

Recapturing the Past—or Welcome (Again) to the 21st Century

ONCE upon a time, long, long ago (sometime in 1997), the Journal made its first tentative steps onto the Internet. We started with our current table of contents, a library of article abstracts taken from Medline (with the help of Ira Rampil, B.S., M.S., M.D., Professor, Department of Anesthesiology, The State University of New York at Stony Brook, Stony Brook, New York), and, I think, Instructions for Authors. In the intervening years, we completed the process of moving our entire current content on-line, and also succeeded in putting approximately 10 yr of “back issues” on-line as well (part as HTML and the more recent years as PDF).

However, during this process, we continued to explore and discuss how we might make our on-line presence “complete.” From the beginning, we talked about the feasibility of back-loading the *entire* contents of the Journal—starting with Volume 1, No. 1 from 1940. We explored mechanisms for accomplishing this goal in the late 1990s, but with little success; the cost of gathering, scanning, and uploading 50 yr of articles was more than we thought could be justified. But we never stopped trying.

Well, finally the dream has come true. As part of the new contract between the American Society of Anesthesiologists and Lippincott Williams & Wilkins (LWW), an agreement was reached to achieve our goal. I’d like to take credit for this, but in fact, it was really due to a change in the plans of LWW and their on-line group, Ovid. For many years, Ovid has been a major provider of electronic journal content to libraries around the country and, in response to many requests (including ours), they came to realize that there was a market for archival content on-line. This was the basis of their decision, well over a year ago, to create the LWW Legacy Archive Collection. This archive was initially marketed to libraries in November 2006 (and has already recouped its production costs) and in July 2007 finally became available *via* the Journal’s Web site.*

If you’re not reading this editorial *via* the Web, please go to the Journal’s Web site. Click on Archive near the top of the page. You’ll see a page that looks just as it has for many years. But scroll down—and keep scrolling and then scroll some more. Finally, you’ll reach the bottom,

under the bar titled 1940. There are two issues: July and September. Open the July issue, and there you will see the first article we ever published (fig. 1), presciently entitled “The Place of the Anesthetist in American Medicine.” And above this you’ll find much, much more.

Why is this important? There are several reasons. Nearly all medical journals are now on-line, and more and more readers are accessing their content electronically. I and many others have said that the future of medical publishing will be entirely electronic; some major journals have already dropped their print versions. Medical libraries are also changing. I’m reminded of an old joke about the *National Geographic* magazine. Someone postulated that the accumulating weight of undiscarded *National Geographics* (which no one ever throws away) would result in the Eastern Seaboard of the United States sinking several feet.¹ Well, imagine the accumulated mass of old journals that reside in our libraries. I’m not sure whether libraries are physically sinking, but financial pressures and the problems of finding a place to keep these archives has led many libraries to cut back on their subscription lists and to reconsider what to keep and what to discard. My bet is that it will become harder and harder for us to gain access to our archival material *via* the traditional means. Having the entire content of ANESTHESIOLOGY on-line obviously eliminates this concern. Now anyone with an Internet connection can retrieve and read any article from the Journal at any time—without the delays (sometimes many days) associated with asking your library (if you have access to a medical library) to retrieve it from their basement stacks (if they still have it).

There is another benefit. As the former Editor-in-Chief, I repeatedly said that the medical literature only began in the 1960s, simply because most researchers used Medline to seek background material. I can’t count the number of times that I read submitted articles describing a “new discovery” when, in fact, the same “discovery” had been published decades earlier, “pre-Medline.” This should (ideally) occur less frequently. Our total content may not *yet* be on Medline, but you now have at least a partially searchable database of contents of ANESTHESIOLOGY (and other LWW journals) that goes back to the beginnings. And I’m going to bet that Medline will be taking advantage of this material to extend their databases even further into the past.

