Recruitment in Pulmonary and Extrapulmonary Acute Respiratory Distress Syndrome

The End of a Myth?

IN this issue of Anesthesiology, Thille and an international group of coworkers recognized for their expertise in acute respiratory distress syndrome (ARDS) bring convincing evidence that positive end-expiratory pressure-induced alveolar recruitment does not differ between patients with pulmonary and extrapulmonary ARDS.\(^1\) The authors recommend that the origin of ARDS should not influence selecting the appropriate positive end-expiratory pressure level: The recruitability of the lungs seems similar in pneumonia, aspiration, inhalation injury, alveolar hemorrhage, pulmonary contusion and secondary lung injury resulting from sepsis, acute pancreatitis, multiple trauma, cardiopulmonary bypass, and massive transfusion.

This multicenter study contradicts the classic and widespread belief that ARDS from primary pulmonary causes is less responsive to positive end-expiratory pressure, prone position, and recruitment maneuvers than ARDS from extrapulmonary causes\(^2\) and outlines some of the methodologic bias originally involved in generation of this belief. Initially, two studies suggested that lung recruitment obtained by increasing intrathoracic pressure resulting from prone positioning was substantially lower in patients with direct injury to the lung compared with patients with secondary lung injury.\(^2,5\) In both studies, recruitment was measured using the quasi–static compliance method, a method that entails a risk of underestimating alveolar recruitment and changes in respiratory mechanics, as pointed out by Thille et al.\(^1\) In the second study reporting different arterial oxygen response to prone positioning between primary and secondary ARDS, the difference in arterial oxygenation, although statistically significant, was of small magnitude and of questionable clinical significance.\(^5\) In addition, questions can be raised regarding the statistical analysis.\(^5\)

A third study, performed in five patients with ARDS caused by severe pneumonia and five patients with extrapulmonary ARDS, reported that lung recruitment after three consecutive sighs was considerably less in the former than in the latter.\(^4\) The method for measuring lung recruitment, however, could be questioned: End-expiratory lung volume was measured by the closed-circuit helium dilution method before and after sighs, and lung recruitment was computed as the sigh-induced change in end-expiratory lung volume, ignoring whether the increase in lung volume was related to (over)inflation of previously aerated lung or to lung recruitment. Another clinical study demonstrated different gas exchange response to nebulization of prostacyclin between primary and secondary ARDS.\(^5\) In six patients with severe pneumonia resulting from infection or aspiration, nebulized prostacyclin decreased arterial oxygenation without changing pulmonary arterial pressure. In contrast, in nine patients with lung injury resulting from extrapulmonary sepsis, necrotizing pancreatitis, or multiple trauma, it significantly improved arterial oxygenation and decreased mean pulmonary arterial pressure. Differences in gas exchange response, however, coincided with differences in lung morphology assessed by lung computed tomography. Primary ARDS had a diffuse loss of lung aeration, whereas secondary ARDS had a focal lung aeration predominating in the lower lobes and sparing the upper lobes. Differences in lung morphology rather than the cause of lung injury likely explain the difference found in gas exchange response because it has been clearly demonstrated that diffuse loss of lung aeration is not specific to pneumonia: Mild forms remain focally distributed, whereas severe forms affect lung tissue diffusely.\(^6,7\)

After the initial report putting forward the idea that pulmonary and extrapulmonary ARDS behave differently in terms of alveolar recruitment and should require specific clinical management,\(^2\) many contradictory studies were published.\(^6,8-14\) Although a higher incidence of lung consolidation and focal loss of aeration is observed in secondary ARDS,\(^6,15\) differences in lung morphology (focal vs. diffuse loss of lung aeration) do not exactly coincide with the cause of lung injury.\(^5,10\) Several studies have reported that alveolar recruitment resulting from increases in positive end-expiratory pressure,\(^9,12,15\) recruitment maneuvers,\(^8\) and prone positioning\(^11\) were not influenced by the cause of lung injury at the early phase of ARDS. Interestingly, in all of these studies, lung recruitment was measured from static pressure-volume curves, and in their study, Thille et al.\(^1\) elegantly dem-

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onstrate that the quasi-static compliance method is inappropriate for measuring recruitment. Finally, Gattinoni et al.14 recently reported a series of 68 ARDS patients in whom computed tomography of the whole lung was performed at airway pressures of 5, 15, and 45 cm H₂O. Contradicting their initial hypothesis,2 patients with primary ARDS had a higher percentage of recruitable lung than patients with secondary ARDS.

