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Aggressive Control of Intraoperative Blood Glucose Concentration

A Shifting Paradigm?

INTRAOPERATIVE management of blood glucose concentration in patients with diabetes mellitus has traditionally focused on avoidance of profound hypoglycemia or hyperglycemia. In contrast, the relative importance of strict perioperative regulation of blood glucose within the normal range has received little emphasis, in large part because the benefits and risks of such a strategy have yet to be convincingly demonstrated in controlled clinical trials. In this issue of ANESTHESIOLOGY, Ouattara *et al.*[1] provide compelling evidence indicating that tight control of intraoperative blood glucose positively affects patient outcome in diabetic patients after coronary artery bypass graft surgery. Using a multivariate analysis, the authors demonstrated that the risk of sustaining cardiovascular morbidity was increased more than sevenfold in patients with refractory hyperglycemia (defined as four consecutive determinations of blood glucose concentration exceeding 200 mg/dl despite insulin treatment) as compared with those in whom blood glucose concentration was more tightly controlled (< 150 mg/dl). The authors used a continuous infusion of insulin administered using a modified Portland protocol to treat blood glucose concentrations greater than 180 mg/dl. The objective of treatment was to maintain the blood glucose concentration between 150 and 200 mg/dl intraoperatively and less than 140 mg/dl postoperatively in the intensive care unit (ICU). Thirty-six percent of the patients enrolled in the study required insulin treatment according to the authors' criteria. Fifty percent of these patients had inadequate control of intraoperative blood glucose concentration. These findings were associated with an increased in-hospital mortality rate (11.4 *vs.* 2.4%) and a prolonged duration of stay (> 96 h) in the ICU (46 *vs.* 19%) as compared with patients in whom better control of blood glucose was achieved.

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The results of Ouattara *et al.* are quite provocative. A question that remains unanswered is whether hyperglycemia is truly a cause of increased cardiovascular morbidity and mortality or whether the correlation of hyperglycemia and cardiac complications is merely an epiphenomenon. Results from animal studies indicate that acute hyperglycemia alone, independent of chronicity, underlying diabetes, or alterations in plasma insulin concentration, adversely modulates endogenous and pharmacologically induced cardioprotective signal transduction pathways.[2] Hyperglycemia increases myocardial infarct size, impairs endothelial function, adversely affects coronary microcirculatory regulation, and attenuates coronary collateral development in part by increasing the production of deleterious quantities of reactive oxygen species and blunting nitric oxide–dependent protective mechanisms.[3] Several recent clinical trials also strongly suggest that aggressive control of blood glucose decreases overall and cardiac-related mortality in a variety of patient subpopulations. In an important prospective, randomized trial, Van den Berghe *et al.*[4] demonstrated that intensive insulin therapy (target blood glucose concentration of 80–110 mg/dl) decreased in-hospital mortality by more than 30% in patients admitted to the ICU as compared with those who received insulin only if the blood glucose concentration exceeded 210 mg/dl. Sixty percent of the patients enrolled in this study had undergone cardiac surgery. Finney *et al.*[5] demonstrated that hyperglycemia in excess of 145 mg/dl predicted an increase in mortality in ICU patients (primarily cardiac and thoracic surgical patients). Krinsley *et al.*[6] reported similar findings in patients admitted to the ICU for a variety of medical conditions involving all organ systems. Interestingly, a multivariate statistical analysis identified administration of insulin as an independent predictor of death,[5] whereas control of blood glucose concentration rather than the dose of insulin correlated with improvements in outcome.[5,7] Taken together, these experimental and clinical findings suggested that insulin may activate prosurvival pathways in myocardium[3] and, further, that control of blood glucose is likely to play an important role in protecting against ischemic injury. Interestingly, Quattara *et al.*[1] showed that preoperative use of insulin was associated with increased postoperative risk, but preoperative insulin treatment did not demonstrate a statistically significant interaction with poor intraoperative glycemic control as an independent predictor of morbidity.

