Anesthesiology 2004; 100:1–2

The Times Are A-Changin'

Should We Hang Up the Stethoscope?

A FEW years ago, a critical care fellow embarrassed me by defending his less than stellar documentation of a patient's physical examination with the following statement to one of my colleagues, "Dr. Hubmayr said that listening to the chest of a mechanically ventilated patient is a waste of time." My colleague thought that I had lost my wits and that I was a terrible role model for our critical care training program. Although I felt quoted out of context and briefly contemplated taking a course in media training, I must confess to a long-held skepticism about the usefulness of lung auscultation in the management of critically ill mechanically ventilated patients. Do I listen to the chest of my patients? Absolutely! After all, one should not ignore new murmurs, extra heart sounds, or pericardial rubs. Do I listen to the lungs? Yes, but largely because patients expect me to. The stethoscope is a powerful bonding tool with patients, especially when an artificial airway prevents them from talking. Frankly, I seem to learn a lot more about breathing from palpation of neck and abdominal muscles, from inspection of chest movements, and from analysis of respiratory variations in airway and vascular pressures than I do from listening to wheezes and crackles. The report by Lichtenstein *et al.* in this issue of the Journal is a welcome reinforcement of my personal bias.[1]

The authors compare the diagnostic performance of three techniques, namely, auscultation, bedside chest radiography, and lung ultrasonography in patients with acute respiratory distress syndrome. Thoracic computer tomography served as the definitive standard for the detection of pleural effusions, consolidation of alveolar airspaces, and alveolar-interstitial (permeability) edema. Given the choice of target conditions, it is not surprising that the stethoscope—at least in the hands of one investigator—performed poorly and had accuracy akin to the flip of a coin. The bedside frontal chest radiograph substantially underestimated the extent of lung injury, which is consistent with a large body of published work, beginning with Gattinoni *et al.*'s original report on computer tomographic findings in acute respiratory distress syndrome.[2] In contrast to auscultation and plain film chest radiography, lung ultrasonography had a greater than 90% diagnostic accuracy for each of the three target conditions and showed excellent spatial correlations with computer tomographic findings.

Considering these observations, is it really time to hang up the stethoscope? Not yet, but I do wish to raise a few caveats about the cost-effectiveness of lung auscultation in the intensive care setting. Much of what we know about lung sound interpretation has been handed down by generations of master clinicians, but is far from supported by a comprehensive database. There are no large-scale population studies in which the acoustic properties of the respiratory system have been assessed and validated against sensitive and specific measurements of lung structure or function. For certain, sophisticated approaches and elegant analyses of lung sound recordings in experimental animals with injured lungs suggest that correlations between acoustic energy transfer, measures of gas exchange, and lung mechanics exist.[3] However, such studies merely provide a proof of concept and do not establish efficacy of pulmonary acoustics in the care of ventilator-dependent patients. Until further research establishes clinical efficacy, we should be mindful that auscultation of the lungs might drive therapeutic decisions, which could cause benefit as well as harm. Does every wheeze warrant a bronchodilator treatment, or every crackle a diuretic or an increase in positive end-expiratory pressure? Clearly not, but such decisions are often made despite the lack of reliable sensitivity and specificity data.

Ultrasound fails to penetrate the gas-containing lung tissue and therefore, to date, has found limited application in the assessment of pulmonary lesions. Nevertheless, in their report the current authors speculate that changes in the appearance of consolidated lung and of air/tissue interface artifacts, which they describe as "rockets and comet-tails," may be useful indicators of lung recruitment. Although this hypothesis is intriguing, the efficacy of ultrasonography as a guide to positive end-expiratory pressure management will be difficult to establish. The literature on lung recruitment and its putative benefits keeps growing, but the link between surrogate physiologic endpoints *oxygenation and respiratory compliance* and the more meaningful outcome variables *survival and lung healing* has yet to be established. There is strong experimental evidence from the bench that recruitment is a desirable therapeutic goal as long as overdistension of other parts of the lung can be

◆ This Editorial View accompanies the following article: Lichtenstein D, Goldstein I, Mourgeon E, Cluzel P, Grenier P, Rouby J-J: Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. ANESTHESIOLOGY 2004; 100:9–15.