Another confusing factor is the difficulty of classifying ARDS in one or the other category. In the study by Thille et al.,1 physicians well known for their expertise in ARDS were unable to classify 37% of the patients. The reasons are multiple. Lung infection rapidly complicates the course of mechanical ventilation, inducing a direct injury to the lung. In anesthetized and ventilated animals, disseminated foci of bronchopneumonia are found only a few hours after the initiation of mechanical ventilation.16,17 In the study of Thille et al., 45% of the patients were included at a late phase of ARDS, a condition that complicates classification. Over time with mechanical ventilation, the risk of lung superinfection rapidly increases and extensive fibrosis may occur, contributing to the mixing of pulmonary and extrapulmonary lung injuries. Conversely, a focal bronchopneumonia, initially limited to the lung parenchyma, may induce secondary septic shock and extrapulmonary lung injury. In patients with multiple trauma, it is not easy to discriminate pulmonary contusion from lung injury resulting from hemorrhagic shock and massive transfusion. Finally, as previously reported,1 it can be difficult to discriminate pulmonary and extrapulmonary ARDS because both of them may coexist in the same patient.

The “primary/secondary ARDS story” illustrates the critical importance of using adequate methodology in physiologic human studies. Inaccurate methodology may lead to incorrect interpretation of the data and false theories. When, in addition, the theory flatters and coincides with good sense—it appears quite logical that a consolidated infected lung recruits less than a lung with alveolar-interstitial edema—then, despite numerous studies unable to confirm the theory, the belief persists for a long time. One should always remember what Mahatma K. Gandhi said in 1921: “An error does not become truth by reason of multiplied propagation, nor does truth become error because nobody will see it.”18

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Preoperative Nonsteroidal Antiinflammatory Agents as Substitutes for Aspirin

Already Too Late?

NONSTEROIDAL antiinflammatory drugs (NSAIDs) produce an antiplatelet activity by inhibiting platelet cyclooxygenase.\(^1\) Their mechanism of action is thus close to that of aspirin. Consequently, NSAIDs have been used to prevent thrombosis in indications similar to those of aspirin use. For example, indobufen\(^2\) and flurbiprofen\(^3\) have been shown to be effective antiarthrombotic agents in patients with coronary syndromes. Moreover, different molecules exert different levels of maximal inhibition,\(^4\) and inhibition within each NSAID molecule is typically dose dependent. In short, NSAIDs differ from aspirin not only by their reversible action on platelet activity but also by not having aspirin’s dose-independent on–off mechanism. In view of the potential adverse effects of maintaining aspirin therapy before scheduled surgery, these considerations provide the rationale to replace aspirin with a drug with a similar, but much shorter, action on platelet activity. If normal platelet activity is recovered within 24 h, the patient would be protected during the substitution period, and platelet function and hemostasis would be back to normal during surgery. NSAIDs could be the ideal substitute for aspirin, but, despite their attractiveness, proof is lacking because studies in the field are few and far between. The study by González-Correa et al.\(^4\) in this issue of Anesthesiology could be understood as a first step toward providing the evidence we require to justify this practice.

The NSAID ibuprofen is a racemic mixture of two enantiomers, \(S(+)\) ibuprofen (dexibuprofen), which is the active enantiomer, and \(R(–)\) ibuprofen, which is inactive. Several studies have demonstrated the antiplatelet activity of ibuprofen on platelet aggregation\(^5\) and on occlusion time measured using the Platelet Function Analyzer 100.\(^6\) In their study, González-Correa et al.\(^4\) show that the antiplatelet activity of dexibuprofen is similar to that of aspirin and that the administration of dexibuprofen, unlike that of aspirin, results in complete recovery of platelet function 24 h after drug withdrawal.

