

# Postoperative Apnea Induced by Fentanyl and Other Multiple Respiratory-Modulating Factors

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## Abstract

**Purpose:** Opioids are concerned as a major cause of postoperative respiratory depression. In the immediate postoperative period, however, other factors can produce instability of breathing such as pain, agitation, and residual effects of anesthetics. Such factors might be overlooked masked by the fear for opioid-induced respiratory depression. We report a case who presented apnea immediately after emergence from anesthesia that we considered was produced by an interaction among such factors accompanied with fentanyl-induced respiratory depression. **Clinical Features:** A 31-year-old woman underwent ovarian cystectomy under general anesthesia with continuous infusions of propofol and remifentanyl, and bolus doses of fentanyl. Transversus abdominis plane blocks with ropivacaine were given upon completion of surgery. She complained of severe wound pain and was agitated at the emergence from anesthesia. Fentanyl 50 µg was administered intravenously. In several minutes, she developed apnea, unconsciousness, and difficulty of mechanical ventilation via a face mask. The estimated effect site concentration at the onset of the episode (2.9 ng·ml<sup>-1</sup>) was approximately the same (3.0 ng·ml<sup>-1</sup>) as after 30 min when she regained consciousness and spontaneous breathing. It indicated that not only direct inhibition of the respiratory center by fentanyl but also other stimulatory and inhibitory factors contributed to respiratory arrest. **Conclusion:** In the immediate postoperative period, transient factors, such as pain, mental instability and anesthetic residues, which are indirectly-related with breathing, can interact each other and with opioids. The interaction would induce apnea through mechanisms combined among direct inhibition of the respiratory center, and modulation of chemical and cortical controls of breathing.

## Keywords

Postoperative Apnea, Opioids, Pain, Chemical and Cortical Controls of Breathing

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## 1. Introduction

Opioids are feared as inducing postoperative respiratory depression [1] [2]. However, breathing is generated in the brain stem respiratory center, and modulated through largely a combination of chemical, reflex, and cortical control mechanisms. We present here a case agonized by respiratory arrest occurring at the immediate postoperative period. The apnea was considered produced not solely due to opioids but by a multitude of factors, either inhibitory or stimulatory to breathing, interrelating with one another. The factors include chemical and cortical controls of breathing, pain, and respiratory mechanics as well as inhibition of the respiratory center by fentanyl. This report emphasizes the importance of comprehensive knowledge of the respiratory effect of opioids, and other factors that can affect chemical and cortical controls of breathing.

Written consent for publication of this case was obtained from the patient. The Institutional Review Board of Tokyo Women's Medical University declared the study exempt from approval.

