

Recrudescence of Malignant Hyperthermia

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RECRUDESCENCE of a malignant hyperthermia (MH) reaction has previously been reported anecdotally, but in this month's issue of *ANESTHESIOLOGY*, Burkman *et al.*¹ present the first detailed evaluation of its incidence and associated factors. Appreciation of the potential for recrudescence of MH reactions is important for the anesthesiologist managing a suspected case because it informs decisions regarding the level of care required after treatment of the acute event. If we accept the data provided by Burkman *et al.* to be reliable, the 20% incidence of recrudescence supports current advice that patients should be monitored for at least 24 h in a critical care environment after resolution of the signs of the acute MH reaction. Furthermore, the presence of certain characteristics might suggest an even longer period of close observation.

Because the study of Burkman *et al.* may impact on postreaction management of possible MH cases, it is appropriate to examine how reliable the data are and how applicable they are to practice outside North America. The study was a retrospective cohort study, and the authors discuss its limitations. The most obvious of these is the subjectivity of the key diagnoses, first the diagnosis of the initial episode as MH and second that of recrudescence. The clinical diagnosis of MH is difficult because there is no single pathognomonic feature and there are multiple differential diagnoses.² Without a definitive laboratory diagnosis, the cohort of Burkman *et al.* will include some non-MH cases, which may have reduced the apparent incidence of recrudescence. On the other hand, the diagnosis of recrudescence is subject to the same vagaries with the additional differential of an inflammatory response in a critically ill patient. It may well be that these presumed overdiagnoses on both numera-

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tor and denominator of the recrudescence incidence ratio have a net neutral effect.

In some senses though, this is academic. Until we have a point-of-care diagnostic test for MH susceptibility, management decisions must be based on the presumed diagnosis of MH and, indeed, recrudescence. By restricting their analyses to cases deemed retrospectively to be "likely MH" on the basis of the MH clinical grading score,³ Burkman *et al.* acknowledge the introduction of selection bias. Inclusion of only 308 of 528 reports to the North American MH Registry may have resulted in underestimation of the true incidence of recrudescence. Even if there were no further cases from the 220 reports not included, however, the 95% confidence interval would be approximately 10-15%. Such an incidence, considering the consequences of not identifying recrudescence and managing it appropriately, would still warrant high dependency care of all patients after an MH reaction.

Having estimated the incidence of recrudescence, Burkman *et al.* next sought to determine which, if any, clinical variables were associated with its development. Considerable caution must be exercised in the interpretation of such data, and the authors of this article are right to stress the difference between association and causation. Significant univariate associations with the occurrence of recrudescence were found for muscular (*vs.* normal/lean) body habitus, increasing duration of the interval between induction of anesthesia and onset of the MH reaction, and the development of a temperature increase (inappropriate rate of temperature rise or temperature $\geq 38.8^\circ\text{C}$) as part of the reaction. Examination of the data indicates, however, that the predictive value for recrudescence will be low for each of the identified variables. A multivariate logistic regression model for prediction of recrudescence using the same variables was also generated. Such analyses can moderate the influence of interdependent covariates, but in doing so, they may exclude the real predictor at the expense of a confounding factor. The model-generating capabilities of the statistical software packages, furthermore, are so powerful at fitting the data that a statistically significant model can be produced even though the contribution to the outcome variable of the selected predictor variables is small. This can be examined using the r^2 value for the model, which estimates the proportion of the variance of the outcome variable that the model explains. The r^2 value of 0.102 for the model of Burkman *et al.* suggests that the identified variables are unlikely to be useful predictors of recrudescence.