These results may indicate that preoperative use of insulin identifies a higher risk group of patients, but acute, sustained intraoperative hyperglycemia independently predicts an increased risk of morbidity. The findings also suggest that it may not be possible to identify relative "insulin resistance" solely on the basis of preoperative insulin requirements, especially in cardiac surgical patients subjected to cardiopulmonary bypass (CPB). It is interesting to speculate that thiazolidinedione insulin-sensitizing agents may improve patient outcome by enhancing the degree to which tight control of blood glucose concentrations may be achieved with exogenous insulin. Large-scale clinical trials will be required to confirm this hypothesis, however.

Does *intraoperative* control of blood glucose concentration make a difference? Few studies have examined the impact of intraoperative management of blood glucose on patient outcome. Furnary *et al.*[8] evaluated the relation between average blood glucose concentration on the day of surgery and during the first 2 postoperative days on cardiac- and non–cardiac-related mortality in 3,554 diabetic patients undergoing coronary artery bypass grafting using CPB. Hyperglycemia at any time during the study period predicted cardiovascular-related mortality. Lazar *et al.*[9] prospectively compared the influence of aggressive control of blood glucose concentration with an infusion of glucose, insulin, and potassium (initiated before anesthetic induction and continued for 12 h postoperatively) and intermittent subcutaneous insulin on morbidity and mortality in patients undergoing coronary artery bypass grafting. Blood glucose concentrations averaged 170 and 140 mg/dl before CPB and in the ICU, respectively, in patients receiving glucose, insulin, and potassium as compared with 210 and 270 mg/dl, respectively, in those receiving conventional treatment. Glucose, insulin, and potassium therapy reduced the incidence of atrial fibrillation, sternal wound infections, use of inotropes, duration of ventilatory support, and mortality. The current results of Ouattara *et al.*[1] extend these previous findings and suggest that less rigid intraoperative glucose control increases the risk of cardiovascular complications. Interestingly, preoperative and postoperative blood glucose concentrations were similar in patients with and without postoperative morbidity. These findings suggest that marginal control of intraoperative blood glucose contributed to the development of adverse outcome in cardiac surgical patients. Whether an even more aggressive glucose management strategy may have further reduced morbidity in this subset of insulin resistant patients remains to be determined. Interestingly, Carvalho *et al.*[10] demonstrated that it was possible to achieve strict regulation of blood glucose during cardiac surgery when an insulin infusion was initiated before the onset of CPB when blood glucose concentration exceeded 145 mg/dl. These authors suggested that an earlier use of insulin, before the development of CPB-induced insulin resistance, may contribute to more efficient preservation of normoglycemia.

In conclusion, strong evidence exists to indicate that hyperglycemia alone, with or without diabetes, contributes to morbidity and mortality in patients at risk for myocardial ischemia and reperfusion injury, including those undergoing cardiac surgery. The preponderance of evidence also supports the contention that strict intraoperative control of blood glucose with continuous intravenous infusion of insulin favorably modifies the risk of major morbidity and mortality in patients during cardiac surgery. Whether these findings will also extend to high-risk patients undergoing noncardiac surgery has not been specifically evaluated. However, data obtained from experimental and clinical studies indicate that hyperglycemia produces a variety of deleterious effects that may adversely influence patient outcome. Therefore, we have proposed a strategy that emphasizes an intensive approach to treating and avoiding hyperglycemia in high-risk surgical patients with the objective of reducing overall morbidity and mortality in these most challenging patients.[3,11]

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Measuring Minimum Alveolar Concentration

More than Meets the Tail

ONE of the most basic defense mechanisms is generation of a vigorous response to a noxious stimulus. This is no more evident than the response to surgical intervention, whereby patients can move violently, and did so all too commonly before the introduction of anesthesia more than 150 yr ago. Therefore, immobility is an essential anesthetic goal, and the achievement of this anesthetic endpoint was used by Eger *et al.*[1] when they developed a standard of anesthetic potency. The minimum alveolar concentration (MAC) is the concentration that prevents gross and purposeful movement in 50% of subjects when a supramaximal noxious stimulus is applied. It would seem obvious that such a stimulus, if applied to an awake animal or human, would evoke an immediate and vigorous response. In this issue of ANESTHESIOLOGY, Mogil *et al.*[2] report data in mice indicating that tail clamping, although supramaximal in terms of the isoflurane requirement to produce immobility, does not always produce an immediate motor response in the awake animal. What might be the reason for this apparent incongruity?

