ported that in isolated rat's cerebral artery, dilation produced by α2-agonist was blocked with inhibition of nitric oxide synthase. Because we did not examine the effect of activation of endothelial α2-adrenoceptors on vascular reactivity of the spinal microcirculation via production of nitric oxide, we cannot exclude the possibility that the change of endothelial function attributable to different physiologic and pathologic states may alter the vasoconstrictive effect of α2-agonists and the effectiveness as local anesthetic additives.

In addition, we previously reported that the pial vascular effects of α2-agonists were modulated via potassium channel activation using a cranial window preparation. The vasoconstrictive effects of dexmedetomidine and clonidine seem to be mediated via activation of α2-adrenoceptors, and partly counterbalanced vasodilation via activation of adenosine triphosphate sensitive potassium channels. Moreover, we also reported that local anesthetics such as bupivacaine and ropivacaine per se affect spinal pial vessels, even to the different direction, affecting the duration during spinal anesthesia. Therefore, it is possible that not only nitric oxide, but also other possible vasoactive condition including adenosine triphosphate sensitive potassium channels activation and concomitantly used local anesthetics could modulate the vasoconstrictive effects of α2-agonists.

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anesthesia were compared and described in the article.8 The model developed by Apfel et al.7 was criticized for lack of analysis of anesthesia-related factors in spite of the fact that induction agents, muscle relaxants, volatile anesthetics, etc., and their dosages were considered in the analysis. Anesthetic agents were not included in the final model because they were found to be statistically nonsignificant.7 What is more Apfel et al. were able to show, that their operation-independent score was able to predict postoperative vomiting in other types of surgery and that a score with consideration of the type of surgery did not increase the accuracy of their model.7 We wonder, why this study was also not quoted.

More importantly, we are concerned that flaws in data acquisition and analysis in Dr Sinclair’s study may have led to wrong conclusions. Postoperative nausea and vomiting is usually defined as any episode of nausea or vomiting within 24 h.10 Sinclair et al. have defined in hospital PONV as “any volunteered report of nausea or observed active retching or vomiting requiring antiemetics.” It remains unclear whether “requiring antiemetic” is related to vomiting alone, active retching or vomiting, or to all three symptoms. Was the need for antiemetics standardized at all? As patients are usually not provided with rescue antiemetics for emetic sequelae after hospital discharge it seems that the definition of PONV outside hospital, which was based on a telephone interview, must have been different to that within hospital. It is possible that this difference in definitions could have been one reason for the low incidence of PONV of 9.1% (according to the text on page 114) or of 7.1% after general anesthesia (according to fig. 1).2 Most previous prospective studies, which have explicitly and separately asked for nausea and vomiting at repeated time intervals have reported average incidences between 20% to 50%.5,7,9 Sinclair et al. have suggested that the low incidence was most likely explained by an “under-reporting by PACU and ASU nurses.” Either way a score whether based on unclear definitions or possibly incomplete nurse assessment of PONV may lead to a systematic error with an underestimated risk of PONV. Therefore, it remains unclear whether the reported three to sixfold incidence after orthopedic procedures is a reflection of the accuracy of documentation or the type of surgery. The importance of considering nonlinearity becomes more apparent when considering the relationship between age and PONV which is bimodal. In children the incidence increases with age,11 whereas in the adult population the tendency is for a decrease in PONV with increasing age.5,7,11 It is obvious that a score which includes age as a linear function would exaggerate the risk of very young children if based on a score developed mainly from adults.

Sinclair et al. have claimed that their study provides “the most comprehensive logistic regression model of patient-, anesthesia-, and surgery-related factors associated with PONV.”1 However, their anesthesia-related factors only considered whether general or regional anesthesia was given, with no reference to drugs given or extent of block. In fact, Carpenter et al. have shown that the choice of drugs for spinal anesthesia as well as the block height above Th4 appeared to be relevant.12 It would seem that the score proposed by Sinclair et al. is not so comprehensive as claimed.

In conclusion, aside from being disappointed that evidence of previous studies was either misrepresented or incomplete, there would appear to be some flaws in data acquisition and analysis which may have led to bias in the results thereby rendering the suggested model less applicable for other centers.

