Rapid sequence induction and intubation (RSII) is an anesthesia induction technique designed to facilitate rapid tracheal intubation in patients at high risk of aspiration. The main objective of the technique is to minimize the time interval between loss of protective airway reflexes and tracheal intubation with a cuffed endotracheal tube. Because the airway is unprotected during this time, it is the most critical period during which aspiration of gastric contents is likely to occur. The concept of RSII gradually evolved after the introduction of succinylcholine in 1951 and the description of cricoid pressure (CP) in 1961. However, the first publication that gathered all the components into a structured RSII technique appeared in 1970. The traditional components of the technique as described in the original publication and in modern textbooks include oxygen administration, rapid injection of a predetermined dose of thiopental immediately followed by succinylcholine, application of CP, and avoidance of positive pressure ventilation (PPV) before tracheal intubation with a cuffed endotracheal tube. It seems from these components that the terms “rapid sequence induction,” as used in anesthesia literature, and “rapid sequence intubation,” as used in emergency medicine literature, are both inadequate and deficient. Because the technique entails both anesthesia induction and tracheal intubation, the term “RSII” is more accurate and descriptive of the technique. It was, after all, the term chosen by Stept and Safar when they first introduced the technique.

Immediately after its introduction, RSII gained wide acceptance and was recommended for anesthesia induction in all patients at high risk of aspiration. Currently, it has achieved a status close to being a standard of care for anesthesia induction in patients with full stomachs. Despite the technique’s widespread use, there is still no agreement on how it should best be performed. Thwaites et al. surveyed how RSII of anesthesia for cesarean delivery was performed in the United Kingdom. They found considerable variations among the respondents on what is often perceived as a standard technique. Morris and Cook reported similar findings when they surveyed the use of RSII in general anesthesia practice. Authors of a more recent survey reported the persistence of these practice variations among anesthesia providers. These differences in the perception and execution of RSII may be attributable to the current lack of a standard RSII protocol. However, they might reflect the current controversy regarding some of the technique’s traditional components. In fact, this controversy may be the reason for failure to establish a standard RSII protocol. This
review is intended to highlight the changing opinion regarding some of the essential components of RSII. However, this review is not intended to analyze the risk-benefit profile of RSII, its efficacy in preventing pulmonary aspiration, or its overall effect on patient outcome.

**INDUCTION DRUG CHOICE**

Unless the patient is completely obtunded and unresponsive, it is always recommended to use an induction drug to avoid awareness. The ideal induction drug for RSII should have a fast and predictable onset to achieve the primary goals of rapid loss of consciousness (LOC) and avoidance of awareness. It should also preferably achieve other important secondary goals. Improving the quality of intubation conditions (ICs) in the setting of inadequate paralysis, inducing minimal hemodynamic disturbances, and blunting the sympathetic responses to laryngoscopy and tracheal intubation are a few examples. Clearly, this long-sought ideal drug is not yet available.

In their original description of RSII, Stept and Safar used thiopental in 80 patients with satisfactory results. However, rapid administration of thiopental can result in serious hemodynamic side effects. Many other IV induction drugs were introduced after the initial description of RSII, which prompted the search for the ideal drug. Ketamine/rocuronium induction was found to result in better ICs compared with thiopental/rocuronium. Ketamine may be the induction drug of choice for a hemodynamically compromised patient. However, it can result in some side effects that render it undesirable in certain patients. White compared thiopental, ketamine, midazolam, and ketamine-midazolam combination for RSII. Midazolam had the slowest onset, thiopental decreased and ketamine increased mean arterial blood pressure significantly, and the ketamine-midazolam combination was associated with more hemodynamic stability and fewer side effects than the other combinations. The use of etomidate for RSII was also investigated with varying results reported. Fuchs-Buder et al. found no significant difference in ICs between thiopental and etomidate 1 minute after rocuronium administration but reported that etomidate attenuated the diaphragmatic reaction to intubation more than thiopental. Conversely, Skinner et al. found that etomidate was associated with worse ICs than propofol when laryngoscopy was performed 1 minute after rocuronium and recommended that the etomidate-rocuronium combination alone not be used for RSII. Etopidate is the most popular induction drug for RSII in the emergency department. Obviously, it is the drug of choice when minor changes in hemodynamics cannot be tolerated because both thiopental and propofol may produce profound hypotension. However, adrenocortical suppression had been reported, even after a single dose of etomidate, making it an undesirable choice in septic patients.