I do not think we should ignore the associations identified by Burkman *et al.* altogether, however, because

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they perhaps point to something interesting even if it may seem intuitively obvious: The more severe the MH reaction, the more likely is recrudescence. It is now recognized that a temperature increase is a relatively late manifestation of MH.² There is no evidence that delay in onset of an MH reaction determines its severity, but in my experience, the attending anesthetist often defines the onset of the MH reaction as the time that he or she started treatment, rather than when signs became apparent. In the study of Burkman *et al.*, the interval between induction of anesthesia and onset of the MH reaction may well be a composite of delay in onset and *delay in diagnosis*. The latter component would be a major determinant of the severity of the reaction. Finally, anthropometric studies have revealed MH-susceptible patients to be more muscular than normal,⁴ whereas the mass of affected muscle during an MH reaction will determine the amount of heat, lactate, and carbon dioxide generated, the oxygen consumption, and the amount of potassium and myoglobin liberated from the muscle.

Support for an association between severity of reaction and recrudescence is, in fact, provided by Burkman *et al.*¹ In a *post hoc* analysis, they found a greater proportion of patients with high MH clinical grading scores in the recrudescence group. It would have been interesting to know the impact of including the clinical grading score on the multivariate logistic regression analysis. Meanwhile, such an association would support a previously hypothesized mechanism for recrudescence.² This mechanism is dependent on the reaction being severe enough to increase the myoplasmic Ca²⁺ concentration sufficiently to cause Ca²⁺-induced Ca²⁺ release⁵ from the sarcoplasmic reticulum, thereby maintaining increased Ca²⁺ cycling after elimination of the trigger drug. Clinical features may then reappear if, for example, muscle activity is further increased,⁶ if Ca²⁺ sequestration is compromised by an exhausted capacity for adenosine triphosphate production, or indeed if falling dantrolene concentrations cease to oppose the sensitized Ca²⁺ release mechanism.¹ However, it should be noted that the first reported cases of recrudescence occurred before the availability of dantrolene.⁷

Burkman *et al.*¹ propose that the specific genetic defect predisposing to MH may influence the likelihood of recrudescence. This also is consistent with the association between recrudescence and severity of the initial reaction, as we have previously demonstrated the influence of specific *RYR1* mutations on "severity" of MH phenotype.⁸ Furthermore, this genetic predisposition to recrudescence has implications for the applicability of findings based on North American patients to other parts of the world because *RYR1* mutations are clustered geographically.⁹ For example, the most prevalent *RYR1* mutation reported in North American and United Kingdom families is p.G2434R,^{9,10,11} but this has a relatively

weak phenotype⁸ and might therefore be expected, on the basis of Burkman *et al.*'s data, to be associated with a relatively low incidence of recrudescence. Different *RYR1* mutations predominate in other countries (p.R614C in France and Italy, p.V2168M and p.I2336H in Switzerland, p.G341R in Belgium).⁹ There are insufficient published data to compare strength of phenotype of most of these mutations with p.G2434R (other than for p.G341R, which is similar⁸). However, should any of these mutations be associated with a stronger phenotype, the work of Burkman *et al.*¹ suggests that the incidence of recrudescence may be higher in the relevant country than in North America. *RYR1* mutations private to individual families predominate in Asia and Australasia,⁹ and so it is difficult to comment on possible differences in the incidence of recrudescence in these parts of the world.

In summary, Burkman *et al.* have provided clinically useful data to strengthen the evidence base for patient treatment after an MH reaction. The methodology used may slightly exaggerate the incidence of recrudescence, which may further vary outside North America depending on the prevalence of individual mutations predisposing to MH. Credit must be given to the North American MH Registry for their dedication to systematic collection of clinical data, which on this scale is unique.

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Communication and Teamwork

Essential to Learn but Difficult to Measure

TEAMWORK is recognized as an essential component of safe patient care. In obstetric practice, a multispecialty team is frequently challenged by the emergent requirement for operative delivery in a parturient who has an underlying serious medical condition or complication of pregnancy. When a crisis complicates patient care, teamwork among healthcare professionals is frequently strained, resulting in more frequent as well as more serious failures in managing critical events. A method to measure team performance is a first step in understanding the elements of successful teamwork. In this issue of ANESTHESIOLOGY, Morgan *et al.*¹ design four complicated obstetric emergencies and evaluate the teamwork skills of obstetric teams managing these simulated events.