Mogil *et al.*[2] determined isoflurane MAC in 11 genetically different mouse strains, reporting a significant MAC variation among the strains. They also examined the latency to move purposefully in response to application of the tail clamp in the absence of anesthesia. Surprisingly, they found that application of a 500-g tail clamp in the awake animal often elicited nocifensive behavioral responses only at surprisingly long latencies (range of means, 1–58.4 s), raising the issue of whether the clamp was truly supramaximal. For this reason, they repeated the experiment using a second tail clamp exerting greater force (2 kg). Not unexpectedly, MAC values were higher across strains using the stronger clamp (range, 0.99–1.59%) compared with the 500-g clamp (range, 0.86–1.2%). Furthermore, response latencies to the 2-kg clamp in the absence of anesthesia tended to be shorter for most strains, although they were actually longer in three mouse strains. Moreover, there was a significant negative correlation between MAC and nocifensive response latencies to both tail-clamp stimuli in the absence of anesthesia. These results indicate that baseline nociceptive sensitivity varies across strains and that this might influence anesthetic requirements such that animals exhibiting greater basal nociceptive sensitivity (*i.e.*, shorter response latencies) have higher MAC values.

What might account for these data? The observation that response latencies were not instantaneous in the absence of anesthesia and that, in some strains, the stronger clamp stimulus was less effective suggested the possibility that the clamp stimulus resulted in stress-induced analgesia. The authors therefore investigated the possibility that the tail clamp elicited an opioid-sensitive form of stress-induced analgesia. They found that in the absence of anesthesia, the opiate antagonist, naloxone, decreased latencies for noxious stimulus-evoked nocifensive responses to both the 500-g and the 2-kg tail-clamp stimuli in all strains. Even in the presence of naloxone, however, the response latencies were not instantaneous, suggesting that additional factors, such as nonopioid stress-induced analgesia, may influence basal nociception. Importantly, the magnitude of naloxone's antianalgesic effect was negatively correlated with the MAC, *i.e.*, the more naloxone reduced the latency to respond while the mouse was awake, the lower the MAC was. This suggests that, depending on the genetic makeup, endogenous opiates might play a role in MAC. However, there have been several studies that showed that naloxone does not alter MAC.[3–6] The data from Mogil *et al.*[2] showing a negative correlation between the extent of stress-induced analgesia and MAC makes us wonder whether this issue has been adequately addressed. Perhaps the aforementioned studies on naloxone and MAC used animals that tended to have low levels of opioid-sensitive stress-induced analgesia, and hence one would not expect naloxone to significantly alter MAC. This prompts us to suggest that a follow-up study be performed wherein the mouse strains studied by Mogil *et al.*[2] be given naloxone followed by MAC determination to address a possible MAC-sparing action of endogenous opioids. Indeed, Dahan *et al.*[7] reported that 129/SV-C57BL/6 mice exhibited a modest increased MAC after naloxone administration.

