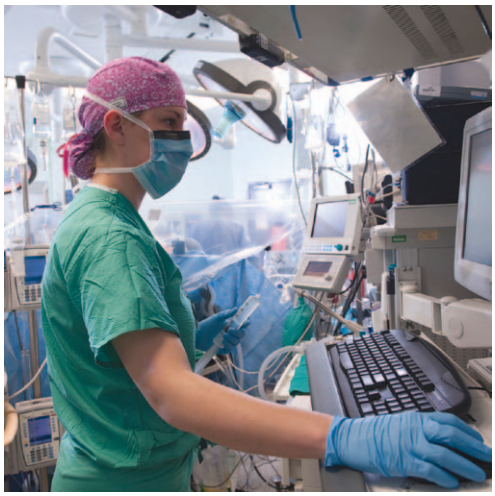
Neurophysiology and Intraoperative Nociception

New Potentials?

GENERAL anesthesia is a neurophysiologic state defined by numerous therapeutic endpoints, including unconsciousness, amnesia, immobility, and analgesia. Despite the fact that the nervous system is the target for all these effects, there is currently no standard intraoperative monitor of neural function. This is due, in part, to the diversity of anesthetic actions throughout the brain and spinal cord. Although there has been significant focus on neurophysiologic techniques to ensure unconsciousness and amnesia, identifying the neural signatures of effective analgesia has received less attention. In this issue of Anesthesiology, Untergehrer *et al.*[1] explore the neurophysiologic measure of nociception as a potential method for guiding pharmacologic interventions.



"… multimodal neurophysiologic monitoring could help distinguish between an increased need for anesthesia* versus *analgesia."

It is first important to distinguish nociception from pain: nociception denotes the neural encoding and processing of noxious or potentially noxious stimuli,[2] whereas pain refers to an accompanying subjective experience. As such, ongoing nociceptive processes cannot be interpreted or reported as "pain" by an anesthetized patient during surgery, leaving the provider searching for objective indices of nociception and its attenuation by analgesics. The indices most commonly used in the anesthetized patient relate to respiratory rate (if the patient is breathing spontaneously) or hemodynamic variables (if paralyzed). However, there is a broad differential for intraoperative changes such as tachycardia or hypertension, and these measures are therefore unreliable. Past studies of nociception have examined numerous parameters, including heart rate variability,[3] heartbeat intervals and plethysmographic pulse wave amplitude,[4] skin conductance,[5,6] pupillary response,[7] and processed electroencephalographic measures.[8,9] Recently, Mathews *et al.*[10] demonstrated that a composite variability index incorporating electroencephalographic and electromyographic variability was superior to conventional hemodynamic measures in predicting an endpoint posited to reflect the balance of nociception and antinociception. However, most of these approaches rely on surrogate measures of nociception and analgesia.

Untergehrer *et al.* took a more direct approach by studying nociception-related evoked potentials. The investigators studied 60 healthy male volunteers, divided into four groups of 15 receiving increasing (but subanesthetic) concentrations of propofol, sevoflurane, remifentanil, and (s)-ketamine. In the baseline state and during two levels of drug exposure, three different neurophysiologic potentials were recorded: mid-latency auditory-evoked potentials (to assess levels of consciousness), visceral pain-evoked potentials (VPEP), and contact heat-evoked potentials (CHEP). VPEP stimulation is generated by a bipolar electrode positioned in the distal esophagus, whereas CHEP stimulation is generated by a contact heat probe applied to the skin. The study found that auditory-evoked potential amplitudes did not decrease and latencies did not increase due to either concentration of the four drugs. These data suggest that there was no global suppression of cortical activity. In contrast, VPEP amplitudes decreased as drug concentrations increased

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◆ This Editorial View accompanies the following article: Untergehrer G, Jordan D, Eyl S, Schneider G: Effects of propofol, sevoflurane, remifentanil, and (s)-ketamine in subanesthetic concentrations on visceral and somatosensory pain–evoked potentials. Anesthesiology 2013; 118:308–17.

for propofol, sevoflurane, remifentanil, and (s)-ketamine. Similarly, CHEP amplitudes decreased with increasing concentrations of propofol, sevoflurane, and remifentanil; ketamine did not result in a statistically significant decrease. Untergehrer *et al.* went on to reveal differential effects of these anesthetics and analgesics on the potentials.

The finding that VPEP and CHEP were reduced in the absence of global cortical suppression (as measured by auditory-evoked potentials and confirmed by permutation entropy) heralds the possibility of neurophysiologic assessment of nociceptive pathways. This would represent an advance beyond the current practice of using hemodynamic changes, nonneurophysiologic measures, or neurophysiologic measures such as frontal electroencephalography, which do not specifically reflect nociceptive processes. The independence of nociception-related and auditory-evoked potentials in this experimental protocol suggests that intraoperative care could be guided by more refined monitoring strategies. For example, consider a situation in which a surgical patient becomes tachycardic. After ruling out primary cardiovascular causes, multimodal neurophysiologic monitoring could help distinguish between an increased need for anesthesia *versus* analgesia. Such a technique could, therefore, help the clinician avoid unnecessary dosing of anesthetics or opioids, which often occurs with an empirical approach. Furthermore, Untergehrer *et al.* provide a tool that might help test and discriminate analgesic drug actions on somatic and visceral nociception. For example, ketamine is known to have potent analgesic effects, but the current study was able to demonstrate a stronger effect on visceral rather than somatic pain. Information such as this could also guide pharmacologic treatment of the surgical patient.

Although the findings are intriguing, we must consider the limitations of the experimental design and the relevance to a real-world clinical setting. First, only healthy, non-anesthetized male volunteers were studied. Can these potentials be measured accurately if cortical function is more profoundly suppressed, as in the state of general anesthesia? Second, it could be argued that VPEP and CHEP do not have the resolution to discriminate fully between hypnotic and analgesic effects, as molecularly and pharmacologically distinct drugs such as propofol (relatively weaker analgesic) and remifentanil (relatively stronger analgesic) were not markedly distinguished by the neurophysiology. Could some of the changes observed be driven by hypnotic effects not reflected in the auditory-evoked potentials? Third, assuming they could be measured, the neurophysiologic parameters of the evoked potentials might be confounded or obscured by surgical nociception itself, the noxious stimulus of interest. Fourth, there are issues of practicality—could a busy anesthesiologist or anesthesia provider implement and monitor multiple evoked potentials? Finally, we must consider the possibility that repeated visceral or somatic noxious stimuli could have adverse consequences themselves, especially if delivered over the course of hours.

Despite these limitations, the data of Untergehrer *et al.* show us "new potentials" for more refined neurophysiologic monitoring of nociception and analgesia. Although we have far to go, their findings represent one step toward the elusive goal of directly measuring and distinguishing the therapeutic effects of anesthetics and analgesics.

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