In this study, teams managed simulated emergency operative deliveries complicated by events such as pre-eclampsia with pulmonary edema, abruptio placentae with massive hemorrhage, amniotic fluid embolism associated with cardiac arrest, and hypoxia associated with failed airway management. In the majority of high-acuity medical environments, teams of healthcare professionals perform specialized tasks and procedures in an interdependent manner. The interrelated team tasks, even in an emergency, usually occur in a logical, sequential, predictable manner, often with little reliance on communication, because the goals are understandable to all of the team members. When complications occur, shared communication and teamwork become essential because the immediate patient management goals may not be clear to all team members.

Morgan *et al.*¹ evaluate team performances using two different scoring methods.¹ The results indicate that raters are consistent when evaluating overall team performance using global ratings, but an in-depth itemized questionnaire (45 questions) that included factors such as confidence, leadership, teamwork, and information sharing could not be scored reliably. This indicates that many of the detailed characteristics of effective team performance remain elusive to measure. The promising study result is that experts

consistently agreed about overall team performance. These consistent overall scores indicate that expert raters do agree on successful as well as problematic team management. The number of raters required (nine raters) to achieve a reliable score would preclude using this type of scoring system as a practical method to compare or rank-order team performances.

Teamwork and communication skills continue to be difficult to capture using traditional rating scales. The development of more effective methods to measure these skills will help to identify the attributes of superior teamwork as well as the root cause of team failures. Currently, team failures are the primary target of system-based patient safety interventions. These approaches that include mandated team checks may reduce some of the more egregious teamwork failures, but ultimately, research that identifies the most effective education and training strategies is needed to improve patient safety.^{2,3}

A number of preliminary studies suggest that team members (surgeon, nurse, critical care physician, and anesthesiologist) may have differing perceptions of the quality of communication in their shared work environments.⁴⁻⁶ Studies involving interdisciplinary healthcare teams are needed to determine why these professionals differ in their view of teamwork. This study is one of the first attempts to develop a method to measure the skills of an interdisciplinary team of healthcare professionals in a high-fidelity training environment. The training curriculum used simulated events that challenge teamwork.

This work by Morgan *et al.*¹ not only represents groundbreaking research in group interactions in complex medical emergencies, but also points the way to more effective medical education. Medical schools have recognized that prospective physicians require teamwork and communication training during medical school. A recent report entitled *Educating Doctors to Provide High Quality Medical Care: A Vision for Medical Education in the United States* (a report of the Ad Hoc Committee of Deans, Association of American Medical Colleges) called for changes in the system of medical education to assure that physicians can "listen and communicate effectively."⁷ The Liaison Committee on Medical Education, jointly sponsored by the American Medical Association and the Association of American Medical Colleges, has also recognized the importance of communication skills and teamwork.⁶ Standard ED-19 notes that "there must be specific instruction in communication skills as they relate to professional responsibilities, including communication with patients, families, colleagues and other health professionals" (Liaison Commit-

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tee on Medical Education).⁷ This committee reviews the content of a medical school's curriculum in these areas as a component of the review of the educational program leading to the M.D. degree.

Medical school curricula have incorporated other methods to train and assess communication skills using more structured situations, such as the Objective Structured Clinical Exam. In addition, assessment of communication skills is now a component of the United States Medical Licensing Examination Step 2[®] (Philadelphia, PA) Clinical Skills Exam.⁶ It is intriguing to consider the use of simulation, as exemplified in the study by Morgan *et al.*,¹ as another modality to teach communication skills.

Teamwork is also drawing increasing attention in medical schools as a component of patient safety and quality enhancement efforts. Students have the opportunity to participate in simulated clinical experiences and receive feedback on their performance as a team member. Increasingly, the importance of an early interdisciplinary approach has been recognized, and training has been implemented to ensure the development of interprofessional communication skills. Efforts are under way at a number of academic medical centers to develop courses in patient safety. At Creighton University, the Foundation in Patient Safety Course includes objectives that include interprofessional communication and a systems approach to understanding human performance fallibility. Similar examples of this curriculum emphasis exist at many medical schools.

