

Does the Advent of (New) Low Tidal Volumes Bring the (Old) Sigh Back to the Intensive Care Unit?

ACUTE lung injury (ALI) and adult respiratory distress syndrome (ARDS) are characterized by the tendency of peripheral air spaces to collapse, particularly in dependent lung areas. The application of a positive end-expiratory pressure (PEEP) and an appropriate tidal volume (V_T) is thought to prevent and reverse the collapse of airways and respiratory units in such patients. Other means to recruit alveoli include frequent position changes, *e.g.* from supine to prone. The introduction of specific inflation maneuvers, using either an intermittent high- V_T volume, or an elevated inspiratory (plateau) pressure, allows significant increases in end-inspiratory and end-expiratory lung volume, and an associated improvement in gas exchange. Clinical results obtained with such recruitment strategies are reported in the current issue of ANESTHESIOLOGY by two groups of well-known clinical investigators.^{1,2} Both articles describe the effects of lung inflation in patients with ARDS, studied in the early or late phases of their disease.

The advent of ventilatory techniques using lower V_T to decrease ventilator-induced lung injury and improve outcome in ALI and ARDS^{3,4} has renewed interest in the requirement for, and the potential benefit of, periodic inflation maneuvers. It has indeed been shown that V_T participates to a significant extent in the opening of collapsed or hypoventilated areas in such patients.⁵ Therefore, it is not surprising that with the new low V_T approach, an old intermittent inflation method, called *sigh*,⁶ would regain some credibility in ventilatory management.

In the first of the two studies discussed here, Salvatore Grasso *et al.* reports the effects of a continuous 40-cm H_2O inflation pressure applied for 3–5 s in 22 patients undergoing controlled mechanical ventilation (MV) with a V_T of 6 ml/kg and a mean PEEP of 9 cm H_2O . Pulmonary gas exchange, respiratory mechanics, and hemody-

namics were assessed. The investigation was done at two different times during the evolution of ARDS, *i.e.* in early (1 to 2 days after beginning MV) or later phases (5–10 days after onset of MV). The results are clearcut: only in the early phase of the disease was a marked positive response in the PAO_2/FIO_2 ratio observed. Patients in the later phases of ARDS had smaller increases in oxygenation, which were associated with a significant decrease in cardiac output during the inflation maneuver. This difference may simply be related to respiratory mechanics; in the early phase of ARDS, the elastance of the lung and chest wall were lower, which means higher compliance values, and hence, larger increases in volume for a given change in distending pressure.

In the second study,² Nicolo Patroniti *et al.* describes thirteen ARDS patients intubated and breathing spontaneously, assisted by an inspiratory pressure support of 12 cm H_2O and a PEEP of 11 cm H_2O , resulting in a V_T of 420 ml. A majority of these patients can be considered to be in an early phase of the disease. The recruitment maneuver applied was similar to that used by Patroniti *et al.*; airway pressure was increased to a mean of 38 cm H_2O for 3.6 s, resulting in a V_T of 1,150 ml. This sigh produced marked improvements in gas exchange and expiratory lung volume and a decrease in respiratory drive.

What can we learn from these two elegant investigations? First, the findings confirm that sustained inflation using a pressure of 30 to 45 cm H_2O results in a marked improvement in arterial oxygenation and has no significant side effects.⁷ Second, the reader will not be surprised to see that in early ARDS, functional respiratory units can be inflated and recruited more easily than in later phases of the disease, and that the gain in arterial oxygenation is more impressive. Similar results have been shown for prone positioning where improvement in gas exchange is greater in patients with pulmonary edema or with early ARDS, as compared with late ARDS or pulmonary fibrosis.⁸ Third, it should not be forgotten that alveolar recruitment and pulmonary gas exchange depend largely on the level of PEEP applied during protective ventilatory strategies.⁹

In conclusion, the two articles on recruitment maneuvers published in this issue add important information for the clinician; however, a number of questions remain. For instance, further studies should explore which single or combined therapy, including higher PEEP levels, regular position changes, and intermittent inflation strategies achieves the greatest sustained improvement in lung function. In addition, the effects on outcome in

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ARDS patients, including end-points such as duration of mechanical ventilation, duration of stay in the intensive care unit, and hospital mortality, must be assessed. It seems likely that understanding the role of factors such as the underlying morphologic features of lung injury, the stage of ARDS, hemodynamic status, and tolerance to increased intrapulmonary pressure will be essential to determining optimal treatment strategies for individual patients.