Dexibuprofen might indeed be an appropriate alternative to aspirin in a perioperative setting.

All is not that simple, however. For many years, some Europeans have often prescribed NSAIDs, in particular indobufen or flurbiprofen, during the 10 days preceding surgery, after withdrawing aspirin. The NSAID is administered twice a day and discontinued 24 h before surgery so that normal platelet function is recovered in time for the intervention. Because these compounds develop a strong antiplatelet activity that is similar to that of aspirin, prescription is thought to carry few risks apart from the usual complications of NSAIDs (gastrointestinal toxicity, renal insufficiency). This preoperative use in coronary patients represents an officially recognized indication in the Summary of Product Characteristics for flurbiprofen in some countries. However, substituting an NSAID for aspirin has never been assessed in comparative trials of the two drugs. Moreover, a recent study by Collet et al.\(^7\) reported 47 cases of acute coronary syndrome among patients in whom aspirin was withdrawn before scheduled surgery. Some of these patients had received flurbiprofen as a substitution, but this did not prevent acute coronary syndrome. Clearly, prescribing even a powerful NSAID in this indication could be questioned.

The study of González-Correa et al.\(^4\) is useful to confirm the potent antiplatelet activity of dexibuprofen and its reversible action. However, it is important to note that their study was performed in healthy volunteers and not in patients. No bleeding events were expected. Moreover, after 14 days, the reduction in prostacyclin synthesis was greater in the dexibuprofen group, potentially shifting the balance arms toward a prothrombotic risk. Therefore, even if this agent develops a reversible platelet activity, further explorations are mandatory to eliminate a theoretical prothrombotic risk.

Actually, it may be that it is the withdrawal of aspirin that should be reconsidered. A small number of fairly common clinical situations undoubtedly require aspirin withdrawal, because even slight worsening of bleeding could have severe consequences. The types of surgery concerned are mainly neurosurgery, prostate surgery, surgery for the posterior segment of the eye, and abdominal aorta surgery. However, the majority of operations can be conducted without withdrawing aspirin.\(^8\) Any worsening in bleeding that has been observed so far has generally not led to an increase in the number of blood transfusions in patients taking aspirin, including those


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undergoing cardiac surgery. In addition, some surgical procedures must be performed while the patient is taking aspirin, and aspirin is introduced preoperatively. This is the case, for example, for carotid endarterectomy and prosthetic femoral–popliteal bypass surgery, as outlined in the evidence-based guidelines of the Seventh American College of Physicians conference on Antithrombotic and Thrombolytic Therapy.9

Another factor to be taken into consideration is perioperative platelet activation in patients with vascular disease. Perioperative infarction occurs most commonly within 48 h of surgery. This has been widely confirmed because physicians use sensitive markers of cardiac ischemia such as troponin I. In such patients, even if platelets are not always activated, they are prone to be activated.10 Consequently, antiplatelet treatment either should not be withdrawn or should be resumed as soon as possible.

Finally, yet another reason for reconsidering aspirin withdrawal is the increasing number of retrospective case series reporting acute coronary syndrome, acute peripheral arterial syndromes, or acute cerebral events in patients who discontinued aspirin before surgery.7,8,11–13

Routine withdrawal of aspirin must therefore be challenged, and practice may even have to change. A large randomized double-blind study (“Stratagem”) comparing continuing aspirin (75 mg) or discontinuing aspirin (placebo) during the 10 days preceding scheduled surgery is currently ongoing in France. The primary endpoint is a composite variable with thrombotic complications, bleeding, and death as components. Results are expected by the end of 2007 (verbal personal communication, June 2005, Jean Mantz, M.D., Ph.D., Professor, Department of Anesthesia and Critical Care, Beaujon University Hospital, Clichy, France).