The overall goal is to train physicians who will be well

grounded in essential communication and teamwork skills. The medical student education program will provide a foundation for further skill development in residency training. The importance of this issue to our patients will mandate that interdisciplinary communication and teamwork skills will be considered prerequisite skills for professional training. Research such as the study in this issue of ANESTHESIOLOGY will and must continue to identify more effective and efficient methods to assess these skills and provide feedback to facilitate improvement.¹ Our patients will expect no less.

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Neurostimulation/Ultrasonography

The Trojan War Will Not Take Place

THE modern era of regional anesthesia began with a simple needle. Some pioneers believed it was not necessary to have an open surgical field to perform regional blocks; indeed, they were able to demonstrate that it was possible to successfully achieve regional blocks by inserting a needle transcutaneously and searching for paresthesias.¹ Despite positive results, this technique had

some major drawbacks, including active patient participation and elicitation of a paresthesia, a sensation that was later shown to be the most unpleasant part of the regional block procedure.² Science was injected into the art of regional anesthesia with the advent of neurostimulation. With the development of more reliable equipment and introduction of safer and more effective local anesthetics, needle guidance by neurostimulation enhanced the safety and efficacy of regional anesthesia.^{3,4} More recently, a new method of performing regional block using ultrasound technology has been introduced in clinical practice. Whether ultrasound offers significant advantages over other aids to regional anesthesia represents a central issue in clinical research in the field. In this issue of ANESTHESIOLOGY, Casati *et al.*⁵ make a substantial contribution to this question, demonstrating that in experienced hands, neurostimulation and ultrasonography have similar success rates and comparable inci-

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dences of complications after multiple injection axillary brachial plexus block. Moreover, patient satisfaction was similarly good with both techniques.

The authors investigated the challenging question of whether neurostimulation or ultrasonography will selectively affect success rate, incidence of complications, and patient acceptance after multiple injection axillary brachial plexus block. Axillary brachial plexus block was a good choice for such a study because this block is considered as one of the most unpleasant when performed with the use of neurostimulation.² This reflects the need at this site to perform three separate stimulations/injections to obtain a high success rate.^{6,7} The results obtained by Casati *et al.*⁵ will not surprise experts in regional anesthesia, who most likely would have predicted no difference between the two techniques in these clinically relevant outcomes, when the blocks are performed by experienced anesthesiologists. Recent progress in the science and application of neurostimulation to localize peripheral nerves has been rapid in many areas. Johnson *et al.*,⁸ for example, applied a computerized model of electrical stimulation of peripheral nerves and contributed new and unexpected important observations with direct clinical application. The increased sophistication of the application of neurostimulation, the availability of bevelled insulated needles, and the description of new approaches have made neurostimulation a highly successful technique in experienced hands (up to 95–97%^{4,9,10}), associated with a low incidence of severe complications.

One of the most relevant issues would be to know whether ultrasound can still increase the high success rate observed with neurostimulation. In fact, observations in cadaver dissections or direct visualization during surgery indicate cases of a thick perineurium or a complex network of connective tissue between the cords at the infraclavicular level, for example. These anatomical variants may explain why a 100% success rate within 30 min will never occur, whatever technique is used. These considerations help to understand why a significant difference between the two techniques regarding success rate will most likely never be demonstrated because the required number of patients to show even a small difference will be tremendously large.