In a multicenter randomized study, Jabre et al. compared the use of etomidate with ketamine for RSII in acutely ill patients. They found similar ICs in both groups, but the incidence of adrenal insufficiency was significantly higher in the etomidate group. The authors concluded that ketamine is a safe and valuable alternative to etomidate and should be considered for RSII in critically ill septic patients. Dobson et al. compared propofol and thiopental for RSII with rocuronium 0.6 mg/kg and found better ICs in the propofol group. The superiority of ICs when propofol is used seems to be attributable to its ability to suppress the pharyngeal and laryngeal reflexes more effectively than any other induction drug. It seems that propofol is the preferred drug when ICs are a concern and hypotension is not. The choice of induction drug does not have such a significant effect on ICs, however, when suxamethonium (rather than rocuronium) is used. Similar ICs were achieved regardless of induction drug, even when succinylcholine was given in low doses. Analysis of all the above data suggests that in the majority of situations in which RSII is indicated, the patient’s clinical condition is the main factor that dictates the choice of induction drug, followed by its effect on ICs. Koerber et al. found significant variation among practitioners in their choice of induction drug for RSII. This was mainly attributable to the different clinical scenarios dictating the choice.

**INDUCTION DRUG DOSE AND TIMING OF NEUROMUSCULAR BLOCKING DRUG ADMINISTRATION**

The dose and timing of administration of induction drugs are other areas of controversy. The traditional recommendation is to rapidly inject a precalculated dose of the induction drug immediately followed by the neuromuscular blocking drug (NMBD). In fact, the term “rapid sequence” means that medications should be given quickly and in rapid succession. Stept and Safar recommended the rapid injection of a predetermined dose of the induction drug (thiopental 150 mg). However, a fixed predetermined dose carries the risk of either underdosing (and the potential for awareness) or overdosing (and the potential for severe hemodynamic changes). Underdosing as a result of a predetermined dose administration might be the reason that a higher incidence of awareness is reported in obstetric or trauma patients who are more likely than others to undergo RSII. However, overdosing can cause sudden and significant decreases in arterial blood pressure, which can be life threatening. This is especially true in the hypovolemic trauma patient whose compensatory mechanisms had already been exhausted. The use of minimal doses of induction drug is advisable in these situations, but titration to effect (LOC) should be performed to avoid awareness. Advocates of the traditional “predetermined dose” technique argue that it results in a shorter time to tracheal intubation because it eliminates the time needed to establish LOC. However, the “sleep dose” technique entails titration of the dose until LOC is established. The NMBD is then given, which may prolong the total induction time. Advocates of the latter induction technique argue that although the total induction time is prolonged, the interval between LOC until tracheal intubation (the at-risk interval) is the same regardless of the technique used for induction. Barr and Thornley compared the total time to intubation when thiopental and suxamethonium were given either in rapid succession or by titration to LOC. Surprisingly, the titration group had a shorter mean time to intubation (70 vs 78 seconds). Currently, there are no data to compare the potential aspiration risks of a longer induction time (with...
titration) versus hemodynamic instability or incidence of awareness that may result after a predetermined dose technique. However, it is worth mentioning that although Stept and Safar used a predetermined dose of thiopental, they left the timing of succinylcholine administration to the discretion of the managing anesthesiologist.

In their recent survey of RSII practices, Koerber et al. found that 54% of the respondents always checked for LOC before NMBD administration, that 10% always gave it immediately after the induction drug, and that 36% of anesthesiologists timed it according to the clinical scenario. These variations denote a change from the traditional technique.