Accepted for publication September 25, 2003. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

avoided. However, there is no agreement on how to define the optimal balance between maximal recruitment and minimal overdistension. Given its limited depth penetration into lung tissue, it is hard to imagine that ultrasonography will prove to be the gauge by which the risk/benefit balance of lung recruitment targeted interventions may be judged.

Encouraged by the superior diagnostic performance of ultrasonography in detecting acute respiratory distress syndrome–related pulmonary lesions, the current authors speculate that frequent lung examinations with handheld ultrasound probes may obviate the need for routine daily chest radiographs, bringing about considerable cost savings. They acknowledge that ultrasound is blind to malpositions of endotracheal tubes or indwelling vascular catheters, consequential findings that are detected in up to 10% of routine examinations.[4] Yet, the cost-effectiveness of obtaining routine daily chest radiographs in mechanically ventilated patients remains controversial insofar as this practice has not resulted in proven reductions in hospital mortality or length of stay.[5]

The focus on the lung examination is obviously important for anesthesiologists and intensivists who treat mechanically ventilated patients. I suspect, however, that the search for a more sensitive and specific lung examination will not be the only reason why several years from now my stethoscope will gather random noise while I bond with my patients *via* a portable ultrasound probe. I can imagine that guided by clinical pretest probability I will take a quick look at the carotids, check the patency of neck and axillary veins, take a peak at right and left ventricular ejection fractions, make sure that bile and urine are flowing without backing up in the gallbladder or renal pelvis, and work my way toward the legs looking for clots.

The trouble with this vision is that currently I am not confident that I know how to use the device in all of its proposed applications. There is a great temptation to just buy a probe and learn as one goes. I consider that to be a mistake. There are experts who can teach us intensivists how to use ultrasound.[6] It will be up to us to make a commitment and learn the strengths and limitations of this technology. This is a prerequisite for testing the efficacy of portable ultrasonography as an adjunct to or even an integral part of the routine examination of critically ill patients. Maybe then I will hang up my stethoscope.

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Anesthesiology 2004; 100:2–4

The Case for Pediatric Drug Development in Clinical Pain Research

THE excellent article by Williams *et al.* in this issue of the Journal highlights the issue of drug response during development by examining the developmental regulation of codeine metabolism and analgesia in a rat model.[1] It is well recognized that in humans, codeine is metabolized to its active metabolite morphine; without this metabolism, analgesia is limited. The O-demethylation of codeine to morphine is mediated by the cytochrome (CYP) P-450 enzyme CYP2D6, an enzyme responsible for the metabolism of a wide range of drugs (http://medicine.iupui.edu/flockhart/p450ref4.html, accessed September 21, 2003). Genetic polymorphism exists for CYP2D6, and individuals can be classified into two groups: extensive and poor metabolizers. Poor metabolizers (who lack active CYP2D6) do not produce morphine; therefore, codeine does not provide efficacious analgesia. What is the situation for neonates? Can they be classified into poor or extensive metabolizers at birth on the basis of phenotype? The present investigators showed that in rats, codeine metabolism is indeed developmentally regulated, with low efficacy in the early postnatal period.[1]

Development has an important effect on CYP P-450

This Editorial View accompanies the following article: Williams DG, Dickenson A, Fitzgerald M, Howard RF: Developmental regulation of codeine analgesia in the rat. ANESTHESIOLOGY 2004; 100:92–7.

