Evidence-based Practice and Neuromuscular Monitoring

It's Time for Routine Quantitative Assessment

OVER the last years, a growing body of information has accumulated in the anesthesia literature about the advantages and pitfalls of various techniques used for quantitatively monitoring neuromuscular function in routine anesthetic practice and the associated incidence (and consequences) of residual neuromuscular block in the postoperative period. Many methods are available, ranging from quantitative strain–gauge techniques, electromyography, acceleromyography, phonomyography, *etc.* However, quantitative techniques are not widely used, with most anesthesiologists relying on visual or tactile assessment of the train-of-four (TOF) ratio, or, in many cases, no neuromuscular monitoring at all. One argument for such qualitative approaches to monitoring is that with modern short and intermediate acting relaxants, residual paralysis is not a clinical problem or, even if patients are not completely reversed by the end of the case, the block will dissipate in a few minutes. Another approach is "reverse everyone," which is viewed by some as uniformly easy, safe, and effective for patients given these agents.

There is now increasing evidence that this relaxed attitude to neuromuscular monitoring is unwise. The study by Debaene *et al.*, published in this issue of ANESTHESIOLOGY,[1] has a clear message to all of us. The authors examined the incidence and magnitude of a neuromuscular block on arrival in the PACU in a large group of relatively unselected patients who had received a single dose of intermediate-duration relaxant for intubation (rocuronium, vecuronium, or atracurium). Patients received no other relaxant during their surgery and did not receive reversal agents at any time. The message is that, while it may be presumed that the attending anesthesiologists felt that adequate neuromuscular function was present at the time of transfer, 45% of the patients arrived in the recovery room with a residual neuromuscular block, defined as an adductor pollicis TOF ratio of less than 0.90! Sixteen percent had a TOF ratio of less

than 0.7. Interestingly, in sufficiently cooperative patients, even clinical tests were frequently abnormal; 15% of tested patients failed a test of head lift. Even in patients tested more than 2 h after drug administration, the incidences of residual paralysis were 10 and 37% (based on a TOF ratio of less than 0.7 or less than 0.9, respectively). The specific relaxant used did not influence these incidences.

The study was not a rigorous study of drug kinetics or twitch depression and recovery. Instead, the authors examined something close to routine clinical practice; that is, the anesthesiologist was free to select the neuromuscular blocking drug, the dose, and whether to use or not use neuromuscular monitoring. There are clearly experimental problems with this approach, and it is unfortunate that the authors did not provide further information about the actual anesthetic practice (in particular whether or not some form of monitoring was used). This limits the external validity of the study. Nevertheless, the results clearly demonstrate that a disturbingly high fraction of patients did not have adequate neuromuscular function on arrival in the recovery room.

Recently, several studies focusing on this kind of broad, unselected patient population have been published.[2–8] They all found an alarmingly high incidence of residual paralysis in the recovery room despite the use of intermediate acting neuromuscular blocking agents (vecuronium, rocuronium, atracurium, and cisatracurium). There are several possible explanations for this unexpectedly high incidence. One reason might be the change in definition of clinically significant residual paralysis from a TOF ratio of 0.70 to 0.90. However, since clinical measures are also commonly abnormal, this cannot be a complete explanation. Thus, it is clear that the widespread belief that intermediate-acting muscle relaxants have a very low tendency to cause residual paralysis (and therefore, that it is not necessary to monitor or even to reverse the neuromuscular block) is very wrong. Combining the results of the current study[1] with the results from several similar investigations,[2–8] there is now sufficient information to support a general change in the attitude towards monitoring and reversal of a neuromuscular block in routine anesthetic practice.

Though anesthesiologists probably have a relatively low threshold for carrying new monitoring equipment into the operating room (*e.g.*, BIS, AEP, ST-analysis, end-tidal anesthetic gas concentrations, *etc.*), few techniques have been documented to affect patient outcome. In this

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respect, neuromuscular monitoring is no exception. However, recent studies of the use of objective (acceleration or EMG) rather than subjective (visual/tactile evaluation) monitoring techniques may help anesthesiologists find a better way to insure safe recovery from a neuromuscular block.

Visual or tactile evaluation of the TOF response is inadequate for evaluating neuromuscular function. Several studies have documented that visual or tactile evaluation of the TOF response correlates poorly with the true TOF fade.[9-11] In fact, even very experienced observers are unable to manually detect TOF or DBS fade at TOF ratio of 0.40–0.60 or more.[10] The failure of these subjective methods, including clinical bedside tests, to detect residual neuromuscular block is once again demonstrated in the current investigation.[1] Consequently, the only way we reliably can assess a neuromuscular block is by objective monitoring methods, such as acceleromyography or EMG. Based on the current literature, it is time to replace our old subjective methods with new objective measurements. Of course, this also means that there is a need for easily used and reliable equipment for this purpose.