Another important question is to know whether ultrasound would decrease the incidence of the most feared complication—neuropathy—which occurs nevertheless in 0.04–0.4%^{3,4,10,11} with the use of neurostimulation. This low incidence of neuropathy in literature reports almost certainly includes some injuries due to surgery and suggests that some injuries in large surveys will always be observed. Given the extremely low incidence of serious neuropathy and its mixed causes, attempting to determine whether one technique to localize nerves for regional anesthesia is safer than another in regard to neuropathy would be a huge undertaking, requiring tens

of thousands of patients to observe even small difference between techniques. Such studies will most likely never be performed. On the other hand, it is conceivable that visualization with ultrasound may further our understanding of the mechanisms of neuropathy after regional anesthesia. For example, Bigeleisen¹² performed axillary plexus blocks with his usual practice of seeking a paresthesia by needle manipulation. When a paresthesia was obtained, he assessed the spread of local anesthetic solution using ultrasound. His observations were astonishing: 85% of the patients had nerve puncture of at least one nerve, and 81% had an intraneural injection of at least one nerve.¹² Surprisingly, 6 months later, no neural damage was noted. This study suggests that injection through the epineurium is common with the use of the paresthesia technique and that some local anesthetics may be injected between the perineurium and epineurium without damaging the nerve.

Supporters of the ultrasound technique will point out that in Casati's study, minor outcomes such as onset of sensory block or number of needle passes favored the ultrasound method over neurostimulation. Supporters of the neurostimulation technique will counter that only three stimulations are really required, rather than four,⁷ making the procedure less unpleasant than in Casati's study, and that thinner needles than used in this study may be used and would further reduce patient discomfort. Regardless, patient acceptance was similar with these methods, and perhaps the important point is not to contrast these conceptually different methods¹³—neurostimulation, an analytic tridimensional technique, and ultrasonography, a descriptive bidimensional one—but rather to understand that combining the two may help to improve our understanding regarding the interactions between the distance between needle and nerve as it relates to muscle response and spread of local anesthetic solution. The dynamic visualization of regional anesthesia will undoubtedly contribute to further refine the scientific basis of regional anesthesia.

Should one technique be chosen over the other? Casati *et al.*⁵ clearly demonstrated that in experienced hands, the major outcomes for performing a single-shot nerve block are similar between the two techniques. Individual practitioners may certainly have different success rates and hence preferences for one technique over another.

Finally, whether these results inform us regarding continuous perineural catheter techniques is worth a comment. Single-shot regional anesthesia does not significantly alter clinical outcomes compared with general anesthesia. McCartney *et al.*,¹⁴ for example, demonstrated that pain severity, morphine consumption, and incidence of nausea and vomiting were similar after ambulatory hand surgery between single-shot peripheral nerve block and general anesthesia. On the contrary, continuous local anesthetic infusion by perineural catheters has significantly improved outcome.^{15–18} Its place-

ment with the use of neurostimulation is well standardized,^{19,20} the search for specific muscle response is well defined,^{3,9,21} and the incidence of infection, a crucial issue in this context, is low.^{3,4} Some of these concerns, particularly the issue of sterility, must be further investigated regarding ultrasound-guided perineural catheters. In any case, as written by J. Giraudoux, the Trojan War will not take place.²²

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Drug-eluting Coronary Stents

What Are the Risks?

DESPITE the initial enthusiasm regarding the efficacy of drug-eluting coronary stents (DES) in the care of the patient with cardiovascular disease, there now seems to be a growing concern about the risk of adverse outcomes related to stent thrombosis. This initial risk became apparent in the perioperative period through a case series in which patients with a recent stent placement (less than 90 days) were at markedly higher risk of

reinfarction or death after presenting for noncardiac surgery.¹ The risk of stent thrombosis has also been debated recently in a series of articles and presentations in which the general utility of DES *versus* bare metal stent placement for decreasing the long-term risk of myocardial infarction and death has been questioned. In this issue of the Journal,² the authors describe a case of very late thrombosis of a DES occurring in the postanesthesia care unit, 12 months after completion of a course of dual antiplatelet therapy. This case and recent evidence in the literature highlight unresolved questions regarding the risks and benefits of interventions aimed at improving cardiovascular outcomes in patients undergoing planned or unplanned noncardiac surgery.