Accepted for publication September 16, 2003. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

enzymes; apparently quite soon after birth CYP2D6 activity increases markedly in humans.[2] Other CYP enzyme activities also appear during the first weeks of life. It is important to recognize that the current study was performed in a rat model using the Dark Agouti rat, which has impaired metabolism of debrisoquine and absence of CYP2D1, in contrast to the control, Sprague-Dawley rats.[3] However, it is now apparent that CYP2D2 expression is also reduced in Dark Agouti rats and that although CYP2D2 also catalyzes debrisoquine metabolism, there are differences in the substrates metabolized by CYP2D1 and CYP2D2.[3] Thus, the Dark Agouti rat is an imperfect model for the polymorphic reduction in CYP2D6 expression in humans. The relationship between CYP2D1 and CYP2D2 development in rats does not necessarily translate to similar developmental changes in CYP2D6 in humans, and it would be dangerous to make such a leap.

Narcotic analgesics have long been administered to neonates and children, despite a fundamental lack of pharmacologic knowledge. In 1965, Way *et al.*[4] studied the effect of morphine and meperidine on the carbon dioxide respiratory response curve and demonstrated that morphine shifts the curve in the newborn infant downward and to the right to a greater extent than meperidine.[4] From these data, it was suggested that meperidine depresses the infant's respiration less than morphine, perhaps because of an immature, "leaky" blood–brain barrier, allowing a greater amount of morphine to cross the blood–brain barrier and gain access to receptor sites within the central nervous system. This highlights that drug metabolism is not the only pharmacokinetic variable that may change during development. Currently, we recognize the importance of a drug efflux transporter protein-P glycoprotein present in the gut and endothelial cells in the blood–brain barrier. This transporter limits drug absorption from the gut and its passage into the brain.[5,6] Other uptake and efflux transporters are also expressed in the brain and control brain drug uptake. The brain and gut are not the only sites where protein-P glycoprotein can be identified. Absence or pharmacologic blockade of placental protein-P glycoprotein, for example, increases fetal drug exposure.[7] Studies are required to define the activity of protein-P glycoprotein and other transporters in various tissues of the body as the neonate matures; such investigation may allow the variability of drug response to be addressed on a more rational basis, leading to the individualization of drug therapy in neonates and small children as they mature and develop.

Human studies are urgently required. Although such clinical studies are difficult to perform in patients ranging in age from neonates to adolescents, they are essential to the development of rational drug dosing in children. Such studies will be stimulated by the Best Pharmaceuticals for Children Act, signed into law in 2002 (http://www.fda.gov/cder/pediatric/index.htm, accessed September 21, 2003). This and the Pediatric Rule have stimulated such clinical investigation (http://www.fda/gov/cder/pediatric/index.htm, accessed September 21, 2003). Thus, to quote Kearns *et al.*, "The provision of safe and effective drug therapy for children requires a fundamental understanding and integration of the role of ontogeny in the disposition and action of drugs."[8]

Does this mean all drugs must be studied in children of all ages? Fortunately, the answer is probably "No." We currently have an understanding of the factors influencing drug absorption, distribution, metabolism, and transport as well as renal excretion. For most of these processes, model compounds are available and could be used to evaluate their activity in children. Evaluation of such model compounds will allow cautious extrapolation to other substrates, which are handled in a similar fashion. Such extrapolation can be made more confidently when large differences are found.

The classic example of the blue baby syndrome induced by chloramphenicol administration is a much-cited example of a drug-induced adverse effect in neonates resulting from their impaired drug metabolism. Fortunately, other examples of such serious consequences of impaired drug metabolism have been rare. The issue of pain control in children is correctly recognized to be of great clinical importance.[9] Defining the underlying factors responsible for variability in pain control in children of all ages will require definition of the variability of plasma drug concentrations (*e.g.*, morphine in this study), the mechanisms for such variability (*e.g.*, pharmacogenetics) and, more difficult, the variability in drug sensitivity. Our current means of drug dosing in children are largely empirical, based on body weight or surface area. Such empiricism assumes a linear relationship between size, enzyme, and drug transporter activity, and receptor expression. We must and should be able to do better. There is much work to be done, but it must be performed in children because the ability to extrapolate from animal models is limited.

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Anesthesiology 2004; 100:4–7

Is There Any Reason To Withhold β Blockers from High-risk Patients with Coronary Artery Disease during Surgery?