Does the use of perioperative objective neuromuscular monitoring exclude residual neuromuscular block in the postoperative period? There are several publications on this theme, all of them pointing towards the same conclusion.[5,8,9,12] Patients being monitored using an objective method will usually arrive in the recovery room with the desired level of recovery, i.e., a TOF ratio of more than 0.70 or 0.80.[5,8,9,12] However, patients exposed to subjective neuromuscular monitoring have a high incidence of residual neuromuscular block, though their anesthesiologists judged them to have recovered adequately.[5,8,9,12] As a corollary, objective monitoring would permit anticholinesterases to be reserved for only those patients who actually need a reversal agent.

One crucial question is do residual effects of muscle relaxants actually affect patient outcome? Or in other words, it is one thing to say that patients are inadequately reversed, based on some form of neuromuscular monitoring, but it is another to conclude that this residual paralysis constitutes an increased risk for morbidity or mortality. In this respect, little data are available for intermediate acting drugs. However, one large outcome study from Scandinavia does shed light on this important topic.[13] Patients with a long-acting residual neuromuscular block due to pancuronium have a higher risk of postoperative pulmonary complications, the risk being further increased with increasing age. For instance, patients greater than 60 yr of age undergoing major abdominal operations have a 40–50% risk of a postoperative pulmonary complication if left with a prolonged residual neuromuscular block in the PACU. This important study should make us all aware of the risk involved when a patient is left with a residual neuromuscular block in the

recovery room. It also illustrates that the duration (time length) during which the patient actually is residually paralyzed is of importance, hence the strong correlation to a long-acting neuromuscular block. In this context, it is important to remember that even medium-acting neuromuscular blocking agents may become long-acting during very modest body hypothermia.[14]

Apart from the interference with pulmonary function, the consequences of a residual neuromuscular block involve other vital organ functions. First, the muscle function and coordination of protection reflexes of the pharynx and upper esophagus are impaired in individuals with a residual paralysis.[15-16] The time course of this pharyngeal dysfunction and dyscoordination is markedly longer than that of peripheral skeletal muscle groups, such as the diaphragm, larynx, hand, and face.[15-17] Since we lack methods for monitoring these vital muscle groups, we must rely on the functional relationship between these muscle groups and the TOF response in the adductor pollicis muscle. Several studies[15-16] clearly show that airway protection and control have not recovered until an adductor pollicis TOF ratio of 0.90 has been reached. Second, the ventilatory response to hypoxia is reduced during residual neuromuscular block due to a direct inhibition of the chemoreceptor activity in the carotid bodies.[18-20] Third, the ability to control the jaw and the tongue and hereby maintain the airway and speech may be impaired such that it can interfere with the protection of the airway, even in an individual without sedation or impaired consciousness.[21] Debaene et al.[1] touch on these matters in their attempts to perform two clinical bedside tests, but they do not more specifically address such effects or discuss alternative explanations for their failure. Anesthetic vapors (e.g., isoflurane and sevoflurane) and propofol may markedly impair the pharynx and esophageal coordination resulting in failed airway protection, even at subanesthetic concentrations.[22] They also cause a dyscoordination of the pharynx.[22] Residual effects from isoflurane, not directly related to sedation, thus may partly explain the inability of some of the patients to cooperate during head lift and tongue protrusion tests.

The message is short and clear—it is time to move from discussion to action and introduce objective neuromuscular monitoring in all operating rooms, not just those occupied by researchers and aficionados of muscle relaxants. I believe that objective neuromuscular monitoring is an evidence-based practice and should consequently be used whenever a nondepolarizing neuromuscular blocking agent is administered. Such monitoring is noninvasive and has little risk, and there are strong reasons to believe that its use can improve patient outcome.

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Perinatal Brain Injury: The Role of Development in Vulnerability

THE article appearing in this issue of ANESTHESIOLOGY by Ditsworth *et al.*[1] reports that cell death in the brains of piglets subjected to 90 min of deep hypothermic circulatory arrest (DHCA) is largely apoptotic, accompanied by activation of caspases 3 and 8, as well as early release of cytochrome c and the presence of Fas. This article raises several issues of interest to anesthesiologists. These include 1) the potential danger of DHCA to the developing brain and whether we can do anything to better protect the brains of these infants during surgery, 2) the role of development in determining the mechanisms of brain injury, and 3) the role of development in susceptibility to brain injury and sensitivity to neuroprotective interventions.

Although DHCA clearly provides significant protection to the brain and other organs from ischemia, the results of this article and prior reports[2-4] demonstrate that DHCA for a sufficient duration does result in brain injury. This finding is not surprising, because the extent of brain injury resulting from ischemia must in part depend on the duration of the ischemic insult, even in the presence of hypothermia. This work and that of others has shown that 60–90 min of DHCA is sufficient to cause brain cell death. Further investigation of the effects of deep hypothermia alone are needed, as well as investigation into the use of low-flow perfusion *versus* intermittent perfusion as a way to protect the brain but still permit adequate surgical conditions.