## 2. Case Report

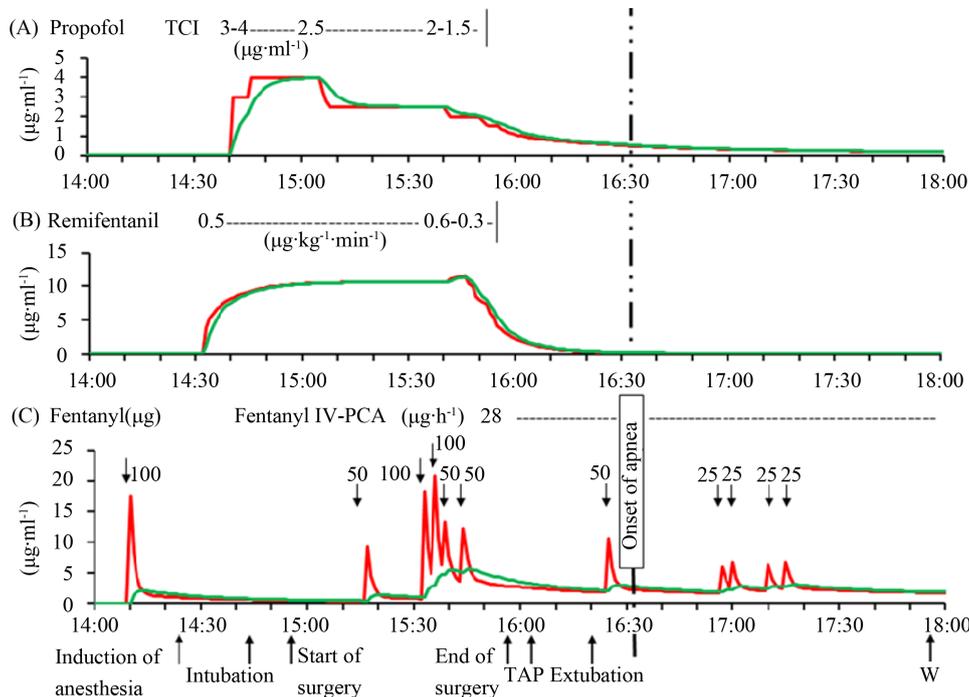
A 31-year-old woman (163 cm, 54 kg) was scheduled for resection of an ovarian cyst. Preoperative routine examinations revealed no abnormalities. She had no history of allergies. At the preoperative visit, she expressed extraneous concerns about postoperative pain seemingly beyond the extent of normal preoperative anxiety. General anesthesia combined with epidural anesthesia was planned. We, however, were forced to halt epidural catheterization due to her intolerance to the procedure despite a prior intravenous (i.v.) administration of 100  $\mu\text{g}$  fentanyl and an affable conduct. General anesthesia was induced with remifentanyl 0.5  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  and a target-controlled infusion (TCI) of propofol targeted at the effect-site concentration of 4.0  $\mu\text{g}\cdot\text{ml}^{-1}$ . Tracheal intubation was facilitated by an i.v. rocuronium 40 mg. Anesthesia was maintained with propofol TCI at 1.5 - 2.5  $\mu\text{g}\cdot\text{ml}^{-1}$  and a continuous i.v. remifentanyl 0.1 - 0.6  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , supplemented with bolus doses of fentanyl 50 - 100  $\mu\text{g}$  each (a total of 450  $\mu\text{g}$ ). One minute before the end of surgery, an i.v. patient-controlled analgesia with fentanyl (IV-PCA, a background rate of 0.52  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  with rescue doses of 28  $\mu\text{g}$  and 20 min lockout intervals) was initiated. The operation time was 62 min. On the completion of surgery, ultrasound-guided transversus abdominis plane (TAP) blocks both sides were administered with ropivacaine 80 mg on each side. Fifteen minutes later, sugammadex 200 mg was administered upon arousal. Immediately following extubation, she not only exhibited agitation and hyperventilation accompanied with occasional breath-holdings, but also complained of severe pain rubbing her lower abdomen. Fentanyl 50  $\mu\text{g}$  was administered, but seemed ineffective. Within a few minutes she suddenly lost consciousness and became apneic. Mechanical ventilation through a face mask with oxygen (8  $\text{L}\cdot\text{min}^{-1}$ ) was initiated instantaneously. It, however, was inefficient, and oxygen saturation dropped to approximately 60%. Supplementation of sevoflurane 5% into the inspired gas gradually ameliorated ventilation difficulty, restoring oxygen saturation to 98%. She regained consciousness and spontaneous breathing 30 min later and complained again of moderate wound pain. Additional four aliquot doses of i.v. fentanyl 25  $\mu\text{g}$  each in 20 min, and a rectal acetaminophen 300 mg did not alleviate pain, and therefore we performed a wound infiltration of ropivacaine 120 mg.

In the ward, IV-PCA was continued for 48 h postoperatively. The patient self-administered rescue doses 12 times for the first 12 h. Oral loxoprofen 180  $\text{mg}\cdot\text{day}^{-1}$  was started on the postoperative day 3, and pain gradually subsided. Otherwise, she experienced an uneventful postoperative course and discharged from the hospital on the postoperative day 7.

The concentrations of propofol, remifentanyl, and fentanyl in the effect sites and in plasma were estimated using pharmacokinetic and pharmacodynamic models developed by Mash for propofol, by Minto for remifentanyl, and by Shafer for fentanyl, respectively. (TIVA Trainer<sup>®</sup> version 9, EuroSiva, The Netherlands). The results were presented in [Figure 1](#).

## 3. Discussion

An amount of fentanyl 50  $\mu\text{g}$ , administered at the emergence from anesthesia was perhaps insufficient as a sole cause of apnea induced by depressing the activity of the respiratory center. Indeed, the estimated effect site concentration of fentanyl at the onset of apnea (2.9  $\text{ng}\cdot\text{ml}^{-1}$ ) was approximately the same as that at regaining spontaneous breathing and consciousness (3.0  $\text{ng}\cdot\text{ml}^{-1}$ ) ([Figure 1](#)). Therefore, it is likely that a multitude of factors, either concerting or conflicting, intertwined complexly one another, producing respiratory arrest as schematized



**Figure 1.** Estimated concentrations at the effect site (green lines) and in plasma (red lines) of propofol (A), remifentanyl (B), and fentanyl (C) during the clinical course. They were estimated using the Marsh model for propofol, the Minto model for remifentanyl, and the Shafer pharmacokinetic and pharmacodynamic model for fentanyl. (TIVA Trainer<sup>®</sup> version 9, EuroSiva, The Netherlands). TAP: transversus abdominis plane blocks; WI: wound infiltration of ropivacaine.