Last, there is history. As many of you know, I’ve long believed in the value of knowing about our professional history. I’ve been lucky enough to have personal access to a complete set of ANESTHESIOLOGY—and I’ve spent many

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* OK, there are a few gaps. About 20 issues of the Journal are still unavailable. The Journal office, the American Society of Anesthesiologists, and LWW have been gathering old issues actively—with many copies donated by American Society of Anesthesiologists members. It shouldn’t take too long to fill in the gaps.

The Beginning of an Answer

ANESTHESIOLOGY

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THE PLACE OF THE ANESTHETIST IN AMERICAN MEDICINE *

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WHAT I have to say here regarding the place of the anesthetist in American medicine is not an encomium either of the men in this field of medicine or of their contributions. I offer no praise of the anesthetist as a scientist or as a humanitarian, nor do I glorify the relief from suffering afforded by his skill and knowledge. If then, I depart, as my negations must signify, from the easy, ingratiating words customarily spoken on occasions of this kind and under a title such as I have chosen, it is with a purpose.

That purpose is not to define the calling of the anesthetist in terms

Fig. 1. The first page of the first article published in ANESTHESIOLOGY, July 1940.

hours browsing through it. It's a sobering experience. What you quickly realize is that our predecessors faced

many of the same issues that face us today. We may have more sophisticated tools and drugs, but the problems we face have not changed. It's also clear that we aren't any smarter than they were. It's wonderful to read about some of their incredibly innovative problem-solving methods, many of which are still in use today. Now all of you have access to the same material, and I urge you to spend some time browsing as I have. You'll be surprised at what you find: some outstanding medicine and science, some serious weirdness—but very little that you won't find interesting.

It may seem odd, but gaining access to our published heritage is only one of the advantages of our move into the 21st century.

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Droperidol-induced Proarrhythmia

The Beginning of an Answer?

IN 2001, the US Food and Drug Administration (FDA) posted a safety alert regarding droperidol use indicating that “cases of QT prolongation and/or torsade de pointes (TdP)” had been reported with this drug.* A warning was issued that contraindicated the use of droperidol in patients with known or suspected QT prolongation, imposed the recording of a 12-lead electrocardiogram before administration in all patients to determine whether a prolonged QT interval was present, and recommended that electrocardiogram monitoring be continued for 2–3 h after treatment to monitor arrhythmias. Moreover, administration of droperidol to patients at risk of developing prolonged QT interval (e.g., patients older than 65

yr or receiving volatile anesthetics or intravenous opiates) was recommended with “extreme caution.” The impact of this warning was reinforced by a consensus guideline published in 2003, which recommended, as a consequence of the warning regarding droperidol, the use of 5-hydroxytryptamine type 3 receptors antagonists as first-line antiemetics.¹ Although droperidol is still available, in some institutions its use was discontinued, as shown by Nuttall *et al.*,² who recorded a dramatic decrease in droperidol use from approximately 12% between 1998 and 2001 to 0% between 2002 and 2005.

Since the FDA warning, controversy has increased, and there has been extensive debate in the anesthesiology literature. Many believe that this warning was unjustified given the efficacy of droperidol as an antiemetic, the lack of published evidence of droperidol-induced arrhythmias during decades of use, and the absence of overt toxicity when administered at low doses. On the other hand, a “precaution principle approach” was justified by the known dose-dependent QT interval prolongation and risks of torsades de pointes at the high doses of droperidol used in psychiatry.

In this issue of ANESTHESIOLOGY, Nuttall *et al.* contribute to the assessment of droperidol's toxicity.² These authors report a retrospective study on QT prolongation/TdP and sudden death in a large anesthesia survey di-

This Editorial View accompanies the following article: Nuttall GA, Eckerman KM, Jacob KA, Pawlaski EM, Wigersma SK, Shirk Marienau ME, Oliver WC, Narr BJ, Ackerman MJ: Does low-dose droperidol administration increase the risk of drug-induced QT prolongation and torsade de pointes in the general surgical population? *ANESTHESIOLOGY* 2007; 107:531–6.

