Fetuses, Fentanyl, and the Stress Response

Signals from the Beginnings of Pain?

SOME scientific discoveries trigger a *de rigueur* consideration of physiologic principles (and our philosophical positions), often catalyzing the need for major changes in clinical practice. The elegant studies reported by Fisk *et al.*[1] in this issue of ANESTHESIOLOGY provide one such example by challenging the scientific precepts that have traditionally driven the clinical approach to fetal and perinatal medicine. This research group has taken advantage of a unique clinical situation to determine whether the endocrine stress responses associated with intrauterine exchange transfusions can be alleviated by fentanyl in the human fetus.

In specialized centers, hemolysis resulting from Rh-isoimmunization can be treated by exchange transfusions, performed on 2–5 occasions by cannulating either the fetal intrahepatic vein (IHV technique) or the umbilical vein at the insertion of placental cord (PCI technique). Transfusions *via* the IHV technique require the insertion of a needle through the abdominal wall, the peritoneal reflection, and the hepatic capsule, thus eliciting endocrine stress responses in the fetus (cortisol, β endorphin),[2] in contrast to the PCI technique, which does not transgress any tissues with sensory innervation and does not seem to elicit any stress responses.

Although it would have been ideal to randomize all patients prospectively to undergo PCI or IHV procedures with or without fentanyl in a crossover design, this was precluded by technical considerations as well as by the fact that not all fetuses require multiple intrauterine transfusions. Therefore, the investigators performed a "paired longitudinal analysis" to compare the IHV-stimulated stress responses with or without fentanyl and an "unpaired cross-sectional analysis" to determine whether the fetal stress responses after IHV transfusion with fentanyl analgesia were comparable to those after the PCI technique. Their findings indicate that fentanyl attenuated the fetal β-endorphin stress responses, but the cortisol responses were not statistically different. One reason for this discrepancy could be that the study had insufficient power to examine a fentanyl effect on the more modest cortisol responses stimulated by IHV transfusions. Steroid biosynthesis in fetal adrenal cortex is immature, resulting in the secretion of precursor adrenocortical hormones in response to pain or stress,[3] which were not measured. Activation of the hypothalamic–pituitary–adrenal axis from the release of corticotropin-releasing factor and related neuropeptides (*e.g.,* arginine vasopressin, norepinephrine) also activates the sympathetic nervous system *via* the posterior hypothalamic nuclei.[4] Perhaps Fisk *et al.*[1] could have measured other endocrine markers (*e.g.,* adrenocorticotropin hormone, catecholamines, or the precursor steroid hormones) to better characterize the fetal responses to IHV transfusions.

The hormonal stress responses seen by Fisk *et al.*[1] do not necessarily indicate fetal pain perception, nor does a fentanyl dose (12.5 μg/kg of estimated fetal weight) administered *after* IHV cannulation equate with fetal analgesia or anesthesia. These authors have adequately discussed the technical constraints, limitations in study design, and alternative explanations for their results. Nevertheless, even to the skeptics, these data provide convincing evidence for pain-induced stress responses in fetuses between 20 and 35 weeks of gestation, confirming previous work by the same investigators[2,5-8] and preliminary findings from others.[9] For example, the pulsatility index of the middle cerebral artery decreased within 70 s after painful stimulation in fetuses from as early as 16 weeks of gestation.[7] Such robust physiologic responses would be unlikely if human fetuses were impervious to the pain induced by IHV needling.

Despite the possibility of direct cardiovascular or hormonal effects,[10-12] the most prominent effect of intravenous fentanyl is analgesia and sedation. Other physiologic changes in the fetus may be a consequence of its analgesic effect.[13] The responses of fetuses given fentanyl in this study were comparable to the physiologic and behavioral responses of preterm neonates receiving fentanyl for analgesia and sedation,[3,14] despite a lower gestational age (22–32 weeks). Therefore, for some clinicians at least, these data may indicate that the human fetus is capable of responding to pain, which can be treated by opioid analgesia. To be convinced, other clinicians may need to see functional magnetic resonance images or direct neurophysiologic recordings from the somatosensory cortex (or the dorsal horn, thalamus, or other brain areas) from fetuses undergoing invasive procedures with or without analgesia.