IN this issue of the Journal, London *et al.*[1] summarize the physiologic foundations and clinical controversies of perioperative β blockers in patients undergoing noncardiac surgery. The presented data provide solid evidence for their efficacy and support a more widespread use for the reduction of perioperative mortality in patients with known or suspected coronary artery disease (CAD), particularly those with diabetes, left ventricular hypertrophy, and renal insufficiency. However, despite their beneficial effects, oddly enough it seems that some physicians are more afraid of the side effects of β blockers than the harmful effects of myocardial ischemia; β blockers are currently underused in the perioperative setting.

How often are β blockers underused? In a recent study, Schmidt *et al.*[2] showed that in 158 patients undergoing major noncardiac surgery, of the 67 who were eligible to receive perioperative β blockers only 25 (37%) received β-blocker therapy. Similar results were shown in a survey of Canadian anesthesiologists.[3] This study revealed that 93% of anesthesiologists agreed that β-blockers were beneficial in patients with known CAD, but only 57% reported β-blocker use in these patients, and only 34% of these regular users continued taking β-blockers beyond the early postoperative period.[3]

What may be the reason for withholding β blockers? The several potential factors preventing more widespread use of β blockers during the perioperative period include (1) β blockers may not be effective enough in reducing perioperative cardiac events, (2) limited experience with respect to timing and dosing of perioperative β blockers, (3) contraindications to β blockers, and (4) availability of effective alternative cardioprotective treatment strategies. These factors are discussed below.

1. β blockers are effective in reducing perioperative cardiac events. A rupture of a coronary atherosclerotic plaque is implicated in about half of perioperative myocardial infarctions, resulting in platelet aggregation and thrombus formation. However, the location of perioperative myocardial infarction is not always related to the location of the culprit coronary lesion. In two separate studies,[4,5] histopathologic analyses of coronary arteries and myocardium revealed that predicting the site of infarction based on severity of underlying stenosis would have been unsuccessful in a majority of the patients. This may indicate the presence of CAD in numerous locations throughout the coronary tree and the possibility that perioperative myocardial infarction may result from plaque rupture and thrombosis at the site of a hemodynamically (in)-significant atherosclerotic plaque. In addition to acute plaque rupture and thrombosis, prolonged myocardial ischemia due to a supply–demand mismatch has been suggested as another mechanism for major cardiac complications. Patients undergoing noncardiac surgery with known CAD or those at risk may have an incidence of perioperative myocardial ischemia exceeding 40% with an associated 9- to 16-fold increased risk for cardiac death and myocardial infarction.[6,7] During prolonged myocardial ischemia, elevated levels of cardiac troponins can be detected verifying structural myocardial damage. Elevated levels of cardiac troponins are confirmed to have prognostic information for perioperative and long-term cardiac complications.[8,9] In a recent study, we demonstrated that asymptomatic perioperative myocardial damage, indicated by cardiac troponin elevations without angina pectoris or new electrocardiographic changes, resulted in a more than 2-fold increase in risk of all-cause mortality during a median follow-up of 4 yr (personal communication, Don Poldermans, M.D., Professor, Department of Vascular Surgery, Erasmus Medical Center, Rotterdam, The Netherlands, August 2003).

β blockers may play a substantial role in the prevention of perioperative cardiac complications. Apart from their direct hemodynamic effect, such as reduction in heart rate and contractility, β blockers may also indirectly influence the determinants of shear stress and reduce inflammation through decreases in sympathetic tone.[10] Reduction in heart rate and pulse pressure by β blockers are also considered important in stabilizing the

This Editorial View accompanies the following article: London MJ, Zaugg M, Schaub MC, Spahn DR. Perioperative β-adrenergic receptor blockade: Physiologic foundations and clinical controversies. ANESTHESIOLOGY 2004; 100:170–5.