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Monitors of Depth of Anesthesia, Quo Vadis?

IN this issue of *ANESTHESIOLOGY*, Struys *et al.* report that bispectral analysis (BIS[®], Aspect Medical System Inc., Newton, MA, USA) and a derivative of the middle-latency auditory evoked response (MLAER) were similar in their ability to track levels of sedation and loss of consciousness during infusions of propofol, and that both had poor predictive power with respect to movement in response to noxious stimulus.¹ The MLAER was analyzed using a soon-to-be commercially available device (A-Line[®], Alaris Medical Systems, Inc., San Diego, CA). The appearance of articles like this one and the increasing availability of monitors that attempt to use cerebral electrophysiologic signals to track depth of anesthesia (BIS[®], A-Line[®], PSA 4000[®] [Physiometrix, N. Billerica, MA]) beg numerous questions. Among them are: What are we trying to accomplish with these monitors and can we accomplish those objectives with the monitors that are available today? As a lesser but related issue, if these monitors are eventually going to be effective (if they are not so now), is success

more likely to occur with the recording of spontaneous electrophysiologic activity (BIS[®], PSA 4000[®]) or with the recording of evoked signals (A-Line[®])?

Before dealing with those questions, clinicians may benefit from considering some of the technical issues pertaining to these monitors. In particular, the principles underlying the processing performed by the A-Line[®] monitor may be unfamiliar to many. The A-Line[®] generates an index derived from analysis of the configuration of the MLAER. Auditory evoked responses have been studied since the early 1980s by groups from London, England (Thornton *et al.*^{2–5}), and Munich, Germany (Schwender *et al.*^{6–9}). However, a commercial device has now become feasible because the increasing availability of compact computing power and refinements in signal processing techniques have essentially made on-line monitoring possible. The MLAER consists of waves, which occur between 20 and 100 ms after auditory stimuli. The MLAER in a normal awake subject consists of a typical configuration with three vertex positive peaks. Increasing concentrations of a volatile agent “stretch” this waveform into a two-wave pattern with reduced amplitude and increased latencies. In at least one study, prolongation of the negative wave (Nb), which occurs normally at about 40 ms, to or beyond a latency of 47 ms, quite reliably distinguished between subjects who could and could not recall events during anesthetic administration.^{2,3} Among the original difficulties was that signal averaging of at least one thousand responses was necessary to extract this signal, making it impractical as an online monitor. The “autoregressive”

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(ARX) modeling technique used by the A-Line® monitor uses advanced filtering techniques to extract the waveform of interest more rapidly. The essence of the technique is that filtering parameters are modified on an ongoing basis. After acquisition of the baseline signal, filtering parameters are adjusted to create what functions as a “keyhole” that will admit only the signal of interest. That allows rapid verification of the continuing presence of that signal. As the signal varies, it cannot pass through the keyhole and it is possible therefore to make rapid notification of change.

The BIS® device is probably more familiar. One of the issues that has been of concern to some clinicians is that the precise workings of the innards of some of these devices (BIS®, PSA®) is proprietary and opaque to the user. While the general approach to the derivation of the BIS index has been described in this journal,¹⁰ the specifics of that index are, in fact, proprietary. It is known that the BIS® is calculated from several variables derived from the electroencephalogram as independent predictors of the probability of consciousness and that these predictors are combined, with various weightings, in a prediction rule to render a measure of hypnosis on a linearized 0–100 BIS® scale. The exact details of the parameters extracted and their weighting in determining the final score are not known to the user. Furthermore, the BIS algorithm is continuously being refined. While improving the reliability of the monitor has obvious merit, it has the potential disadvantage of making the validity of comparisons of results obtained by investigators using different versions of the monitor uncertain. This also leaves the clinician uncertain as to whether conclusions drawn from the study of earlier versions of the monitor remain clinically valid.