The clinical and philosophical importance of these findings hinges on the authors' assertion that a functional pain system develops in the human fetus by the third trimester of pregnancy. Even if their nociceptive pathways and reflexes are physiologically active, do humans consciously experience pain from intrauterine needling? Does consciousness occur at birth or does it exist *in utero*?

Fetal behavior *in utero* must be differentiated from that of premature infants because of the possibility that the process of birth and the demands of independent survival may trigger the expression of consciousness. Perhaps the widespread and abundant expression of *c-fos* and other genes immediately after birth[15] reflect the neuronal correlates of consciousness "developing" at birth. Evidence from the studies of postnatal behavior in preterm infants, which show multiple parallels with the behavior and capabilities of term infants, could be used to support the hypothesis that consciousness develops at the moment of birth.[16] However, the question of fetal consciousness is fraught with intense controversy. The British Commission of Inquiry into Fetal Sentience[17] declared that fetuses may be conscious from 6 weeks of gestation, whereas the Royal College of Obstetrics and Gynaecology[18] countered that fetuses cannot be considered sentient before 26 weeks of gestation. Hormonal or circulatory responses do not vouchsafe conscious pain perception, although their absence would be more likely if sensory stimuli from these invasive procedures were not reaching the thalamus and hypothalamus.

Afferent inputs can alter the activity of neurons in the neocortical alange by 20 weeks of gestation, when thalamocortical and cholinergic afferents form synapses with the upper subplate neurons,[19] whereas noradrenergic and dopaminergic fibers start to penetrate the subplate zone by 13 weeks of gestation and reach the cortical plate by 16 weeks.[20] Thalamocortical axons penetrate the primary somatosensory cortex by 24 weeks of gestation,[21] providing the final anatomic link for the developing somatosensory system. Therefore, somatosensory evoked potentials were recorded from the sensory cortex of 25-week preterm neonates.[22] From approximately 20 weeks of gestation, electroencephalo-graphic recordings and ultrasound studies can differentiate sleep states and wakefulness,[23,24] as well as responses to touch[25] and sound.[26] Experimental paradigms investigating the prenatal acquisition of memories in the third trimester of pregnancy further support the concept of fetal consciousness.[27] To us, all these lines of evidence suggest that fetal consciousness develops from about 20–22 weeks of gestation.

Accumulating data may confirm or refute these tentative conclusions. However, we believe that current practice should incorporate the use of some form of analgesia or anesthesia for human fetuses subjected to surgical or invasive procedures. Direct administration of fetal anesthesia is the exception rather than the norm; most commonly, the mother is given systemic analgesia or general anesthesia for the procedure.[28] A few specialized centers currently perform numerous surgical procedures for the correction of anatomic malformations (*e.g.*, those leading to hydronephrosis, hydrocephalus), and the complexity, range, and numbers of these procedures seem to be increasing.[29] As more and more anesthesiologists are called on to deliver anesthesia and monitor women undergoing these procedures, the needs of the fetal patient should also be kept in mind.[30–32]

Major fetal surgery or repetitive invasive procedures performed without consideration for the analgesic and anesthetic requirements of the fetus[33] may or may not have the same long-term consequences associated with prolonged or repetitive neonatal pain. These have been the focus of intense inquiry recently.[34–38] Because of the epochal developmental changes occurring in the immature brain during the third trimester of pregnancy, exposure of the unanesthetized fetus to surgery or invasive procedures may have an increased potential for long-term neurodevelopmental consequences.[39] Neonatal rats treated with opioids require much higher doses for subsequent clinical effects,[40–42] whereas the long-term neurodevelopmental consequences of prolonged opioid exposure in ex-preterm neonates seem to be relatively benign.[43]

The limited evidence available suggests that fetal analgesia, provided for short periods with judicious doses of opioids, may have relatively few long-term detrimental effects and should be given during invasive *in utero* procedures. With this line of investigations, Fisk *et al.*[1] have opened the door for the development of an entirely new field of fetal anesthesia, requiring the development of newer clinical skills, innovative anesthetic techniques, and perhaps novel ways of examining immediate and long-term clinical outcomes.