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* <http://www.fda.gov/medwatch/SAFETY2001/inapsine.htm>. Accessed June 5, 2007.

vided into two 3-yr time periods before and after the FDA warning. This study showed a significant decrease in the overall proportion of patients with QT prolongation, TdP, or death within 2 days following surgery after the eviction of droperidol. During these 6 yr of observation, almost 300,000 surgical procedures were performed, and only three cases of potential or certain TdP were observed. Except for two cases occurring after cardiac surgery, which is known to be a risk factor, one case of sudden death was observed in a 48-yr-old woman after orthopedic surgery. Although not proven, the responsibility of droperidol could not be ruled out in this patient because she received prophylactic droperidol 10 h before she was found to be in cardiac arrest. Interestingly, another QT-prolonging agent, ondansetron, could have played a role in the occurrence of this adverse event. Even if the droperidol exposure was assessed from the records of only 1 per 1,000 of the entire population, the authors calculated the maximum risk of arrhythmia induced by droperidol to be 3.6 per 10,000. However, if taking into account this case of sudden death where droperidol had a possible role, this maximal risk would increase by 50% to 5.4 per 10,000. Finally, the authors conclude that the FDA warning is "excessive and unnecessary."²

Does this study provide sufficient evidence to question the FDA warning on droperidol and call for its withdrawal?

Several drugs with limited effects on QT interval duration have recently been removed from the market because they had the potential to cause QT interval prolongation and TdP.³ Although the potential for TdP is extremely low, it can lead to death in some subjects. This, in itself, is sufficient to mandate some form of warning. The International Conference on Harmonisation and Medicine Agencies in the United States, Europe, and Japan have issued guidelines on preclinical and clinical drug development targeting the effects of new chemical entities on ventricular repolarization.†‡§ Old drugs are also concerned when they are being developed for new indications or populations or when administered at a new dose or route of administration that results in significantly higher exposure than those previously approved. Briefly, a drug is considered to bear a potential risk of proarrhythmia when the maximal increase of QTc interval, compared with placebo, has an upper bound of the 95% confidence interval over 10 ms.§

Droperidol has several electrophysiologic characteristics that the guidelines view as potentially harmful. Droperidol blocks HERG, one of the main ionic currents

that underlies QT interval duration.^{4,5} Results of clinical evaluations are not consistent. White *et al.*⁶ failed to demonstrate statistically significant QT interval prolongation with 1.25 mg droperidol. However, they found a 22-ms QT prolongation with droperidol compared with 12 ms with placebo, and their study was only powered to detect QTc change of 15% (*i.e.*, approximately 60 ms). In a study that was not placebo controlled, we found a 17-ms QT interval prolongation with 0.75 mg droperidol. Therefore, although not definitively proven or studied according to the guidelines, droperidol can prolong the QT interval even at a low dose and belongs to the increasing list of noncardiac drugs for which some form of warning is justified.

Although the level of QT prolongation indicated as problematic in the International Conference on Harmonisation guideline may seem very low and is not necessarily associated with proarrhythmia, it emphasizes the pharmacodynamic response rather than the perceived epidemiologic risk. From a safety point of view, such a conservative approach is appropriate. For example, despite limited QT interval prolongation,⁸ isolated cases of TdP were reported to the FDA during terfenadine use,⁹ whereas its risk in the population was shown to be similar to that of other antihistamines in epidemiologic studies.¹⁰ That is, it is clear that the risks of TdP with QT-prolonging drugs can be underestimated in epidemiologic studies and still exist in some individuals. This justifies the regulatory policy of putting warning boxes on all QT-prolonging drugs. Therefore, from a regulatory point of view, the study by Nuttall *et al.* does not in itself justify removal of the warning on droperidol use. Nevertheless, these authors should be commended for performing the first epidemiologic study addressing the issue of sudden death and torsades associated with the use of droperidol. Their results should prompt the FDA to reconsider and lessen the warning on droperidol.

Setrons also have the capacity to block HERG at high concentrations,¹¹ and although their influence on QT prolongation has not been extensively studied clinically in the perioperative period, there are indications that at least ondansetron can induce QT prolongation in this setting.⁷ Given that this drug may have contributed in part to one case of sudden death,² the study of Nuttall *et al.* emphasizes the need to reinforce the observation of setrons' effects on ventricular repolarization.