To return to the questions posed in the first paragraph, there are several possible objectives in the use of monitors of depth of anesthesia. Preventing awareness is the one that has made the biggest “splash” with the public and may perhaps loom largest with some clinicians. However, preventing unwanted hemodynamic responses, avoiding motor responses to noxious stimulus, preventing autonomic and adrenergic responses to stress, minimizing expenditures on anesthetic agents and expediting both awakening and postanesthesia care unit (PACU) discharge are all objectives that have been considered. All may be worthwhile. However, while it may be possible to argue that the depth of anesthesia monitors mentioned above (and perhaps others) can be potentially useful adjuncts to achieving various of these end-points, it is difficult to build a case from the published literature that they can do so definitively. The exception may be the use of BIS® monitoring in expediting awakening and discharge and reducing the cost of anesthetic agents. However, because we do not wish the economics of medicine to be the focus of this editorial, we will not plunge deeply into an examination of the

merits of these two applications of monitors of depth of anesthesia. Suffice it to say that it is our opinion that the economic and outcome benefits of these applications, using any device, are not clearly established. The most recent related publication that we have seen demonstrated that BIS® monitoring resulted in a 3.6 min reduction in time to responsiveness ($P < 0.05$), a 12-min reduction in time to PACU discharge (NS) and a 2.1 ml reduction in the consumption of isoflurane ($P < 0.05$) in patients undergoing 2 h of anesthesia for hip or knee replacement procedures.¹¹ That isoflurane reduction results in cost savings of US .21¢ at both the University of California, San Diego Medical Center and the Utrecht University Medical Center (where a 100-ml bottle of isoflurane costs approximately US \$10.00).

With respect to the other potentially valid reasons for employing these monitors, clinicians must be certain that their use for one purpose does not actually defeat others. For instance, if clinicians undertake to use one of these depth of anesthesia monitoring modalities to reduce anesthetic agent costs or expedite PACU discharge by maintaining patients below but close to some threshold perceived to correlate with loss of conscious perception, is it possible that the autonomic responses to stress (the consequences of which, granted, are ill defined) will actually be increased? Or, if the chosen threshold is not highly reliable in terms of assuring the absence of conscious perception (awareness), is it possible that clinicians, in the course of achieving cost savings will actually and unwittingly increase the incidence of awareness? The data of Sandin *et al.* indicate that, in a large population of patients undergoing elective or urgent surgery with neuromuscular blockade, awareness occurs with an incidence of approximately 1 of every 556 patients.¹² In the study of Wong *et al.* mentioned above, the patients in the BIS® monitoring group were given anesthetic agents in sufficient amounts to maintain BIS® level between 50 and 60.¹¹ Let us, for argument sake, say that the average BIS level achieved in those patients was 55. If patients with a BIS level of 55 have the potential to formulate memory just 0.5% of the time (1/200), then there is the potential that the clinicians might actually cause the occurrence of awareness at a rate higher than that, which occurs spontaneously in a nonmonitored population (1/556). A more detailed consideration of this concern has already appeared in this journal.¹³ This line of reasoning is not intended to discourage clinicians from exploring the application of these monitors, but rather to encourage applying them with an understanding of the sensitivity and specificity of those monitors. The ideal monitor for the detection of an event that occurs at low frequency (such as awareness) is one for which the range of values seen in patients who do and do not have the end-point of interest essentially never overlap (high sensitivity and specificity). The data of Struys *et al.*, indicate that this is probably not the case for