The results reported by Ditsworth *et al.*[1] focus on the mechanism of brain cell death following DHCA. Their observations strengthen the argument that much of the cell death is apoptotic by demonstrating activation of caspases 3 and 8, as well as cytochrome c release from mitochondria, a step often necessary for activation of the caspase proteases that kill the cell. Making the distinc-

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tion between different types of cell death is not a purely academic one, since different mechanisms of cell death may suggest different strategies for protection. Necrotic cell death involves swelling rather than condensation of the cell and internal organelles, random DNA fragmentation, early disruption of organelles without formation of apoptotic bodies, and early loss of plasma membrane integrity.

In contrast, apoptosis is a type of cell death with a distinct morphology consisting of nuclear condensation, early preservation of nuclear and cytoplasmic membranes, and relative preservation of cellular organelles.[5] Apoptotic cell death plays a key role in the normal development of the central nervous system.[6] As each region develops, the number of cells is reduced from the number initially generated so that the number of different types of neurons is appropriate,[7] and the number of astrocytes and oligodendrocytes is matched to the number of neurons and axons. This process results in developmentally determined vulnerable periods for specific cell populations. For example, cerebral white matter injury consisting of periventricular leukomalacia and hypomyelination are the anatomic correlates of cerebral palsy. These forms of brain injury are thought to be due to the specific vulnerability of premyelinating oligodendrocytes in the mid to late third trimester of human pregnancy when ischemia or infection/cytokine exposure may result in excessive loss of oligodendrocytes and a reduced number of mature myelinating oligodendrocytes.[8,9] This response to ischemia is not seen in older patients or animals, suggesting that the tendency of a cell to undergo apoptosis is developmentally regulated. This concept is further supported by the recent observation that expression of caspase 3 decreases during postnatal development,[10] but it increases in very old animals.[11] In addition, the pro-apoptotic Bax molecule and associated release of cytochrome c is increased in brain mitochondria from immature compared to mature animals, further indicating that early postnatal brain cells are primed to undergo apoptosis.[12]

Thus an important aspect of understanding brain injury due to cerebral ischemia requires understanding the role played by development. Although several investigators argue against a role for apoptosis in adult brain ischemia, there is much better agreement that apoptosis plays an important role in the response to ischemia in the perinatal period. Work from several laboratories studying normothermic ischemia clearly suggests that apoptotic cell death in the brain is developmentally regulated, with apoptosis being readily detected after models of perinatal hypoxia/ischemia, but less prominent in adult models of cerebral ischemia.[13-22]

Many genes involved in the cell death process have been identified. Many biochemical changes and specific signaling pathways have been shown to participate in this process. Apoptosis may result from imbalances in signaling pathways (such as lack of growth factors), may be initiated by activation of membrane receptors, and has several potential pathways for execution. These include (1) activation of proteases called caspases that carry out the cell death,[23-26] (2)participation of mitochondria in the release of proapoptotic proteins,[27,28] and (3) regulation by the bcl-2 family of proteins.[29]

Several steps in the apoptosis cascade have provided new ways to reduce ischemic cell death in models of cerebral ischemia. Caspase inhibitors and overexpression of antiapoptotic regulatory proteins (such as bcl-2) have been shown to be effective at reducing ischemic brain injury in animal models.[30-35] Despite this type of evidence, due to the heterogeneity of the morphologic picture in cerebral ischemia, there is still disagreement about the extent to which cell death during stroke involves apoptosis, necrosis, or a combination of both.[36-40]

Complicating our understanding of the mechanisms of cell death are recent findings that suggest that there are multiple methods of genetically controlled cell death and that the morphologic picture of apoptosis does not always correlate with activation of caspases nor does the appearance of a necrotic death rule out an active genetically determined type of cell death. Genetically determined types of cell death independent of caspase activation have been described,[41,42] which may still display the cellular morphology of apoptosis. Cell death in which activation of caspases is important but results in necrosis-like morphology has also been reported.[43] Recent data suggest that both caspase-dependent and caspase-independent forms of cell death are involved in cerebral ischemia.[44]

In addition to changes in the mechanisms of brain cell loss with development, the effect of the same insult changes with age. Vulnerability or the extent of injury observed in response to an ischemic insult increases as a function of age. Vulnerability to ischemia changes rapidly with age in the perinatal period as demonstrated in a study of combined focal ischemia–hypoxia in rat between the ages of postnatal days 1 and 7.[45] Brains of postnatal day 5 rats showed markedly less injury than did brains of postnatal day 7 animals. Similar changes in response to injury have also been seen in brain cell cultures.[46] Thus, although a given duration of ischemia may result in less severe injury in an infant, because this deficit will be present throughout life, it is still a matter of great concern.

Understanding differences in the mechanisms of brain injury provoked by ischemia in neonates compared to adults will lead to the development of age-specific protective strategies. At this time, a great deal remains to be learned about age-specific responses to cerebral ischemia, and the efficacy of potential protective strategies should be evaluated in both perinatal and adult models of cerebral ischemia.

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