Finally, if one considers the estimated maximal risk of droperidol-induced proarrhythmia (3.6 per 10,000), this would still represent a risk 60 times greater than that of epidural hematoma after epidural anesthesia, whose risk is approximately 1 in 168,000 in the United States.¹² Even if it is not fatal, no anesthesiologist worldwide would consider the risk of epidural hematoma negligible and accept to perform everyday epidural anesthesia without any caution. Therefore, although the precise format of the warning certainly remains a matter for

† <http://www.ich.org/cache/compo/502-272-1.html#S7A>. Accessed June 5, 2007.

‡ <http://www.ich.org/cache/compo/502-272-1.html#S7B>. Accessed June 5, 2007.

§ <http://www.ich.org/cache/compo/475-272-1.html#E14>. Accessed June 5, 2007.

debate, the warning itself is still justified because one has to be more stringent on safety issues than on efficacy issues.

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Pragmatic Treatment versus Elaborative but Incomplete Testing

A Hobson's Choice?

THE study by Hoeks *et al.*¹ in this issue of *ANESTHESIOLOGY* indicates that only an astonishingly low 21% of patients for whom the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend preoperative noninvasive cardiac testing were actually tested. Anesthesiologists (in The Netherlands) thus do not strictly follow the ACC/AHA guidelines on preoperative cardiac testing in patients undergoing vascular surgery. Is this substandard care, or are there probably valid reasons for this approach?

A considerable percentage of patients scheduled to undergo vascular surgery are high-risk patients because of concomitant coronary artery disease. Postoperative myocardial ischemia and infarction are serious adverse events accounting for up to 40% of postoperative fatali-

ties and increased duration and costs of hospital stay, and significantly contribute to long-term mortality.²⁻⁵ Detailed preoperative assessment and risk-reduction strategies have been proposed to ultimately improve outcome.^{6,7} However, there is uncertainty about whether such algorithms indeed improve outcome.⁸⁻¹⁰

A first question of course is whether in daily practice physicians actually adhere to such algorithms. The study by Hoeks *et al.*¹ in this issue of the *Journal* gives some interesting insights. In patients enrolled in the Euro Heart Survey Program (Sophia Antipolis, France), only 21% of patients for whom the ACC/AHA guidelines recommend preoperative noninvasive cardiac testing were actually tested. Conversely, 89% of those for whom no testing was recommended by the ACC/AHA guidelines were indeed not tested. Therefore, in the Euro Heart Survey Program, the majority of patients scheduled for vascular surgery did not undergo preoperative cardiac testing. Interestingly, long-term outcome was nearly identical in patients preoperatively tested or not, irrespective of the recommendations by the ACC/AHA guidelines.

This study asks many interesting questions: Does this mean that such guidelines are of limited value? Are they simply too complex to be followed? Do anesthesiologists consider patients treated with β -blockers, statins, and antiplatelet drugs as already maximally protected periopera-

This Editorial View accompanies the following article: Hoeks SE, Scholte op Reimer WJM, Lenzen MJ, van Urk H, Jörning PJG, Boersma E, Simoons ML, Bax, JJ, Poldermans D: Guidelines for cardiac management in noncardiac surgery are poorly implemented in clinical practice: Results from a peripheral vascular survey in The Netherlands. *ANESTHESIOLOGY* 2007; 107:537-44.

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tively, so that any further testing would not change the medical treatment? Is the cardiac testing capacity actually available for additional preoperative testing in due time? Is additional cardiac testing affordable in times of budget restriction? Do anesthesiologists fear that any further testing might result in a cardiologic intervention transforming a stable coronary plaque into an unstable coronary plaque with the need for dual antiplatelet treatment of largely unknown duration while the patient is at an increased risk of coronary (stent) thrombosis perioperatively?