The mechanism by which stress-induced analgesia occurs is not completely understood, but it likely involves brainstem and spinal cord antinociceptive circuitry that has been intensely investigated during the past four decades.[8] Electrical stimulation in the midbrain periaqueductal gray was originally reported to prevent nocifensive responses during laparotomy in awake rats.[8] In humans, stimulation of the periaqueductal gray decreases anesthetic requirements 30%.[9] If the periaqueductal gray is involved in stress-induced analgesia in humans, it might be expected that stress may influence anesthetic requirements, but this has not been extensively investigated. There is little doubt that humans exhibit stress-induced analgesia, as suggested by reports

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that more than one third of patients admitted to a hospital for severe injuries did not experience any pain at the time of injury.[10] Furthermore, humans exhibit diffuse noxious inhibitory controls, whereby acute pain elicited by a noxious stimulus can be reduced by a preceding painful stimulus.[11] In general, the extent to which stress and anxiety modulate endogenous antinociceptive systems to thereby influence anesthetic requirements has not received much attention and, based on the study of Mogil *et al.*,[2] seems to be a worthwhile topic of further study.

To standardize MAC determination, Eger *et al.*[1] used a supramaximal stimulus. Noxious stimuli were applied to several sites, including the tail, paw, mucous membrane of the mouth, and trachea. Among these, they determined that clamping the tail of an animal seemed to be supramaximal, in that the other stimuli required lesser concentrations of anesthetic to prevent movement. Subsequently, most investigators have used tail clamping, although most parts of the body have been used, including the ears, paws, and dew claws. Likewise, in humans, a variety of stimuli have been applied at various sites. Zbinden *et al.*[12] used electrical stimulation, deep muscle pinching, and intubation. The recurring theme has always been whether the stimulus is "supramaximal." A supramaximal stimulus was originally based on the premise that increasing the intensity would not increase anesthetic requirements. Although application of more than one supramaximal noxious stimulus does not seem to increase anesthetic requirements,[1] it is unknown whether application of two or more submaximal noxious stimuli require more anesthesia compared with when either one is applied separately. Surgical patients are subjected to a wide variety of noxious stimuli, some that would be considered supramaximal and others that are likely submaximal. Although noxious stimuli can be applied with increasing intensity and time and across more and more dermatomes, the motor response achieves a maximum: One can withdraw one's arm or leg only so quickly with a finite amount of force. Hence, when the motor response reaches a maximum, increasing the stimulus intensity does not elicit further movement.

One limitation of the MAC concept is its "all-or-none" nature. However, movement resulting from noxious stimulation can be variable in its quality and quantity. When a clamp is applied to the tail of an anesthetized animal, it might move immediately, and continue to move if the clamp is left on, or it might not move until 59 s later. In both situations, however, the movement would be considered positive. At equipotent sub-MAC concentrations, we have observed less movement with halothane than with isoflurane, suggesting that anesthetics might differ in the manner in which they depress movement.[13,14] In addition, determining MAC is subjective: It requires the investigator to state that the animal (or human) either did or did not display "gross and purposeful movement."

For more than four decades, anesthetic potency has been measured using MAC. This is a remarkable record for a concept that has some limitations. Nonetheless, we remain committed to the MAC concept as it measures a clinically relevant phenomenon. We have all had patients who moved vigorously during surgery, and although the anesthetic concentration is likely to be sufficient to produce unconsciousness and amnesia, either rightly or wrongly, to the other healthcare workers in the operating room, this movement is the *sine qua non* of an inadequate anesthetic. In addition, patient movement can sometimes be disastrous, depending on the nature of the surgery. The data from Mogil *et al.* demonstrate that there are likely to be genetic factors that influence anesthetic requirements and that pain modulation systems might be involved in responses to the "supramaximal" stimuli normally used to determine MAC.[2] Understanding these genetic factors, pain modulation systems, and how anesthetics produce immobility will go a long way to developing safer anesthetics.

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Preventive Analgesia to Reduce Wound Hyperalgesia and Persistent Postsurgical Pain

Not an Easy Path

IN perioperative medicine, we continue to examine relatively brief anesthetic treatments during and immediately after surgery for evidence of substantial, sustained postoperative benefits. This preventive concept is being tested against postoperative cognitive dysfunction, deficits caused by neurologic injury, adverse perioperative myocardial events, the systemic inflammatory response, and the risk of developing persistent postsurgical pain. In this issue of ANESTHESIOLOGY, Lavand'homme *et al.*[1] describe analgesic protocols that decrease the area of hyperalgesia surrounding an incision and influence late, residual pain after colectomy.