OTHER PHARMACOLOGIC ADJUVANTS IN RSII

Opioids

Traditionally, opioids were not included among the induction drugs in RSII. The reason is that older opioids had a slower onset and longer duration than newer ones. To be effective, opioids should be administered well before anesthesia induction, which may not be feasible in an urgent, RSII situation. Concerns that adequate oxygen administration might not be achieved because of their respiratory depressant effect also made opioids unpopular for RSII. However, with the introduction of newer and faster-acting opioids, several studies investigated their use in the RSII setting. Administering fentanyl 2 µg/kg before thiopental, propofol, or etomidate plus succinylcholine resulted in a more stable hemodynamic profile than that seen without the use of fentanyl. Alfentanil and remifentanil have an even faster onset, and can be very effective in attenuating the pressor responses associated with laryngoscopy and tracheal intubation. In healthy premedicated patients anesthetized with thiopental and succinylcholine, the administration of alfentanil 30 µg/kg provided a near-complete attenuation of cardiovascular and catecholamine responses to tracheal intubation. Similarly, the administration of remifentanil 1 µg/kg allowed better control of the hemodynamic responses during RSII in unpremedicated patients receiving thiopental and succinylcholine. Opioids were also found to improve ICs by facilitating tracheal intubation after rocuronium administration for RSII. Co-administration of alfentanil 20 µg/kg with either propofol or thiopental and rocuronium resulted in ICs similar to those achieved after a thiopental-succinylcholine induction. The addition of a fast-acting opioid to the induction regimen in RSII also allows decreasing the dose (and thus the side effects) of induction drugs. Although opioids were not included as a traditional component of RSII as proposed by Stept and Safar, many practitioners currently administer a fast-acting opioid before the induction drug. Others still prefer the traditional RSII technique and avoid the use of opioids before anesthesia induction. They argue that the opioid-induced decrease in respiratory drive if intubation fails and the occurrence of rigidity and/or vocal cord closure with inadequate relaxation are well-documented potential side effects that may jeopardize patient safety during RSII. The latter is not usually a concern when succinylcholine is used because of the resulting fast and intense block that prevents these unwanted side effects.

Lidocaine

Similar to opioids, there are opposing opinions regarding the benefits of using lidocaine in RSII. Advocates use it to attenuate the hemodynamic responses to laryngoscopy and intubation, improve ICs in the setting of partial paralysis, blunt the increase of intracranial pressure in traumatic brain injury, and decrease the incidence of injection pain with propofol. Opponents avoid it because of the lack of sufficient evidence of these benefits, except for decreasing injection pain, and because of the risk of hypotension. Several minutes are needed after lidocaine administration for it to be effective, which may not always be practical in emergency RSII situations.

Succinylcholine: The Optimal Dose

To facilitate rapid tracheal intubation, relaxation with succinylcholine has always been the cornerstone of RSII. Inadequate doses, it is unparalleled in establishing a fast, profound, and reliable degree of relaxation. The dose of succinylcholine that is considered an “adequate dose” remains controversial, however. In their original description of RSII, Stept and Safar used 100 mg succinylcholine/70 kg body weight, 2 to 3 minutes after pretreatment with curare. Earlier, Hodges et al. used only 50 mg succinylcholine with no pretreatment after rapid IV injection of thiopental in obstetric patients. Cromartie used 60 to 80 mg 3 minutes after pretreatment when he first described RSII in combat casualties with full stomachs. However, most of the studies that followed these initial reports considered the “gold standard” dose to be 1 mg/kg without curare pretreatment and 1.5 mg/kg when curare is used to prevent fasciculations. These doses were not questioned until recently when concerns about apnea duration were raised. Heier et al. found that, when ventilation was not assisted after a 1 mg/kg dose of succinylcholine, hemoglobin desaturation <80% occurred in 4 of 12 volunteers. To shorten the duration of apnea and avoid desaturation if ventilation could not be established, a reduction in succinylcholine dose was investigated. The lowest dose that produced the most clinically acceptable ICs (95%) was found to be 0.6 mg/kg in 2 separate studies. Because these studies included patients undergoing elective surgery, the use of low doses cannot be recommended in true RSII situations. Conversely, doses even higher than the traditional 1 mg/kg were recommended by others. Advocates of higher doses argue that 1 mg/kg may not guarantee perfect conditions in all patients when tracheal intubation is attempted 60 seconds after administration. After a 1 mg/kg dose, excellent ICs were found in only 63% to 80% of patients; acceptable ICs (which may be associated with some diaphragmatic reaction or extremity movement) were found in 92% to 98% of patients, and the remainder were unacceptable ICs. It seems that the goal of excellent ICs by 60 seconds in every patient is unachievable, even with higher succinylcholine doses. Naguib et al. found that even a dose of 2 mg/kg did not guarantee excellent conditions in all patients after 1 minute and recommended a dose of 1.5 mg/kg for RSII. However, there is a general agreement that the succinylcholine dose must be increased if defasciculating doses of nondepolarizing NMBDs are used to achieve satisfactory ICs.
DEFASCICULATION BEFORE SUCCINYLCHOLINE