These are important topics of great clinical interest, and they are currently vividly debated. The study by Hoeks *et al.*¹ adds new information but has significant limitations. First, the number of patients enrolled in this retrospective observation is rather small. Moreover, the precise definition of cardiovascular outcome and its assessment remains unclear from the article. Patients as young as 18 yr were compared with elderly at-risk patients bearing a significant burden of arteriosclerosis. Arbitrary definitions with respect to “advanced age” and grading of risk within the vascular surgical patients (“low,” “intermediate,” and “high”) were applied by the authors in their analysis, and no information about possible confounding variables, such as the perioperative use of cyclooxygenase-2 inhibitors, sulfonylurea drugs, or α_2 agonists, was detailed. Most importantly, the authors do not report on whether β -blockers, statins, and platelet inhibitors were given in the context of a long-term chronic treatment or whether these drugs were newly introduced perioperatively and whether the heart rate of β -blocked patients indeed was in the protective target range. Also, no information is provided about contraindications for β -blockers or about serious side effects because of preventive medical treatment. Finally, it is unclear whether the AHA guidelines are similarly applicable to patients undergoing semiinvasive endovascular stenting procedures during sedation as opposed to patients having open surgical procedures during anesthesia.

The cited guidelines may advise the anesthesiologist to consider clinical predictors of increased perioperative cardiovascular risk, exercise capacity of the patient, and surgery-specific risks.^{6,7} A combination of clinical predictors and low exercise capacity (usually ≤ 4 metabolic equivalents [METs]) ask for noninvasive cardiac testing, and the further steps are determined by the results of such testing. A valid question now is whether such noninvasive testing is indeed necessary or whether one could not simply opt to apply the maximum medical protective strategy without testing as if testing would have recommended such treatment.^{10,11} In fact, the therapeutic options are few: Chronic β -blockade, statin, and antiplatelet therapy should be continued. Preoperative acute β -blocker treatment may be beneficial in these patients as well,^{12,13} but there are well-designed perioperative β -blocker studies questioning the efficacy of this therapy.¹⁴⁻¹⁶ Preoperative initiation of statin therapy is

even more controversial, albeit likely to be efficacious as well.¹⁷⁻¹⁹ Unfortunately, it is not reported in the article by Hoeks *et al.*¹ whether β -blocker and statin therapies were continued chronically or newly introduced preoperatively.

Do we miss some high-risk patients by skipping noninvasive testing, and would this result in an adverse outcome when we simply treat (in the absence of contraindications) all high-risk patients with perioperative β -blockers and statins and continuing antiplatelet drugs? One might argue that Boersma *et al.*²⁰ had identified in 2001 a small subgroup (2% of a selected population) in which perioperative β -blockade did not reduce postoperative cardiac complications and thus myocardial revascularization was proposed. Interestingly, the same group of researchers recently tested this proposal in the very subgroup of high-risk patients with extensive ischemia in preoperative testing in a prospective randomized trial and found no benefit of preoperative revascularization as opposed to optimized medical treatment, either at 30 days or at 1 yr.²¹ This is in keeping with previous studies in lower-risk patients where coronary artery bypass grafting before vascular surgery or percutaneous coronary interventions also did not improve long-term outcome.^{22,23}

Today, percutaneous coronary interventions involve placement of stents, many of which are drug-eluting stents in a majority of cases.^{21,24} During the reendothelialization period, these stents are highly thrombogenic, patients must be treated by a dual antiplatelet regimen of at least 12 months, and all elective surgery should be postponed for at least 1 yr according to current recommendations.²⁵ Even later stopping of clopidogrel may be associated with an increase of stent thrombosis and major adverse events such as myocardial infarction and death.²⁶⁻²⁸ Because any coronary intervention *per se* renders plaques unstable, these procedures should, whenever possible, be avoided preoperatively. Therefore, not testing high-risk patients preoperatively but treating them medically with β -blockers and statins and continuing antiplatelet therapy may not be a hazardous but more likely a beneficial regimen. In addition, one third to one half of postoperative myocardial infarction are linked to unstable plaque rupture,^{29,30} and it can be expected that preoperative stress testing will miss a significant proportion of patients at high risk of postoperative myocardial infarction; unstable plaques cause only moderate coronary stenoses and are usually silent during stress tests.³¹ On the other hand, cardioprotective drugs are potentially dangerous and may harbor significant side effects.³² Despite the fact that studies assessing the outcome of patients with or at risk of coronary artery disease have not proved a real benefit of preoperative testing,⁸⁻¹⁰ larger studies may be necessary before generally adopting such a regimen.

