Unfortunately, the methods chosen by the authors do not allow us to determine whether the critical factor in hypoxic apnea is the level of sympathetic tone or simply the absolute blood pressure. It would be interesting to see whether hypoxic apnea occurs in rabbits in which hypotension is induced by a nonsympatholytic mechanism (hypovolemia, sodium nitroprusside) as well as mechanisms involving blockade of the sympathetic system (trimethaphan, epidural anesthesia). Similarly, it would be interesting to see whether hypoxic apnea could be avoided in rabbits undergoing epidural anesthesia using nonsympathomimetic interventions (volume loading, vagolytics) rather than administration of adrenergic agonists. Although it is certainly possible that the critical factor is oxygen delivery to the brain, as mediated by arterial oxygen content and arterial blood pressure, the authors'[1] methods do not rule out the possibility of specific, sympathetic modulation of respiratory drive mediated through the thoracic sympathetic system.

The authors[1] are to be commended for shedding light on the issue of unexpected cardiorespiratory arrest in patients undergoing spinal or epidural anesthesia. At the same time, their work raises provocative questions about apnea in infants and control of respiratory drive.

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In Reply:—We have no data regarding the age dependence of the ventilatory response to hypoxia during epidural anesthesia. The rabbits (approximately 2 kg) we studied are not mature, heightening the relevance of Dr. Gunter's comparison to human infants. Although we did not typically see the hyperventilatory phase before arrest as described by Dr. Gunter, that mirrors the pattern of neural activity identified in the central nervous system.[1,2] Regarding the mechanism of apnea, we noted a similar response to hypoxia in the absence of sympathetic blockade in animals with hypotension caused by problems with surgical preparation, such as excessive blood loss. This suggests that circulatory compromise, not sympathetic block *per se*, is the critical component that sets the stage for hypoxic arrest. Findings from our study[3] that support (but do not prove) the key role of circulatory compromise include the lack of a change in ventilation after sympathetic block alone and the effectiveness of hemodynamic resuscitation in preventing arrest.

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Predicting Long-term Postoperative Cardiovascular Outcomes

To the Editor:—Referring to the article of Badner *et al.*,[1] Dr. Mangano[2] encourages assessment of the value of perioperative observations and interventions for predicting quality of life, event-free survival, and cost. Badner *et al.*[1] furthers this goal by relating postoperative signs and symptoms to longer-term risk of myocardial infarction (MI) and associated mortality. This valuable data set could provide even further insight into the risk profile for MI and MI-related mortality among surgical patients by a more complete analysis of the available information.

Badner *et al.*[1] confirm that postoperative heart rate is strongly associated with postoperative MI (PMI). For reasons that are not clear, however, lower opioid use was more strongly associated with PMI than was blood pressure, history of angina and MI, and previous bypass surgery. Only height, weight, age, and nitrate use were predictive among the other patient characteristics that were investigated.

The use of multivariable statistical models could be helpful in further developing and interpreting risk profiles. For example, only heart rate measured on days 1 and 2 after surgery were associated with PMI. This does not imply, however, that elevated heart rate before or after these days is unimportant. If preoperative heart rates are also available, we could develop models that would evaluate the combined effects of heart rate before surgery and change in heart rate during time after surgery and of the absolute postoperative heart rate. In this way, we could determine the features of the time course of heart rate that most contribute to risk—an analysis that might be of interest in itself, but also useful for suggesting therapeutics to reduce risk (see Mangano *et al.*)[3]

If the data set and number of endpoints were larger, the development of risk profiles could make use of multivariable regression models to evaluate simultaneously the relative contributions of demographics, clinical characteristics, and medical history to risk of MI, death, or both (see Marshall *et al.*[4]). But, even in a smaller data set, we could evaluate the combined effect of a few characteristics in this way. Such analysis might start by investigating the relationships among the predictors of PMI and death, by determining whether patients with higher heart rates received less opioid. Then, multivariate models could help in identifying which characteristics independently predict adverse outcomes. For example, if higher heart rate is associated with less opioid use, then predictive models that include both variables would help to determine whether the opioid use reduced death because of its effect on heart rate or independently of that effect.

Such models could also help in the development of a definition or definitions for MI that best predict future cardiac disease outcomes. Although the authors found no difference in cardiac outcome in the four definitions of MI presented, more sophisticated statistical methods might help to further define MI according to the prediction of subsequent events. Such definitions might help in risk stratification. Such analyses must be based on all surgical information, not just MI-related deaths, because deaths from competing risks may result in biased analyses unless properly incorporated into statistical models. The reason is that deaths from causes indirectly related to MI eliminate the risk of MI for the patient.

Development and validation of risk profiles for MI and other adverse surgical outcomes may necessitate larger databases for adequate precision. The valuable data set of Badner *et al.*[1] might be combined with other sources of information to ensure adequate power for these investigations.

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In Reply:—We thank Drs. Litwack and De Grutolla for their interest in our manuscript investigating postoperative myocardial infarction (PMI) after noncardiac surgery. As indicated, they would have preferred the use of multivariable statistical models in our data analysis. To answer their questions regarding change in heart rate and opioid use and the relative contributions of demographics, we performed a stepwise logistic regression using the variables listed in tables 2 and 3 of our original manuscript and postoperative change in heart rate. The main results are shown in the table. One can see that age and nitrate usage again were significantly linked with PMI. Change in heart rate on postoperative day 4 was determined to be a risk factor for PMI. Interestingly, hypotension in the postanesthetic care unit was the most significant risk factor for PMI. The decreased narcotic requirements in PMI patients again were not a significant risk factor. As indicated in our manuscript, we cannot determine whether the heart rate changes were the cause or the result of the PMI because of our lack of continuous heart rate recording. Similarly, postanesthetic care unit hypotension may have been an early clinical sign of the developing PMI and not a causative event because our enzyme assays were not performed before postanesthetic care unit arrival.

We cannot answer their question regarding the definition of MI and subsequent events because we did not, nor do we, have the ability to determine the occurrence of all non-MI deaths that occurred. Lastly, we would be happy to share our database, as suggested, to enable the development and validation of risk profiles for MI and other surgical outcomes with appropriate investigators.