A small dose of a nondepolarizing NMBD given 3 minutes before succinylcholine was found to reduce the incidence of muscle fasciculations, myalgias, and other side effects of succinylcholine. The early description of RSII included the administration of a small dose of d-tubocurarine before succinylcholine; thus, the practice was referred to as “precurarization.” There is no doubt that pretreatment with a nondepolarizing NMBD is beneficial in nonemergent settings, but its routine administration before succinylcholine in RSII situations has been challenged. For the pretreatment (defasciculating) dose to produce its desired effect, 3 minutes should elapse before succinylcholine administration. Timing of administration is important, because the benefits of the technique may be lost if succinylcholine is given earlier. However, in most RSII situations, the need for immediate airway control and protection does not allow a more leisurely administration of medications. Even when there is enough time, however, adherence to the timing of succinylcholine administration in many clinical settings may not be perfect. From another perspective, there has been a tendency to increase the defasciculating dose over the years. The recommended dose should be one-tenth of the dose that increases the force of muscle contraction by 95% of the NMBD used. In the case of rocuronium, this is equivalent to 0.03 mg/kg (approximately 2 mg/70 kg body weight). Extra time is needed for calculations and dilutions, which again may not be practical in an RSII situation. Defasciculation may also result in pharyngeal muscle weakness that is even more likely to occur if the dose is not precisely calculated or if the patient is unusually sensitive to NMBDs. The sense of weakness and difficult breathing may be very distressing to the patient. Pulmonary aspiration can occur before induction of anesthesia because of loss of upper esophageal sphincter tone and inability to swallow. However, defasciculation had been recommended in certain types of RSII situations, such as in patients with penetrating eye injuries or increased intracranial pressure. It is to be noted, situations, such as in patients with penetrating eye injuries.

THE USE OF NONDEPOLARIZING NMBDS FOR RSII: THE PRIMING AND TIMING TECHNIQUES

When succinylcholine is contraindicated, a nondepolarizing NMBD can be used to facilitate tracheal intubation. However, the onset time is much slower than that after succinylcholine administration, which may expose the patient to the risk of aspiration before tracheal intubation. Increasing the dose of the NMBD can shorten the onset time but will result in a very prolonged block. The priming and the timing techniques were introduced to optimize the use of nondepolarizing NMBDs for RSII. These techniques’ purported advantage is that they allow a short induction-to-intubation interval similar to that after succinylcholine administration, without prolonging the block duration. However, there are opposing opinions and concerns regarding the usefulness, efficacy, and risks of both the priming and timing techniques. Mehta et al. and Schwarz et al. separately introduced the priming technique in 1985. The first group used pancuronium 0.015 mg/kg as a priming dose that was followed 3 minutes later by the intubating dose (0.08 mg/kg) after anesthesia induction. They found that 95% twitch depression occurred between 59 and 86 seconds, and good to excellent ICs were achieved in all patients 60 seconds after administering the intubating dose. The second group used vecuronium 0.015 mg/kg as a priming dose followed 6 minutes later by vecuronium 0.05 mg/kg as an intubating dose and found that intubation time had decreased to 61 seconds. Both groups concluded that this priming technique can be used for RSII when succinylcholine is contraindicated. Ortiz-Gómez et al. compared tracheal intubating conditions 1 minute after 1 mg/kg succinylcholine, 0.6 mg/kg rocuronium with no priming, and 0.57 mg/kg rocuronium 4 minutes after using different priming techniques. They found that priming rocuronium with a nondepolarizing NMBD resulted in ICs comparable with those of succinylcholine. They also found a significant difference in onset between all the groups and the group that had received only rocuronium with no priming. Conversely, other investigators failed to reproduce these results and reported failure of the priming technique to provide a faster onset or better ICs. The use of priming technique was found to cause distressing symptoms in a large proportion of patients; these symptoms may also be accompanied by respiratory impairment, especially in the elderly. An incident of pulmonary aspiration after a priming dose of vecuronium was also reported. Obviously, the same concerns that apply to defasciculation before succinylcholine administration also apply to using a priming dose before anesthesia induction. The lack of time allowed for the priming dose to work effectively, the patients’ sense of weakness and breathlessness, aspiration concerns, and failure of the technique to hasten the onset of satisfactory ICs in some studies are serious concerns of the priming technique. Kopman et al. found that the optimal priming dose should only be one-tenth of the ED_{95} to limit some of these undesirable side effects. Obviously, for the technique to be adopted, several points should be considered, including the best NMBD to be used for priming; the optimal priming dose; the best priming interval; the optimal intubating dose; and the optimal time to attempt laryngoscopy and intubation after the intubating NMBD dose. Han and Martyn compared onset and tracheal ICs after a large bolus of rocuronium with those after the use of the priming technique both in burn patients and controls. They found that a dose of 1.5 mg/kg rocuronium (equivalent to 5 times ED_{95})...
produced similar onset with superior ICs compared with using the priming technique. The timing principle entails using a single bolus of a nondepolarizing NMBD followed by the induction drug, which is administered at the onset of clinical weakness (ptosis or arm weakness). Koh and Chen used atracurium according to the timing principle and found that the ICs 1 minute after induction were similar to those achieved with succinylcholine. The authors concluded that atracurium given according to the timing principle can be an alternative to succinylcholine when RSII is indicated. Unfortunately, the use of this technique is associated with the same risks that can occur after priming, including pulmonary aspiration before anesthesia induction. The use of both the priming technique and the timing principle has decreased significantly since the introduction of rocuronium, which has a faster onset than older nondepolarizing NMBDs.