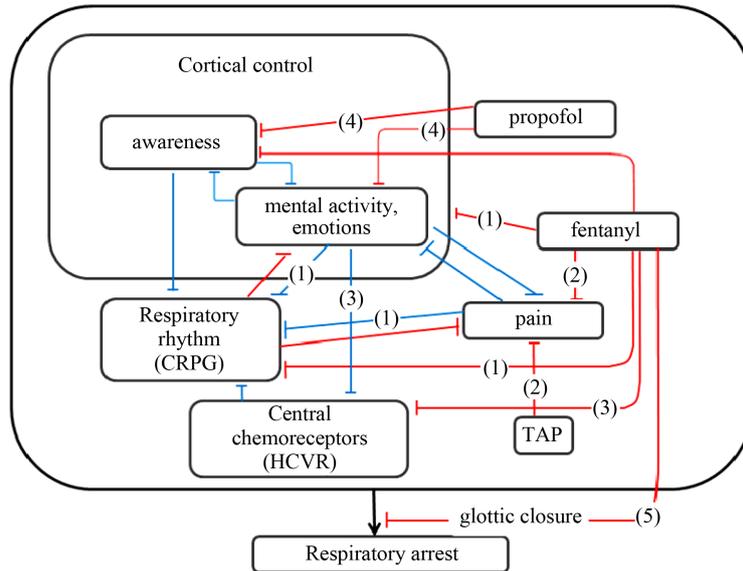
in **Figure 2**. Plausible mechanisms responsible for the apnea that we consider are: 1) an excitation of the respiratory center by pain and instabilities in mentality and emotions, and contrarily an inhibition of the respiratory center by fentanyl; 2) a reduction of pain-augmented respiratory drive by fentanyl and TAP blocks; 3) hyperventilation by emotional distress and pain leading to hypocapnia, and a blunted ventilatory response to carbon dioxide by fentanyl; 4) respiratory depression due to residual narcosis by propofol; and 5) glottic closure induced by fentanyl. Considering the marginal concentrations estimated of remifentanyl both in the effect site and in plasma, the effect of remifentanyl would be negligible.

At the emergence from anesthesia, the patient was agitated and complained of severe wound pain. Emotional upset stimulates the respiratory center [3]. Pain works itself as a respiratory stimulant [4] by acting both on the respiratory center [5] and on the central chemoreceptors [6]. Both emotional disruption and pain aggravate each other [7], further stimulating breathing and thus leading to a vicious spiral of hyperventilation. On the other hand, respiratory inhibitions, though each small, by residues of propofol and fentanyl administered during anesthesia [8] might still remain at the period. It is, therefore, likely that the patient's breathing was maintained on a delicate balance between stimulatory and inhibitory effects of these factors.

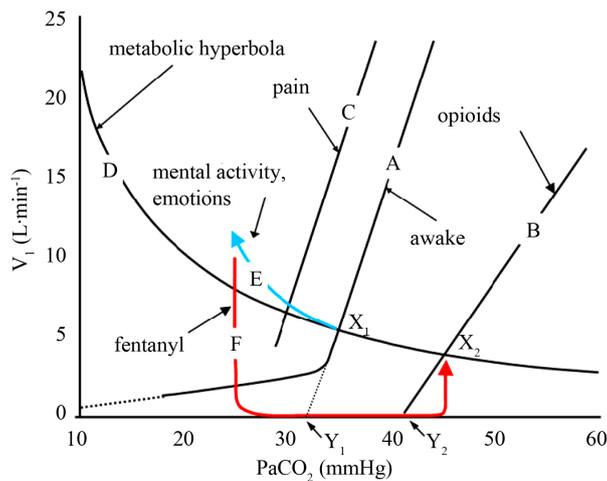
It is possible that two analgesic regimens, TAP blocks and i.v. 50 µg fentanyl, at the emergence from anesthesia disrupted the balance, resulting in apnea. The TAP blocks reduced wound pain, possibly diminishing pain-augmented respiratory drive. Indeed, several studies and case reports indicated an important role of pain in the maintenance of breathing. Combes *et al.* [9] demonstrated in patients treated postoperative pain by i.v. morphine that complete pain resolution by supplemental peripheral nerve block worsened respiratory depression. In patients medicated large doses of slow-release opioids without successful relief of cancer or chronic pain, spinal cordotomy or epidural analgesia produced life-threatening respiratory arrest [10]-[12]. These studies suggest that unrelieved pain offsets opioid-induced respiratory depression, thus helping barely keep respiratory drive. It was indicated that complete resolution of pain attained by spinal cordotomy or epidural analgesia diminished pain-stimulated respiratory drive.