Accepted for publication August 25, 2003. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

vulnerable plaques. As a result of these properties of β blockers, the intensity of myocardial ischemia is reduced and the extent of myocardial infarction can be decreased. Several studies have demonstrated the clinical efficacy of perioperative β-blocker use to decrease cardiac complications in patients with risk factors or those with known CAD who are undergoing noncardiac surgery. Mangano *et al.*[11] randomly assigned 200 patients to receive atenolol or placebo before the induction of anesthesia, immediately after surgery, and daily throughout their hospital stay. There was no difference in the incidence of perioperative myocardial infarction or cardiac-related death. During long-term follow-up, the mortality was 10% in patients who had been previously given atenolol and 21% in the controls. A more recent study of Poldermans *et al.*[12] randomized patients to bisoprolol an average of 30 days preoperatively with dose adjustment to achieve a resting heart rate of 60 beats per minute or less, and patients continued to receive β blockers for an average of 2 yr. The results of these studies, combined with previous investigations, show a protective effect of β blockers for perioperative myocardial ischemia and support the hypothesis that perioperative β-blocker use can substantially reduce cardiac risk among high-risk patients undergoing noncardiac surgery.

2. Timing, hemodynamic targets, and duration of perioperative β-blocker use. Currently, there is no consensus about the optimal timing of institution of perioperative β blockers, duration of therapy after surgery, or hemodynamic targets. On the basis of our own experience, treatment with perioperative β blockers should start as soon as the eligibility of a high-risk patient for surgery is confirmed. If possible, this should occur days or weeks before surgery with dose adjustment to achieve a resting heart rate of 60 beats per minute or less.[12] London *et al.*[1] clearly state that provision of perioperative β blockade may allow better assessment of tolerance to therapy and perhaps might take advantage of "cellular-level" effects of β blockade, but these advantages are strictly speculative. Adjusting treatment to resting heart rate alone may not be an adequate measure of β blockade, which could be most accurately assessed by response to exercise or adrenergic challenge. In that respect, in patients at intermediate- or high-risk who are already receiving β blockers, additional noninvasive testing as part of the routine preoperative risk assessment with dobutamine stress echocardiography could be useful in facilitating additional titration of β blockers in relation to the heart rate at which myocardial ischemia is induced. A few studies are available to derive recommendations for the duration of β-blocker use. Mangano *et al.*[11] demonstrated that patients receiving perioperative β blockers experienced fewer cardiac events throughout the 2-year study period than those in the placebo group. Poldermans *et al.*[13] showed that a selective β1 blocker bisoprolol reduced cardiac death and myocardial infarction in high-risk patients for as long as 2 yr after successful major vascular surgery.

3. Adverse effects of perioperative β blockers. Contraindications such as the presence of severe left ventricular dysfunction, exacerbation of reactive airway disease, insulin-dependent diabetes, or worsening of symptoms of peripheral vascular disease may be important reasons to withhold β blockers. Despite these "classic" contraindications, several investigators have demonstrated that perioperative and long-term administration of β blockers was well tolerated with no substantial increase of adverse effects, despite that many of these patients were known to have CAD, pulmonary disease, diabetes mellitus, and intermittent claudication.[11–16] The use of cardio-selective β blockers, such as bisoprolol or metoprolol, given their lower potential for adverse effects at routine clinical doses, may further encourage physicians to use these agents in patients with relative contraindication to β blockers. The potential absolute contraindication to β blockers, such as major atrioventricular nodal conduction disease in the absence of a pacemaker, severe asthma, or a strong reactive airway disease, may preclude patients from tolerating β blockers. In such situations, α2 agonists or less invasive anesthetic and surgical techniques should be considered.