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Common Practice and Concepts in Anesthesia: Time for Reassessment

Is the Sniffing Position a "Gold Standard" for Laryngoscopy?

ANESTHESIA training begins with a long series of "commandments." One of these is "Direct laryngoscopy is

This Editorial View accompanies the following article: Adnet F, Baillard C, Borron SW, Denantes C, Lefebvre L, Galinski M, Martinez C, Cupa M, Lapostolle F: Randomized study comparing the "sniffing position" with simple head extension for laryngoscopic view in elective surgery patients. ANESTHESIOLOGY 2001; 95:836–41.

best performed with the patient's head in the 'sniffing position' because it permits a better laryngeal view." This dictum has rarely been questioned before Adnet *et al.*[1,2] reassessed the value of the sniffing position in their series of clinical investigations. Using magnetic resonance imaging techniques,[1] they measured the angles of three anatomic axes (mouth [MA], pharynx [PA], and larynx [LA]), and demonstrated that neither the sniffing position nor simple neck extension achieved alignment of the three axes. Conversely, both positions resulted in approximately equal angles between the line of vision and LA as compared with the neutral head position. Although that study was performed in awake human

volunteers without a laryngoscope in place, the results called into question the so-called three-axes alignment theory and the superiority of the sniffing position.

In this issue of ANESTHESIOLOGY, the research group of Adnet *et al.*[2] extended their work and evaluated whether the sniffing position produced better glottic visualization during direct laryngoscopy than simple neck extension did. The study was performed in 456 anesthetized, nonparalyzed adults. They found that the incidence of difficult laryngoscopy (defined as Cormack grade 3 or 4) was 11.4% in the sniffing position and 10.7% with simple neck extension. In addition, the distribution of Intubation Difficulty Scores (a measurement also developed by this group) did not statistically differ between the two positions. This study confirmed the results of their magnetic resonance imaging assessment in clinical settings.

This kind of rigorous reassessment of a critically important clinical issue deserves our highest regard. However, their findings should not be carelessly interpreted. While I agree with inappropriateness of the three-axes alignment theory, the *inferiority* of the sniffing position for direct laryngoscopy was not shown in either the current trial or their previous magnetic resonance imaging study. Although they demonstrated that simple neck extension is as good as the sniffing position in most situations, they also showed that the sniffing position is advantageous in obese patients and patients in whom head extension is limited.

It was a great shock for me to learn that the sniffing position had become a "gold standard" since the historic article of Bannister and Macbeth[3] published in 1944 and to realize how many anesthesia textbooks had recommended this as the best head and neck position for laryngoscopy and had adopted the three-axes alignment concept as a theoretical background. Although the sniffing position has an advantage over the neutral head position for laryngoscopy, it is surprising that a systematic search for a better head and neck position has not captured the interest of the anesthesia community. Even the excellent studies performed by Adnet *et al.*[1,2] do not answer the question "What is the best head and neck position for direct laryngoscopy?"

The anatomy and biomechanics of the head and neck differ significantly among patients and, moreover, change differently in response to head and neck positioning. Furthermore, varying responses to external laryngeal pressure and different types of laryngoscope blades further complicate this issue. With this complexity, all possible combinations cannot be easily tested. What is needed is a new conceptual framework to understand the mechanisms of laryngoscopy, a framework that moves beyond the three-axes alignment theory. Adnet *et al.*[1] demonstrated that in comparison with the neutral head position, the sniffing position and simple neck extension both reduced the angle between MA and PA but increased the angle between PA and LA. This
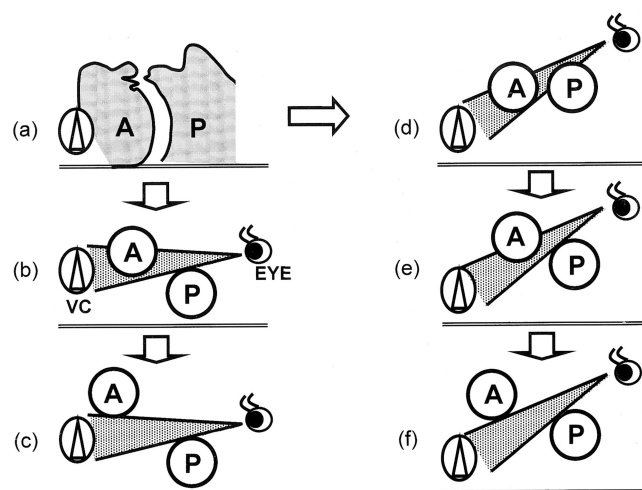