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In Reply—We are grateful for the opportunity to respond to the remarks of Apfel et al. Although we are concerned about the degree to which we have been misunderstood and misquoted, we regret that Apfel et al. have been misled by our introductory statement. By simply stating that we have developed and validated a mathematical model to calculate the risk of postoperative nausea and vomiting (PONV) in a large population of ambulatory surgical patients, we did not intend to suggest that this was a new concept. Our work is different from previous studies, as our study focus is ambulatory surgical patients whereas other work focused more on inpatients.

This would not be supported by the studies which we quoted in the discussion. In our view, presenting the limitations of previous mathematical models does not “dismiss” them. Rather, it outlines areas in which improvements can be made. Although we were not aware of the editorial by Korttila, due to its recent publication in Acta Anaesthesiol Scand at the time of our submission to Anesthesiology, we welcome his contribution, which highlights the persistent problem of predicting PONV among our patients.

We applaud Palazzo and Evans for the introduction of logistic regression analysis as a tool for quantifying the impact of patient factors on the probability of PONV. Their model was developed for the prediction of PONV among patients undergoing minor orthopedic surgery. When tested by Toner et al. in a larger, heterogeneous patient group, the overall correct prediction rate of the model was 71%. Despite our omission of this finding in our study, we agree with Toner et al. that this is in fact not substantially greater than chance alone would allow. Although the model is most effective in predicting the risk of PONV in groups of patients, it is less capable of estimating PONV for individual patients. In clinical practice, we believe that most anesthesiologists would be interested in predicting the risk of PONV in their individual patient, based upon patient, anesthesia, and surgery-related factors.

Our study does not claim that the studies of Koivuranta et al. and Apfel et al. were criticized for “no analysis” and “lack of analysis,” respectively, of anesthesia-related factors. In our view, mathematical models, which do not incorporate a variable for anesthesia-related factors, are limited. Since many patient and surgery-related factors can not be changed in the perioperative period, there must be, within the equation of the model, provision to allow for input of anesthesia-related variables. The mathematical models proposed by Koivuranta et al. and Apfel et al. do not permit users to determine the impact of a modification in anesthesia technique. Our comprehensive mathematical model includes patient, anesthesia, and surgery-related factors associated with PONV.

Nurses in the PACU and ASU collected our data. Postoperative nausea and vomiting was defined in the check-off forms, which were used by the nurses in the PACU and ASU. Although the definition was printed on the check-off forms for clarification regarding patients in the PACU and ASU, patients who were contacted by phone were nonetheless asked about episodes of nausea or vomiting at home. The main difference is that patients in the PACU and ASU who experienced nausea or vomiting were treated, since antiemetics are standardized for those patients.

Apfel et al. have tried to explain a method of “under-reporting by PACU and ASU nurses,” demonstrating their lack of understanding regarding the structure of our PACU and ASU staffing. Nursing assignment in the PACU and ASU is not according to surgical subspecialty. Rather, all nurses provide postoperative care for any surgical subspecialty patient. Therefore, the potential for an “incomplete assessment,” as proposed by Apfel et al., does not exist. The claim that we have suggested that the low incidence of PONV was “most likely explained by” under-reporting by PACU and ASU nurses is incorrect. Although under-reporting because of high work load may be a limitation of the study, the high number of D+C procedures and ophthalmology surgery performed at our hospital, both with low incidences of PONV, may be the most likely explanation for the low incidence of PONV.

Apfel et al. allude to a discrepancy between two percentages quoted in the text and figure 1. The two percentages, 9.1% and 7.2%, refer to different incidences. The 9.1% incidence of PONV refers to all subjects at 24 h (those who responded to the 24 h interview), while the 7.2% is the incidence of PONV among general anesthetic patients during their postoperative stay.

Apfel et al. recommended the inclusion of an interaction term between duration and type of anesthesia into the model, suggesting that duration is important for general but not regional anesthesia. During the data analysis, this interaction term was not found to be statistically significant (P = 0.45, although we had sufficient sample size to detect an association). Therefore, it was not included in the final model. We did not mention it in our manuscript because of space limitations.

