatory responses may also be important. Wakefulness provides tonic excitation to the brain stem respiratory neurons and its absence during normal sleep can attenuate both HVR and HCVR, causing hypoventilation, particularly during rapid eye movement sleep (17). Opioid-induced sleep may therefore magnify the effect on respiratory control (“double trouble”), although to date there has been little done to investigate this relationship.

We propose that there is a systematic relationship between ventilatory chemosensitivity and susceptibility to OIRD and speculate that the implementation of clinical tests and interventions aimed at assessing respiratory chemosensitivity could mitigate the risk of OIRD. If this hypothesis is confirmed, testing of patients before opioid administration could identify high-risk patients. At present, the assessment of the ventilatory responsiveness to hypercapnia and hypoxia is primarily done in a laboratory setting, and current constraints on portability, ease of use, discomfort to patients, and time needed to obtain the measurements all limit the application of this technology to the clinical setting. However, it should be possible to design a simple system to measure the ventilatory effects of a CO2 challenge before and after administration of a short-acting opioid using a simple mask system (15). For patients undergoing surgery, preoperative identification of those at high risk for OIRD by adapting a traditional physiological technique for clinical use could improve the perioperative care of these patients and reduce adverse respiratory events associated with opioid therapy. This information could facilitate selection of a specific anesthetic technique, prescription of more conservative opioid dosing, or preferential use of regional anesthesia and nonopioid analgescics adjuncts. The observation that low HCVR can be increased by respiratory muscle training (16) suggests a prevention strategy that could further mitigate the risk of OIRD. In addition, these patients may benefit from enhanced, multimodal continuous respiratory monitoring in the postoperative period that includes a monitor of sleep state.

The fact that chemosensitivity measured over weeks or months is somewhat variable (9, 25) could be considered a weakness of this hypothesis. However, compared with the interindividual variability in the general population, the temporal variability over weeks is small. Moreover, variation in HCVR may actually reflect meaningful fluctuating degrees of individual susceptibility to OIRD.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
Author contributions: J.V.F.P. and R.E.M. conception and design of research; J.V.F.P. and R.E.M. analyzed data; J.V.F.P. and R.E.M. prepared manuscript; J.V.F.P. and R.E.M. revised manuscript; J.V.F.P. and R.E.M. approved final version of manuscript.

REFERENCES