The search for preventive analgesic treatments with prolonged benefits continues in part because pain research has emphasized the plasticity of the nociceptive system and pain memory. The perioperative period is ideal for translating concepts such as pain memory, plasticity, and preventive treatments because the nature of the injury (surgery), its onset, duration, and degree are generally known; in addition, the patients can be assessed before the injury to evaluate the role of predisposing factors (hereditary, psychosocial, and others).

The first widespread attempt to translate the concept of plasticity and postoperative pain was in trials of the timing for administration of anesthetic and analgesic treatments. Now, it is generally agreed that starting an analgesic treatment before surgery has minimal benefits compared with starting the treatment after surgery begins or even administering the treatment at the conclusion of surgery.[2] However, before we conclude that plasticity has little role in postoperative pain, recognize that clinical plasticity may depend on a variety of factors such as the particular surgery, the type and duration of analgesic treatment, the stimulus modality tested, and the preoperative characteristics of the patients.

Experimentally, plasticity has been described using a variety of models.[3,4] Plasticity may be present on nociceptive nerve terminals producing enhanced responses in these primary afferents, *i.e.*, peripheral sensitization; however, a far greater emphasis has been made on plasticity of pain transmission in the central nervous system, from which several models have been described. The question for anesthesiologists and surgeons is how these plasticity models should be applied to perioperative care. Furthermore, what treatments and for how long should we combat neuroplasticity in the perioperative period?

The study by Lavand'homme *et al.*[1] uses a combination of intraoperative, intravenous ketamine administration (an *N*-methyl-D-aspartate receptor antagonist with other pharmacologic properties) and an intraoperative or postoperative epidural analgesic cocktail in patients undergoing colectomy for malignancy. In addition to the pain assessments, the *area* of punctate mechanical hyperalgesia was quantified and almost eliminated by each of the preventive analgesic techniques. The area of punctate hyperalgesia is a measurement not typically used in clinical pain management.[5] It is thought to represent a measurement of central sensitization and therefore plasticity because the area encompasses uninjured tissue surrounding the incision. However, there was only a modest, although significant reduction in early postoperative pain scores, but no differences between postoperative pain scores with or without *intraoperative* epidural analgesia or with or without *postoperative* epidural analgesia.

Other studies using intraoperative and/or postoperative, intravenous ketamine with or without epidural analgesia[6–8] have documented suppression of the area of punctate wound hyperalgesia by ketamine. However, despite continuous suppression of the area of hyperalgesia after the ketamine infusion was stopped, the postoperative pain scores were not reduced,[6,7] questioning the relation between reduction in the area of wound hyperalgesia and clinical pain. Other studies have also shown a discrepancy between quantitative sensory testing at the incision site compared with pain scores and analgesic effects of opioids[9,10] or ketorolac.[10] In contrast, Katz *et al.*[11] found wound von Frey pain thresholds and pain scores to be lower after a preventive epidural analgesia *versus* no epidural, but interpretation is hindered because of more horizontal incisions in the epidural group, which may result in less dermatomal involvement and pain than with a vertical incision. A study of the secondary hyperalgesia response to a *preoperative* heat injury found no correlation between the quantitative sensory testing findings and the pain response to the subsequent knee operation,[12] again questioning the relation between the area of postinjury hyperalgesia and the intensity of clinical pain.

Therefore, the surgical data are not entirely consistent[6,7,9–12] compared with studies of other pain models in humans and preclinical incisional pain models where

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the area of hyperalgesia and secondary hyperalgesia are clearly plastic, modulated by pretreatments, and inhibited for periods extending beyond the expected duration of treatment.[13–15] However, with all the popularity associated with plasticity in scientific studies, it is refreshing to discover a few consistencies—this area of secondary hyperalgesia in clinical postoperative pain seems to have commonalities with some aspects of plasticity that have been extensively characterized in preclinical studies. Clearly, further data are required to establish the relation between wound hyperalgesia and clinical pain in various surgical models and with various preventive analgesic techniques.