The story may be even more complicated. According to the current guidelines of the ACC/AHA, the patient's

perioperative cardiovascular risk can be estimated from (1) the medical history, (2) the type of surgery, and (3) the physical performance, which ultimately determines preoperative evaluation and the choice of prophylactic therapy. However, information from the patient's genetic background is not part of these guidelines but may be of paramount importance and help to individualize perioperative medicine to improve outcome.^{16,33} So-called "average" beneficial and detrimental effects observed in clinical trials may result from subgroups of patients with a particular genetic background. Accordingly, not all patients may profit from β -blockers to the same degree because of patient-specific genetic polymorphisms related to pharmacodynamic properties of receptors and/or pharmacokinetic properties of drug metabolism. In the β -Blocker Evaluation of Survival Trial study,³⁴ Arg389 homozygotes of the β_1 -adrenergic receptor treated with bucindolol had the largest benefit in mortality reduction (-38%), whereas Gly389 carriers had virtually no clinical benefit from bucindolol therapy compared with placebo.³⁵ Equally important and maybe more pertinent to this discussion, based on their genetic background some patients may be more reliably detected as being at high risk in dobutamine stress echocardiography than other patients.³⁶ Therefore, preoperative genomic testing should be integrated in future guidelines to tailor testing and treatment to the genetic background of patients. Because patient genotyping will be soon available to clinicians, updated guidelines should take into account these new perspectives.

From a theoretical point of view, to ultimately achieve our goal of improving patient outcome, we may have to test more thoroughly, including preoperative genomic profiling, to treat efficaciously based on genetic background. However, for the time being, we need a pragmatic approach. Hence, putting our resources into perioperative medical treatment and high-quality intraoperative and postoperative anesthesia care may be more efficacious than elaborative but incomplete preoperative testing.

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Management of Uncontrolled Hemorrhagic Shock

Toward a New Clinical Approach?

HEMORRHAGE remains a major cause of early death after trauma. A recent review of all consecutive deaths in a level 1 trauma center revealed that irreversible shock with or without central nervous system injury accounted for 37% of all causes of death.¹ Resuscitation of hypotensive victims is based on the rationale that adequate perfusion of vital organs should be restored as soon as possible. However, one of the side effects of most methods of increasing organ perfusion is an elevated blood pressure, which, in the face of uncontrolled hemorrhage, may increase bleeding and have adverse consequences that could outweigh the potential benefits of improved perfusion. Resuscitation of patients in hemorrhagic shock concentrates essentially on fluid administration, with ongoing debates on the time, the volume, and the nature of solution to be used. The use of vasopressor agents, although not recommended as first-line treatment of patients with hemorrhagic shock, might help to restore rapidly blood pressure to the desired level, while limiting the volume of fluid infused. In this issue of *ANESTHESIOLOGY*, Poloujadoff *et al.*² examined the effects of norepinephrine in combination with saline infusion on short-term survival in ketamine-anesthetized

rats undergoing uncontrolled hemorrhagic shock. Using a well-recognized experimental model, the authors nicely showed that the administration of an intermediate dose of norepinephrine in combination with fluids in either a hypotensive or a normotensive resuscitation strategy resulted in improved short-term survival. Interestingly, all animals receiving the higher norepinephrine dose died, as did the animals undergoing the normotensive resuscitation strategy with the use of fluids only.