**MANUAL VENTILATION**

Avoidance of PPV before tracheal intubation has been the classic recommendation in RSII. Advocates for this traditional approach claim that gastric insufflation can occur with PPV, thus increasing the likelihood of regurgitation and aspiration before securing the airway. Earlier reports describing the technique contained conflicting opinions regarding this point. Whereas some authors clearly stressed that PPV is contraindicated, others found it acceptable. Advocates of the non-PPV traditional technique argue that after adequate oxygen administration in patients with normal airways, there should be no need for PPV because the time from LOC until tracheal intubation is usually short. They also argue that with PPV, the risk of gastric insufflation and regurgitation may increase.

Recently, the Difficult Airway Society in the United Kingdom published guidelines on its Web site for the performance of RSII (www.das.uk.com/guidelines/rsii.html). A footnote in the guidelines stated that gentle mask ventilation (inspiratory pressure <20 cm H2O) before tracheal intubation is acceptable to some experienced practitioners. Manual bag-mask ventilation did not result in gastric insufflation when airway pressures were kept <15 cm H2O even in the absence of CP. With application of CP, no gastric insufflation occurred even when the inflating pressure was increased to 45 cm H2O. In fact, Sellick’s original article stated that when CP is applied, PPV could be used without increasing the risk of gastric distension. Whether gentle ventilation before tracheal intubation affects the incidence of regurgitation and aspiration is not known. However, after a failed intubation attempt, the use of rescue gentle ventilation does not result in aspiration in the majority of situations. The lack of harm from gentle PPV does not justify its clinical use during RSII unless it is also associated with some desirable effects.

Currently, some experts strongly recommend the routine use of PPV before tracheal intubation in certain RSII situations. Hypoxemia can develop in obese, pregnant, pediatric, and critically ill patients before tracheal intubation is accomplished, or in the true emergent situations in which effective oxygen administration (denitrogenation) cannot be completed satisfactorily. Even after adequate administration of oxygen, some patients develop hypoxemia very rapidly after anesthesia induction because of their low functional residual capacity. If the tracheal intubation attempt is unsuccessful, severe life-threatening hypoxemia can develop before even starting the rescue drill. Advocates of the use of PPV argue that avoiding the risk of hypoxemia at this point outweighs the potential risk of gastric insufflation. However, it is to be noted that the prior argument applies only to the prophylactic use of PPV, because both parties agree that rescue ventilation should be instituted (with CP maintained) if hypoxemia develops at any time during the course of RSII. Although debatable, another potential advantage of manual PPV during RSII is that it allows testing the adequacy of mask ventilation, thus providing an early warning that can be critical in avoiding major airway disasters. However, the predictive value of such “testing” of the airway is likely very low.