Given that the area of wound hyperalgesia may be decreased by specific analgesic treatments but inconsistently associated with reduction of clinical pain, the question arises whether these *early* nociceptive responses are related to the well-established risk of persistent postsurgical pain.[16] First, there is agreement that the intensity of early postoperative pain may predict the risk of development of a chronic pain state.[16] However, whether this relation is caused by neuroplasticity or preoperative disposing factors[12,16,17] remains to be evaluated. Previous studies of various analgesic techniques, including epidural analgesia, have not been consistent to document a clinical meaningful relation between the reduction of acute postoperative pain and persistent pain[18–23] despite early reduction in wound hyperalgesia in one study.[11,22] Other approaches using venlafaxine,[24] gabapentin and mexiletine,[25] or a topical local anesthetic[26] have reported some positive effects on chronic pain, but these results have not been consistent with a clinically significant reduction in early postoperative pain scores.

However, in all but one[11,22] of these studies,[18–26] no detailed assessments of wound hyperalgesia were performed, and therefore one cannot comment on the mechanisms for a potential reduction of a chronic pain state. In the study by Lavand'homme *et al.*,[1] follow-up data after 1, 6, and 12 months postoperatively showed an elimination of persistent pain by the preventive epidural analgesic techniques compared with control, which also included ketamine. These findings are somewhat surprising compared with the relatively minor effect on early postoperative pain scores but are consistent with the reduction in the area of early postoperative wound hyperalgesia, whatever the type of preventive analgesia. However, in the studies on persistent postsurgical pain,[1,6,18–26] the study design has often been suboptimal and leaves many questions to be answered: In the study by Lavand'homme *et al.,*[1] the patients underwent surgery for rectal cancer, but no specific information is given on tumor state and tumor follow-up, wound complications, stoma application, chemotherapy, radiation therapy, and psychosocial factors or on the site, type, and severity of the chronic pain state.

Although there is agreement that persistent postsurgical pain represents a clinically significant problem,[16] much research is needed before we will have a clear answer to its pathogenesis as well as its prevention and treatment. Important topics to be included in future studies are *preoperative* assessments of pain responses to a nociceptive stimulation, because these may correlate to early postoperative pain responses[12,17] and because the intensity of early postoperative pain may correlate with development of chronic postoperative pain.[16] In addition, the analgesic intervention should include multimodal techniques with several drugs to combat peripheral and central neuroplasticity[27] and with a sufficient duration of treatment as long as significant wound inflammation and hyperalgesia persists. The role of the intensity of an afferent neural blockade must also be assessed, because the dose regimens used in the epidural studies[1,6,18–22] probably only provided a limited afferent blockade of the input to the spinal cord.[28] Also, a detailed description of the surgical model regarding type of tissue injury, type and length of wound incision, surgical technique, risk of nerve lesions, and disease-specific data (cancer, chemotherapy, radiation therapy, and others) is required. Finally, the late postoperative follow-up should include detailed neurophysiologic assessment of the wound area, detailed characteristics of the chronic pain state and its social consequences, and detailed psychosocial assessment to understand the pathogenesis and treatment possibilities for persistent postsurgical pain. This specifically applies to the role of nerve injury, which may be the most important pathogenic factor leading to persistent postsurgical pain.[16,29,30]

In summary, factors influencing the area of wound hyperalgesia indicate that this plasticity shares properties with those under intensive study by basic scientists. The relation between the area of wound hyperalgesia, analgesic intervention, and the intensity of acute and persistent postsurgical pain may not appear as an easy path for the anesthesiologist and surgeon but is worthwhile to pursue. Hopefully, future studies will help us to understand in which directions to go to reach the answer.

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