The main objective of fluid resuscitation from uncontrolled hemorrhagic shock is to increase oxygen delivery to vital organs to maintain viability yet not to increase bleeding before hemostasis. The optimal fluid for this limited fluid resuscitation still needs to be determined. Among near isotonic crystalloids, there is increasing experimental evidence that lactated Ringer's solution is superior to normal saline for resuscitation of uncontrolled hemorrhagic shock and could be associated with improved survival.^{3,4} Although the type of fluid may be of importance, it seems even more crucial to adapt the amount of fluid to be given according to predefined clinical endpoints ("controlled" resuscitation).⁵

In patients with hemorrhagic shock, current international resuscitation guidelines recommend the use of vasopressors if pulseless electrical activity or bradysystolic rhythm is imminent. In a liver trauma model with uncontrolled and otherwise lethal hemorrhagic shock in pigs mimicking these conditions, vasopressin but not epinephrine or fluid resuscitation enhances short-term survival.^{6,7} In a similar model, resuscitation with small-volume hypertonic hyperoncotic hydroxyethyl starch combined with either norepinephrine or vasopressin resulted in similar survival

This Editorial View accompanies the following article: Poloujadoff M-P, Borron SW, Amathieu R, Favret F, Camara MS, Lapostolle F, Vicaut E, Adnet F: Improved survival after resuscitation with norepinephrine in a murine model of uncontrolled hemorrhagic shock. *ANESTHESIOLOGY* 2007; 107:591-6.

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rate, hemodynamic profile, and restoration of brain energy metabolism.⁸ However, the use of vasopressor agents could also have potential advantages in the resuscitation from early stages of hemorrhagic shock. They increase venous return to the heart through their effect on venous vascular tone. They could be efficacious in treating the vasodilatory component of hypotension. Their use could also help to restore rapidly blood pressure to the desired level, while limiting the volume of fluid infused, which might be of particular interest when hemorrhage is associated with traumatic brain injury. In these conditions, there is experimental evidence that resuscitation strategy combining fluids and vasopressors improved outcome compared with fluids or vasopressors alone.^{9,10} The results of the study of Poloujadoff *et al.*² are in line with these observations.

In these different models of hemorrhagic shock, with or without associated traumatic brain injury, vasopressin did not demonstrate a clear superiority over catecholamines characterized by prominent α -adrenergic properties, such as phenylephrine or noradrenaline. Vasopressin restores vascular tone in vasoplegic shock states by at least four known mechanisms: activation of V1 vascular receptors, modulation of adenosine triphosphate-sensitive K^+ channels, modulation of nitric oxide, and potentiation of adrenergic and other vasoconstrictor (such as angiotensin II) agents. Because of its possible effects on myocardial contractility and coronary vasculature, its use in the context of hemorrhagic shock should be reserved to situations unresponsive to volume replacement and catecholamines vasopressors.¹¹

As emphasized by Poloujadoff *et al.*,² anesthetic agents may interfere with the cardiovascular response to hemorrhage of the experimental animals. Most of the anesthetic agents block the sympathetic response to stress in a dose-dependent manner. However, the sympathetic system plays an important role in the redistribution of blood flow from organs with relatively low oxygen demand, such as the splanchnic area and the skin, to tissues with high metabolic demand, such as the brain and the heart. This redistribution of blood flow allows the organism to adjust oxygen extraction when oxygen delivery to the tissues is reduced. By blocking the sympathetic response to stress, anesthetic agents could alter this compensatory mechanism, thereby reducing the tolerance of experimental animals to hemorrhage.¹² Ketamine,

which possess indirect sympathomimetic properties, had the lesser effect on tissue oxygen extraction capabilities.¹² These observations could explain the favorable effects of ketamine in different models of hemorrhagic shock in comparison with other anesthetic agents.

Although it requires clinical validation, the approach proposed by Poloujadoff *et al.*² seems quite attractive. Indeed, the combined use of fluids and vasoconstrictors to restore and to maintain a predefined target perfusion pressure according to the patient's condition might be the more efficient approach, while reducing the risks of side effects associated with the use of each treatment alone.

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