Drug-eluting stents were initially popularized because these stents were thought to remain patent for a longer period of time compared with their bare

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metal counterparts. However, the BASKET-LATE trial demonstrated that despite improvements in target vessel revascularization, there was a substantial increase in late rates of myocardial infarction and death in patients treated with DES compared with bare metal stents after discontinuation of clopidogrel.³ In an observational study of 4,666 patients, extending clopidogrel use from 6 to 12 months in patients with DES, but not bare metal stents, was associated with a reduced risk of myocardial infarction or death.⁴ These findings suggested that continuation of clopidogrel might provide protection against late stent thrombosis; however, the optimal duration of such therapy was undefined. In the current report, stent thrombosis occurred perioperatively after a 12-month course of clopidogrel was completed, but when aspirin was discontinued 10 days before surgery. The occurrence of thrombosis after aspirin withdrawal substantiates the importance of maintaining this antiplatelet therapy in the perioperative period in patients with DES.

The question of the optimal preoperative evaluation of a patient with a drug-eluting coronary stent remains controversial. One of the main reasons to perform testing is to determine whether there is myocardium at risk for ischemia, and whether the coronary artery anatomy is amenable to preoperative revascularization. In the Coronary Artery Revascularization Prophylaxis trial,⁵ patients with single- or double-vessel coronary artery disease who had a percutaneous coronary intervention did not have improved perioperative and long-term outcome compared with patients who had medical therapy alone. In addition, several authors have shown that noncardiac surgery within the first 30–90 days after coronary stent placement is associated with increased thrombosis or bleeding diatheses, depending on the extent of anticoagulation.⁶ These results suggested that preoperative revascularization may not provide a benefit and may increase the risk of complications during subsequent noncardiac surgery. Therefore, when consideration is given to performing preoperative testing and possible use of percutaneous coronary intervention, the risks and benefits of testing/intervention must be carefully weighed. Given the lack of efficacy of coronary stents for single- or double-vessel coronary interventions in this population generally, one might ask whether there is any value to performing further diagnostic testing in the asymptomatic patient with a coronary stent in place. In these authors' opinion, the potential yield will be small to negligible because it would be unlikely that any additional interventions would be contemplated. Therefore, proceeding with surgery as the authors describe is a prudent and reasonable approach.

The value of other medical therapies to decrease cardiovascular risk in patients with DES undergoing noncardiac surgery is unclear. The American College of Cardiology/American Heart Association focused update on

perioperative β -blockade⁷ stratified β -blockade treatment recommendations on the basis of the degree of preoperative risk. The value of β -blocker therapy in low-risk patients or patients without ongoing ischemia and who currently were not taking β -blockers has been questioned. Several studies have been unable to demonstrate a benefit in low-risk patients; however, these studies did not specifically address the question of β -blocker therapy in patients with coronary stents. Similarly, although statin drugs favorably impact overall cardiovascular outcome, the benefit of statin therapy in patients with coronary stents is not clear.

The potential for DES thrombosis influences the overall assessment of benefit and risk in patients who are considered for preoperative testing and revascularization. In a study of 770 intermediate-risk patients, those patients randomly assigned to receive no testing and tight heart rate control with β -blockers for major vascular surgery had similar outcomes compared with the group receiving testing with or without preoperative revascularization.⁸ Therefore, testing may be of little value in low-risk patients or in intermediate-risk patients treated aggressively with β -blockers. It is probably reasonable to reserve preoperative revascularization for high-risk patients, with consideration given to the use of DES *versus* bare metal stents depending on the feasibility of completing a course of antiplatelet therapy before surgery and to continue aspirin indefinitely.

In conclusion, this report illustrates the occurrence of acute coronary stent thrombosis as a sudden and unexpected event, which, in this case, occurred postoperatively and remotely from discontinuation of clopidogrel. Treatment was initiated quickly, and proceeding to the catheterization laboratory makes the most sense in these situations. The case exposes this important and potentially lethal complication in the perioperative care of patients with DES, and should lead clinicians to consider how assessment of both benefit and risk should impact decision making before, during, and after surgery.

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