4. Alternative cardioprotective treatment strategies. Prophylactic coronary revascularization prior to surgery could be an attractive alternative approach for the management of CAD in patients who have been identified as having increased risk for cardiac complications. This may not only improve perioperative outcome, but it would also result in better long-term survival after surgery. No prospective, randomized trials have addressed the effectiveness of coronary bypass grafting (CABG) for reducing the incidence of perioperative cardiac complications.[17,18] The findings of retrospective studies suggest that, when indicated, CABG might reduce the risk of cardiac complications. However, one should consider that the combined risks of CABG and noncardiac surgery might exceed the risk of noncardiac surgery alone. A possible less invasive alternative to preoperative CABG would be percutaneous transluminal coronary angioplasty with coronary stenting, provided that a delay of surgery of at least 6 weeks is acceptable. In two recent studies it was shown that patients treated with percutaneous transluminal coronary angioplasty and coronary stenting were at high risk for perioperative mortality, stent thrombosis, or bleeding complications.[19,20] The frequency of these events was higher among patients undergoing surgery within 6 weeks of stent placement. Until randomized trials become available, it is recommended to follow the American College of Cardiology/American Heart Association guidelines and to perform CABG or percutaneous transluminal coronary angioplasty if they are indicated independently of the need for noncardiac surgery.

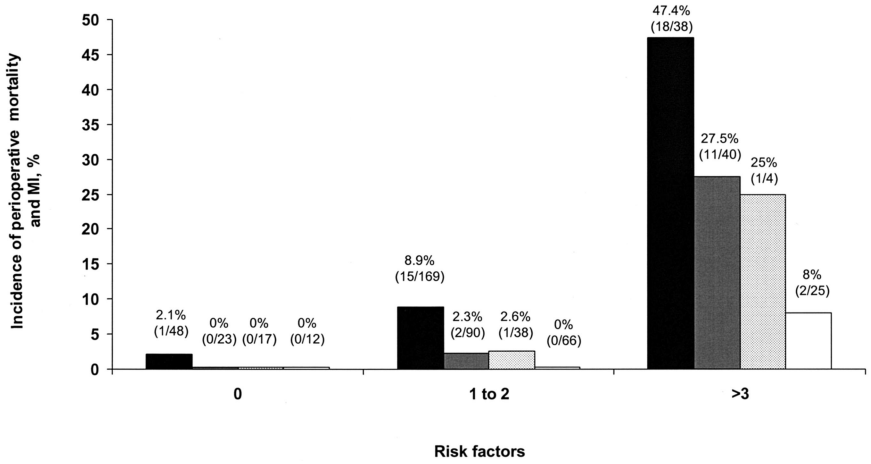

Fig. 1. Incidence of perioperative mortality and myocardial infarction (MI) in 570 patients undergoing abdominal aortic aneurysm surgery. *Filled bars* = no medication use; *gray bars* = β blocker use only; *dotted bars* = statin use only; *open bars* = combination of β-blocker and statin use. Results are based on the number of clinical risk factors (age > 70 yr, current angina, previous MI, heart failure, previous cerebrovascular event, diabetes mellitus, renal insufficiency and pulmonary disease) and on statin and β-blocker use.

Recently, data have been reported about the cardioprotective effect of lipid-lowering medications, such as hepatic hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) (fig. 1). Poldermans *et al.*[21] demonstrated that statin use was associated with a more than 4-fold reduction of perioperative mortality in patients undergoing vascular surgery.

Recommendations: The findings of these studies and the work of London *et al.*[1] reveal that despite that perioperative β blockers have proved beneficial in high-risk patients, they are still underused and enhancing β-blocker use should be a priority. Practice guidelines of the American College of Cardiology/American Heart Association and the American College of Physicians may provide one possible approach for improving the use of perioperative β blockers in patients with known CAD or those at risk who are undergoing major noncardiac surgery. According to these guidelines and previous clinical studies, β blockers should be prescribed to all patients with one or more risk factors correlated with higher risk of cardiac complications. Cardioselective β blockers such as bisoprolol or metoprolol should be started days to weeks before a planned surgical procedure, aiming at a resting heart rate of 60 beats per minute. During surgery, additional intravenous β-blocker therapy can be administrated, whereas after surgery in patients with multiple risk factors for CAD, β blockers should be continued to reduce long-term cardiac complications.

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