**THE CP CONTROVERSY**

CP was described by Sellick in 1961. Using a cadaver, he found that applying backward pressure to the cricoid cartilage against the cervical vertebrae could occlude the upper esophagus and prevent regurgitation of fluid into the pharynx. Sellick then tried the same maneuver during anesthesia induction in 26 patients at high risk of aspiration. None of the patients experienced regurgitation or vomiting when the pressure was applied, and 3 patients had immediate reflux into the pharynx upon release of the pressure after tracheal intubation. Sellick’s maneuver (CP) gained wide acceptance and was incorporated later as an essential component of RSII. Since then, CP has been considered the lynchpin of RSII and the expected standard of care during anesthesia induction for patients at high risk of aspiration. However, several reports of fatal regurgitation and aspiration despite the application of CP appeared in the literature. Although it is impossible to determine whether the failure of the technique was attributable to its improper application or the technique itself, the safety and effectiveness of CP came into question, and its continued use has been criticized. The frequency with which the technique is applied incorrectly, timing of its application, and reproduction of the effective force were quoted as technical limitations to success. In his report, Sellick described the use of “firm” pressure but did not quantify the actual force needed to occlude the esophagus or how this force could be reproduced in the clinical setting. Earlier recommendations to use a force of 44 N (4.45 kg) were later modified to 10 N (1 kg) in the awake patient, to be increased to 30 N (3 kg) upon LOC. Applying the correct force is vital because application of a lower force can lead to incomplete occlusion, whereas an excessive force can lead to airway compression and limit laryngeal visualization. Sellick described the application of CP with the head and neck in extreme extension for the esophagus to be tethered against the cervical vertebrae. The sniffing position, which is usually used before and during laryngoscopy, may not yield the same success in occluding the esophagus.

Extreme opponents claim that even when correctly applied, CP results only in increasing, and not decreasing, the risk of aspiration. Premature application may lead to retching and vomiting. CP was also found to decrease the lower esophageal sphincter (LES) tone from 24 to 15 mm Hg when a force of 20 N was applied, and the LES tone further
Rice et al.96 performed another magnetic resonance imaging study to evaluate subjects as a result of CP.95 In response to the above study, May 2010

PATIENT POSITION DURING INDUCTION OF ANESTHESIA

Stept and Safar7 recommended the semisitting, V position, in which the trunk is elevated 30° to counteract regurgitation, and feet are elevated to prevent hypotension. The idea was to raise the larynx above the LES by a distance that exceeds the maximal expected intragastric pressure to avoid soiling of the tracheobronchial tree in case of regurgitation. The head-up position was also advocated for RSII in operative obstetrics.36 Opponents of this position argue that if active vomiting (rather than passive regurgitation) occurs, then gastric material could reach the larynx, and aspiration is inevitable because of gravity.101 Others argue that the head-down position is more advantageous because any vomitus or regurgitated material will be directed away from the trachea, because the carina will be higher than the larynx in this position.102 A third group of practitioners prefers the supine position because it allows easier and, thus, quicker intubation and reports it to be safe as long as CP is applied properly.103 Regardless of the body position, the head and neck should always be placed in the sniffing position to facilitate visualization and tracheal intubation.104,105

In summary, the failure to establish a standard RSII technique may be attributable to the changing opinion regarding some of the technique’s traditional components. The choice of induction drug is mainly dictated by the clinical scenario. Titration of the induction drug to LOC avoids under- or overdosing. NMBDs may be given after establishing LOC because the critical period is essentially similar to that resulting after the rapid succession injection technique. Inclusion of a fast-acting opioid in the induction regimen is currently recommended to improve tracheal ICs and to blunt the pressor responses associated with airway manipulation. The optimal dose of succinylcholine ranges from 1.0 to 1.5 mg/kg with no defasciculation, to 1.5 to 2.0 mg/kg when defasciculation is used. The use of defasciculation should be limited to appropriate situations. Because the use of the priming technique to speed tracheal intubation may be associated with serious complications, its use has decreased dramatically, especially since the introduction of rocuronium. Prophylactic gentle manual ventilation before tracheal intubation has been recommended in certain patient populations. The application of CP is still a highly debated controversy. The best position for induction and intubation in patients with full stomachs is still debatable. All these controversial components of RSII result in wide practice variations. For a standard RSII protocol to be established and followed by all practitioners, these issues need to be addressed, studied, and resolved. ⇨

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May 2010 • Volume 110 • Number 5 www.anesthesia-analgesia.org 1323

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