Therefore, the dogma of aspirin withdrawal before surgery must be reconsidered, and we must move toward a case-by-case analysis. Available published data, which are admittedly still too scarce, seem now to favor the maintenance of antiplatelet treatment, in particular aspirin, in many clinical situations. NSAID substitution must be evaluated clinically with either dexibuprofen or other short-life potent NSAID agents on a risk–benefit basis. However, taking into account the iatrogenic risk of even short-term use of NSAIDs and the potential increase in perioperative bleeding,14 the question could be, Preoperative aspirin substitution with NSAIDs: Isn’t it already too late?

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"IT’S not like ten rats and a t test" was Fred Cheney’s reassuring comment as we struggled through yet another rewrite of the Pediatric Perioperative Cardiac Arrest (POCA) manuscript. Indeed, outcomes research is not easy. The investigator attempts to objectify a data set that remains stubbornly nuanced, subjective, and incomplete. It is likely that Randall Flick, M.D., and his coauthors from the Mayo Clinic would agree. In this issue of Anesthesiology, Flick et al. report the incidence of and outcomes from perioperative cardiac arrest (PCA) in anesthetized children at the Mayo Clinic during the past 17 yr. Mayo Clinic investigators have been pioneers in the use of the electronic medical record for the creation and maintenance of a single-institution outcomes database. In the current report, PCA occurred most often in children with congenital heart disease as a result of factors not related to anesthesia. While cardiac surgery accounted for only 5% of all procedures, 87.5% of all arrests occurred in patients with congenital heart disease, usually during cardiac surgery as a result of failure to wean from cardiopulmonary bypass. Anesthesia factors were related in only 7.5% of all arrests, with an incidence of 0.65 per 10,000 anesthetics. Only six anesthesia-related arrests occurred in noncardiac cases during the 17-yr study period.

Interpretation of outcomes data is also not easy for the reader, given the absence of standardization among the myriad studies published during the past five decades. The reader must closely examine the fine print: What were the demographic characteristics of the patient population (e.g., age, American Society of Anesthesiologists physical status, surgical category, and emergency status)? How was “anesthesia related” defined (e.g., “preventable,” “associated,” “causative,” “human error”)? What time frame was included in the term “perioperative” (postanesthesia care unit discharge to 30 days)? Was reporting voluntary or mandatory? Only by appreciating these definitions and other details of methodology can the reader interpret the Mayo Clinic findings and put them in the context of previous reports of cardiac arrest in anesthetized children.

As a single tertiary referral center, the Mayo Clinic is probably not representative of the population-at-large of patients, physicians, or surgical procedures. Nonetheless, the data presented by the Mayo researchers are of high quality. Numerator and denominator data are reliable, given that reporting was mandatory and occurred within a single institution. Patient demographics and total caseload were known with a high degree of reliability. Underreporting was possible but unlikely.

The authors compare their results to those of the POCA Registry. However, the Mayo Clinic and POCA Registry data banks are very different, each with strengths and weaknesses. In the POCA Registry, more than 60 institutions contributed PCAs to a central data bank maintained by the American Society of Anesthesiologists Closed Claims Project staff at the University of Washington. Underreporting or biased reporting (e.g., withholding sensitive cases) occurred at an unknown rate. Participating institutions contributed their annual patient demographics and total caseload with a variable degree of reliability and accuracy. Therefore, incidence calculations were probably less reliable than those from the Mayo Clinic series, given the likely inaccuracy of both numerator and denominator.

On the other hand, the POCA Registry has accumulated many PCAs from multiple institutions, allowing analysis of cause of arrest and factors related to arrest. An inclusive definition of “anesthesia related” facilitated this process. Cases were deemed anesthesia related if anesthesia personnel or the anesthesia process played at least some role (ranging from minor to total) in the genesis of cardiac arrest. Flick et al. applied a more restrictive definition of anesthesia related. For example, arrest from massive trauma, embolic events, uncontrolled hemorrhage, and the metabolic consequences of massive transfusion (including hyperkalemia) were defined as “non–anesthesia attributed.” Patients “in extremis” upon arrival to the operating room were also excluded, even if
Opioid Self-administration

A Better Way to Evaluate Analgesics in Animal Models?