either the BIS[®] or the parameter extracted from the MLAER by the A-Line[®] monitor¹. For confirmation, the reader should consult figure 3A,B of the Struys *et al.* article.¹ Those authors assessed the level of sedation with the Observer's Assessment of Alertness/Sedation (OAAS) scale. Fig 3A and B present box plots for the BIS[®] and AAI (A-Line ARX Index) values achieved for patients at various OAAS levels of sedation. A comparison of the values from the two monitors at sedation level 3 ("responds only after the name is called loudly and/or repeatedly"), and 0 ("no response after painful trapezius squeeze"), reveals that values that correspond to unresponsiveness to noxious stimulus in some patients correspond to responsiveness to voice in others. To relate this once again to the paper of Wong *et al.*,¹¹ in the group studied by Struys *et al.*, there were apparently many patients with BIS[®] scores between 50 and 60 who were responsive to voice command or to minimal prodding.¹ Again we say that while these monitors may be useful adjuncts to various clinical objectives, including rapid awakening and cost savings, these monitors do not yet have the high level of discriminative power to be definitive methods for identifying depth of anesthesia end-points, and data from them must be considered with careful simultaneous attention to all of the other traditional signs that we have used to assess depth of anesthesia.

Other potential clinical objectives were mentioned earlier in this editorial. With respect to the use of these monitors to anticipate and prevent movement to noxious stimulus, the results of Struys *et al.* reveal the poor predictive power of both the A-Line[®] and BIS[®] monitors. Predicting and preventing autonomic response to stress was also mentioned. To our knowledge, there have been no investigations that have attempted to correlate these electrophysiologic monitors with autonomic responses.

The second question was whether spontaneous signals or evoked responses were more likely to be the basis of effective monitors of depth of anesthesia. Ultimately the answer to that question will be an empiric one derived from studies like that performed by Struys *et al.*¹ Intuition should count for little in medical science; Aristotle's intuitions retarded progress in medicine for a thousand years. Nonetheless, it seems likely that extracting definitive depth of anesthesia information from the spontaneous activity of many millions of neurons representing many disparate subpopulations will be very difficult. Not all anesthetic agents interact with the same populations of receptors or have the same effects on axonal conduction and, accordingly, the constellation of the effects of our various anesthetic agents and their myriad combinations on the total neuron pool is likely to be very varied. That is not to say that, with a sufficient number of observations, indices that describe the electrophysiologic behavior of that total neuron pool cannot be extracted. That is precisely the approach that was

used in the empiric derivation of the BIS index, which arguably tracks level of sedation more effectively and consistently than any of the electroencephalogram derivatives that preceded it. Yet it still has not achieved, even in the context of pharmacologic monotherapy (propofol), the sensitivity and specificity (again see fig. 3A, in the article by Struys *et al.*) that would be ideal for a monitor of depth of anesthesia. Superficially, it would appear that tracking the response of a much smaller subpopulation of neurons (*i.e.*, the neural pathway corresponding to an individual evoked response) should be easier. Certainly, the effects of anesthetic agents on evoked responses (the auditory evoked response in the case of the A-Line[®] monitor) are likely to be much easier to describe empirically. But once again the problem that our anesthetic agents do not all interact with the same populations of receptors or have the same effects on axonal conduction will intrude. While the auditory evoked response may provide a good correlation in individual patients with depth of anesthesia for one class of agents (and it appears to do so with volatile agents^{2,3} and propofol), it may offer a much less apparent correlation for others (*e.g.*, narcotics,⁸ benzodiazepines⁹) that have less effect on the auditory pathway. Whatever the potential for the use of MLAERs as a measure of the depth of anesthesia, they suffer one very substantial disadvantage. The empiric observations are that the MLAER becomes attenuated to the point of near unrecordability relatively early after loss of consciousness. Therefore, its most obvious application may be in the prevention of awareness while its potential applicability in prevention of movement, prevention of cardiovascular responses and prevention of autonomic responses to noxious stimulus or to stress seem likely to be more limited. It may ultimately prove, if we deem the grail of depth of anesthesia monitoring worth pursuing, that the optimal monitor of depth will be one that integrates parameters extracted from both spontaneous and evoked cerebral electrophysiologic signals.

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