Furthermore, the 50 µg fentanyl administered immediately after the emergence from anesthesia decreased pain intensity, awareness, and emotional instability, that would reduce in an interactive manner those respiratory

stimulating effects [5] [6] [8] [13] [14]. In addition to a direct inhibition of the respiratory center, chemoreceptor depression by the 50  $\mu\text{g}$  fentanyl would be enhanced under the hyperventilation-induced hypocapnia, more likely inducing apnea (Figure 3) [15]. Besides, we experienced a difficulty in mechanical ventilation via a face mask at the onset of apnea. It indicated that opioid-induced laryngeal closure might take some role in the respiratory arrest [16]-[19].



**Figure 2.** Plausible model interpreting respiratory arrest induced in the patient. CRPG, HCVR, and TAP denote the central respiratory pattern generator (the respiratory center), hypercapnic ventilatory response, and transversus abdominis plain blocks, respectively. Bracketed numbers are either stimulatory or inhibitory effects listed in the text. See the text in detail. Blue and red lines indicate stimulatory and inhibitory effects, respectively.



**Figure 3.** Effects of opioids, pain, and emotions on the hypercapnic ventilatory response (HCVR).  $V_I$ , inspiratory minute volume and  $\text{PaCO}_2$ , arterial carbon dioxide tension, respectively. Lines A, B, and C indicate HCVR while awake, affected by opioids, or pain, respectively. The curve D indicates the metabolic hyperbola. Arrows E and F indicate ventilatory responses produced by emotional instability and a bolus dose of fentanyl. Points  $X_1$  and  $X_2$  indicate resting breathing levels while awake and during an administration of fentanyl. Points  $Y_1$  and  $Y_2$  are the apneic thresholds.

The aforementioned mechanisms are only speculative, and we are unable to propose explicit mechanisms that produced apnea in the patient. We, therefore, may need to consider technical misconducts that could have precipitated the patient's breathing condition. Residual remifentanyl still existing in the venous route could have caused apnea. It was, however, unlikely because the remifentanyl infusion was terminated with the syringe unhitched more than 30 min before the apneic episode. Accidental retrograde infusion of remifentanyl into the i.v. fluid bag would be another possibility. It is also negated since a one-way valve was in place between the syringe line and the i.v. fluid bag.

We might lack a thoughtful anesthesia management. First, the patient revealed apnea some 30 min after TAP blocks and at the emergence from anesthesia. Griffiths *et al.* [20] reported that 3 mg·kg<sup>-1</sup> of ropivacaine administered by TAP blocks in adult female patients resulted in potentially toxic plasma concentrations with the peak concentration occurring 30 min post-injection. Latzke *et al.* [21] demonstrated that a time to the maximum concentration of plasma ropivacaine was 0.44 ± 0.36 h (mean ± SD) after injection in 8 healthy volunteers administered 150 mg ropivacaine by TAP block. However, neither signs of neurotoxicity [22] nor cardiovascular instability were detected in our case. It indicates that the central effect of ropivacaine on the respiratory depression, even if it existed, would be negligible. Though, we might better administer TAP blocks preoperatively. Second, we administered bolus doses of fentanyl while applying a continuous infusion of remifentanyl. We intended to use fentanyl for a smooth transition from remifentanyl for anesthesia to postoperative IV-PCA fentanyl. However, a short duration of the surgery (62 min) made us to administer fentanyl in the midst of remifentanyl infusion. Third, high preoperative anxiety was shown to be negatively associated with recovery from anesthesia and control of postoperative pain [23]. A use of anxiolytics in addition to analgesics might be an appropriate choice at the emergence from anesthesia since the patient could be expected to be susceptible to postoperative agitation, considering her fragile mentality [24]. Fourth, an insufflation of sevoflurane in an attempt to relieve ventilation difficulty might be inappropriate [25]. However, we were unable to immediately prepare intravenous glottis dilators such as a muscle relaxant and propofol when we faced with the ventilation difficulty.

#### 4. Conclusion

In the immediate postoperative period, transient factors such as pain, mental instability, and anesthetic residues, which are indirectly related to breathing, can interact with each other and with opioid. Such interactions can induce apnea through mechanisms combined among direct inhibition of the respiratory center, and chemical and cortical controls of breathing. This report emphasizes the importance of comprehensive knowledge of the respiratory effect of opioids, and other factors that can affect chemical and cortical controls of breathing in the postoperative pain management.

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