Apfel et al. discussed the bimodal, nonlinear association between age and PONV, stating that there is an increase PONV incidence with age among young children, and decrease of PONV incidence among adults. Because our patient population did not include pediatric patients (out of 17,638 patients, only 14 patients were younger than 14 yr of age, and only an additional 32 patients were 14 yr of age), the association between age and PONV incidence was fairly linear in our data set. Our model is only applicable in the age range of the study patient population (11–98 yr). We caution against extrapolating our

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12. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R: Regression analysis as a tool for quantifying the impact of patient factors regarding the structure of our PACU and ASU staffing. Nursing assignment in the PACU and ASU is not according to surgical subspecialty. Rather, all nurses provide postoperative care for any surgical subspecialty patient. Therefore, the potential for an “incomplete assessment,” as proposed by Apfel et al., does not exist. The claim that we have suggested that the low incidence of PONV was “most likely explained by” under-reporting by PACU and ASU nurses is incorrect. Although under-reporting because of high work load may be a limitation of the study, the high number of D+C procedures and ophthalmology surgery performed at our hospital, both with low incidences of PONV, may be the most likely explanation for the low incidence of PONV.

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Apfel et al. recommended the inclusion of an interaction term between duration and type of anesthesia into the model, suggesting that duration is important for general but not regional anesthesia. During the data analysis, this interaction term was not found to be statistically significant (P = 0.45, although we had sufficient sample size to detect a
model to an age group, which is outside of the age range of our study population (e.g., to very young patients, where, in fact, the predicted risk can be exaggerated using our model). However, the scope of our current investigation did not include pediatric cases. The increase in the incidence of PONV among pediatric patients and the decrease in the incidence of PONV with increasing adult age means that the association is not linear if we combine pediatric and adult patients. It does not mean that a bimodal distribution exists between PONV and age, in which there should be two peaks in the distribution. There is one peak (i.e., one mode) in late childhood, with a lower incidence of PONV in early childhood and adulthood.

We have developed and validated a mathematical model to calculate the risk of PONV among ambulatory surgical patients. We believe that this model will predict patients’ risk of PONV and promote efforts to reduce the incidence of PONV.

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**Perturbation of Lipid and Protein Structure by General Anesthetics:**  
**How Little Is Too Little?**

*To the Editor:*—Lipid-based theories of general anesthetic action have long endured because numerous studies have shown that the *in vivo* pharmacology of an anesthetic correlates remarkably well with its ability to perturb the structural properties of simple lipid bilayers. The Meyer-Overton correlation between anesthetic potency and hydrophobicity, the inactivity of nonanesthetic long chain alcohols and highly halogenated volatile compounds (nonimmobilizers), and pressure reversal have all been demonstrated in studies using protein-free lipid bilayers. Nevertheless, a most persuasive and often mentioned argument against lipid-based theories is that at clinically relevant concentrations, anesthetics induce only small perturbations in lipid bilayer structure. For example, halothane reduces the transition temperature between a lipid bilayer’s liquid and gel phases by only 0.5°C at anesthetic concentrations and by only 5°C even at 10 times the minimum alveolar concentration (MAC). An equivalent reduction in order parameter may be obtained by raising the temperature of the bilayer by less than 1°C. Similarly, halothane reduces the transition temperature between a lipid bilayer’s liquid and gel phases by only 0.5°C at anesthetic concentrations and by only 5°C even at 10 times the minimum alveolar concentration (MAC). I was, therefore, very interested to read the study by Johannson et al. quantifying the effects of isoflurane and halothane on structural properties of bovine serum albumin, a lipid-free protein model used in mechanistic studies of anesthetic action. What did their studies show? At approximately 1 MAC, isoflurane and halothane increased the fluorescence anisotropy of bovine serum albumin by 1%. An equivalent reduction was obtained by raising the temperature of bovine serum albumin by approximately 1°C. Similarly, isoflurane and halothane raised the transition temperature between the folded and unfolded states of bovine serum albumin by less than 1°C at anesthetic concentrations and by only 3–4°C even at 10 times MAC. Studies of anesthetic binding to other protein models have been similarly unable to demonstrate significant anesthetic-induced changes in protein structure. Thus, anesthetics induce similarly small changes in the structural properties of lipids and proteins. For consistency, shouldn’t we now conclude that such insensitivity argues strongly against a protein site of anesthetic action?

The inability to detect significant anesthetic-induced structural changes in either lipid or protein model systems highlights the practical (and obvious) limitations of such studies: we can only measure what we can measure. Fluorescence anisotropy, denaturation temperature, phase transition temperature, and order parameter have been used by biophysicists for many years as indicators of lipid bilayer and protein structure in large part because they are easily quantitated. There is no compelling theoretical reason to believe that changes in these properties directly accounts for the functional effects of anesthetics on relevant targets in the central nervous system. In fact, it seems quite likely that the anesthetic state results from changes in other lipid and/or protein physical properties that are not so easily measured.

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