IN this issue of ANESTHESIOLOGY, Martin et al.1 take on some vexing issues surrounding analgesic evaluation and opioid management of chronic pain. Although there are many interesting facets to their studies, it is the issue of interaction between pain and opioid self-administration that lies at the heart of their contribution. The data provided are not only relevant to the treatment of neuropathic pain, which is modeled in their studies, but also to understanding how pain might modify susceptibility to the development of opioid addiction.

One motivation for undertaking these studies was that we normally measure analgesic effects against nociceptive responses evoked when “neuropathic” tissue is stimulated. Thus, the hind paws of animals sensitized by virtue of some type of nerve injury are typically prodded with mechanical devices or heated with focused light to cause readily quantifiable withdrawal responses. These methods are robust, easy to learn, and generally reproducible between laboratories. Therefore, journals are filled with reports of reductions in allodynia or hyperalgesia used as evidence of a drug’s analgesic potential. Unfortunately, it may be the spontaneous or continuous aspects of the human pain experience that lead patients to seek treatment for their chronic neuropathic pain as

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opposed to the evoked pain more commonly modeled in animals. Similarly, reductions in the area of allodynia or hyperalgesia surrounding surgical wounds does not consistently correlate with lower overall postoperative pain scores. We also need to recognize soberly that robust antiallodynic effects of test compounds in animals have not always correlated well with useful antialgesic effects in humans. Unfortunately, there are many fewer methods described for quantifying the relatively subtle spontaneous behaviors, and the measurements themselves can be very time-consuming.

In their report, Martin et al. show that nerve-ligated but otherwise unperturbed rats self-administered a range of opioids in a manner consistent with providing analgesia. Self-administration was measured using an apparatus that delivered an intravenous dose of opioid when the rats pushed a lever placed above their enclosure’s floor. The investigators based their conclusions on both the size of the doses required for maintained self-administration and the measured duration of effect of those doses. In essence, it seemed that the nerve-ligated rats would bolus themselves with opioid only if the dose delivered provided analgesia, and would redose when the effect wore off. The self-administration of opioids by sham operated rats followed a different pattern. Self-administration in the absence of pain is commonly used as an index of abuse liability of a drug.

Although the study might not be judged conclusive, it is exciting to think that we may be able to evaluate pain and analgesic effects based on a complex self-administration behavior rather than by poking a sensitized hind paw with a stiff piece of monofilament. The presumption is, of course, that whatever motivates the rat’s self-administration behavior better reflects human pain than the evoked responses typically used. Time and a good deal of additional experimentation will tell.

Another key observation in these studies was that nerve-ligated rats showed less evidence of positive opioid reinforcement than the sham-operated controls. Although it had been observed previously that nerve-ligated animals showed less positive opioid reinforcement using the conditioned place preference testing paradigm, the more sophisticated self-administration approach had not been used. Specifically, after nerve ligation, doses of heroin, morphine, and other opioids previously capable of supporting self-administration became less effective. It was not until the rats were given analgesic range doses that the nerve-ligated rats would self-administer opioid. Furthermore, when the neuropathic sensitization was reduced with intrathecal clonidine, heroin was poorly reinforcing even at high doses.

These observations may have important implications regarding the ongoing controversy about opioid abuse potential when these drugs are administered for pain. Although the existing literature is incomplete, opioid treatment for chronic pain seems to have a relatively low likelihood of leading to opioid addiction in patients without substance abuse histories. Prescription opioids, however, are commonly abused substances, and the rate of prescription opioid abuse is increasing. It is possible that the methodology introduced by Martin et al. could help us to understand whether there is in fact some form of protection from opioid abuse conferred by chronic pain, and under what circumstances that protection exists. At the very least, this research group has provided another piece of evidence that systems related to pain and addiction share some common ground.

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