Fig. 1. Schematic explanation of dynamic configurational changes during direct laryngoscopy procedures with simple neck extension (*b, c*) and the sniffing position (*d–f*). (*a*) Original structural configuration, (*b*) neck extension on the flat table, (*c*) laryngoscopy, (*d*) placing a pillow, (*e*) slight extension of the plane of the face, (*f*) laryngoscopy. A = obstacles located anterior to the oral airway space (tongue, epiglottis, mandible, and others); P = obstacles located posterior to the oral airway space (upper teeth, maxilla, head, and others); VC = vocal cords. Shaded area represents visual field.

suggests that approximation of the *three* axes is not essential for the glottic view but rather indicates that reduction of the angle between MA and PA, caused by upper cervical extension, is fundamental to aligning the line of vision and LA. Unfortunately, this kind of axial theory does not take into consideration the interaction between anatomic axes and surrounding structures, or laryngoscopy itself.

Cormack and Lehane[4] explained, based on anatomic consideration, that three main factors block the line of vision during laryngoscopy: upper teeth and forward displacement of the larynx and downward displacement of the tongue. Their explanation can be developed into a more generalized concept, which may be useful in understanding the steps in dynamic structural interactions during laryngoscopy as well as mechanisms of difficult laryngoscopy. Our aim during laryngoscopy is to reach the vocal cords through the originally curved, oral airway space (fig. 1). As illustrated in figure 1a, there are two groups of obstacles between our eyes and the vocal cords: obstacles located posterior to the oral airway space (upper teeth, maxilla, head, and others) and obstacles located anterior to the airway (tongue, epiglottis, mandible, and others). Raising the head from the table in the sniffing position (anterior flexion of the lower cervical spine) produces upward movement of both obstacles (fig. 1d). Slight extension of the facial plane from the horizontal (extension of atlantooccipital joint) moves the posterior obstacles downward (fig. 1e). In contrast, simple neck extension on a flat operating table produces upward movement of the vocal cords and anterior ob-

stacles (fig. 1b). Considering that the essential action of direct laryngoscopy is to move the anterior obstacles upward, caudally allowing complete visualization of the vocal cords (figs. 1c and f), the fundamental role of positioning is to shift the posterior obstacles downward, ensuring posterior field of vision, whereas optimal position of the laryngoscopist's eyes may differ between positions. Furthermore, backward and upward movement of the vocal cords by externally applied forces may result in improvement of the visual field. Unfortunately, although this "obstacle theory" explains why limited neck extension prevents proper rearrangement of the obstacles during positioning, it does not clarify the mechanisms by which this is offset by the sniffing position. However, the theory does predict difficulty in visualization of the vocal cords when the obstacles are abnormally located (receding mandible, hanging epiglottis, prominent upper incisors) or increased in size (macroglossia, tumors, swelling, obesity) or when movement is limited in response to positioning and laryngoscopy (limited mouth opening, limited neck extension, obesity). For example, obesity may increase the size of the obstacles, limit the movement of the anterior obstacles, and, of course, also interfere with the laryngoscopy handle. Although conceptual understanding of the mechanisms underlying direct laryngoscopy is crucial for reducing the chances of airway misadventures and improving the safety of endotracheal intubation, this theory or any other new concept needs scientific validation.

Finally, I would like to make one comment. It is tempting to argue that recently introduced alternative intubation techniques make some of these issues obsolete. Although the introduction of new airway management techniques (*e.g.*, fiberoptic devices, intubating laryngeal mask airways)[5] may someday render direct laryngoscopy an anachronism, that time is far in the future. In the interim, I strongly urge anesthesiologists to follow the lead of Adnet *et al.*[1,2] in seeking better techniques through systematic and scientific examinations of the basic biomechanics of laryngoscopy.

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