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Perioperative Myocardial Reinfarction: A Glimmer of Hope—A Note of Caution

A HISTORY of myocardial infarction increases 30–300-fold a patient's chance of sustaining a future perioperative myocardial infarction.[1–3] This risk is greatest shortly after the infarction and decreases with time. Reports during the previous two decades have shown little change in this rate. In this issue, Rao, Jacobs, and El Etr[4] report a series of 733 such patients managed between 1977 and 1982 in whom only 1.9% had recurrent perioperative myocardial infarction develop. This appears to represent a substantial reduction from the 7.7% experienced at their hospital between 1973 and 1976. Although the authors explicitly do not attribute this reduction to any specific factor, they imply that this benefit is due to more aggressive and prolonged monitoring, leading to early recognition and prompt treatment of hemodynamic aberrations.

Several important issues are raised by this report. First, is the reported reduction real or an artifact resulting from differences in patient selection and/or methods? Second, if it is real, does this study identify in a trustworthy way the chief contributing factors? Third, if not, how can these factors be so identified?

If the patients in the two groups reported by Rao *et al.* are comparable, the investigators have demonstrated a real and important reduction in reinfarction and mortality. For 20 years, an incidence of reinfarction of 6–8% has been the accepted standard. Although it would be easy to ascribe perioperative reinfarction rates greater than those achieved by Rao *et al.* to a "sicker" patient population, such a glib dismissal of these data is unwarranted. Perhaps it is time to reset our sights. However, the following reservations regarding the methods and statistical analyses employed argue for caution in accepting all the conclusions drawn by Rao *et al.* First, studies using historic controls (Group I in Rao *et al.*) are prone to bias.[5–7] Study groups that appear comparable on "measured" variables or risk factors, in fact, may not be so because of differences in unmeasured or unidentified variables. For instance, in this study, the reduction in reinfarction conceivably could be due to differences in unidentified risk factors such as changes in presurgical drug regimens or a host of unrecognized, uncontrollable factors. The importance of this issue is evidenced by the many examples in the medical literature of apparent differences in outcome due to different treatments in unrandomized studies, which have proven spurious when studied by prospective randomized trials. Only truly randomized studies can ensure that systematic but undetected bias has not occurred.

Second, the identification of factors responsible for the reduction in mortality by statistical testing of multiple subgroups is unreliable. As emphasized by a recent editorial in ANESTHESIOLOGY, such multiple comparisons are unduly likely to lead to apparent statistical significance purely by chance.[8] Thus, for instance, in table 2 of Rao *et al.*, the single subgroup comparison that attains a nominal P value of less than 0.05 perhaps should be considered as having a far greater than 5% probability of having arisen purely by chance. The stratified data analyses of tables 1, 2, 4, 5, and 7 in the article by Rao *et al.* do, however, demonstrate a favorable trend in most instances. The probability of observing an effect in such a great proportion of the analyses, purely by chance, is exceedingly small. Though this lends credence to the authors' claims of an overall reduction, the subgroup analyses nevertheless should be interpreted with extreme caution.[9] Third, comparisons suggested by inspection of data are not true tests of hypotheses. In this article, about 350 retrospectively identified hypotheses could have been tested. If this were so, one or two dozen such comparisons might be expected to achieve a 5% level of significance by chance alone. These potential problems are particularly apparent in tables 4 and 7, because the groups appear

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to have been based on hypotheses derived from inspection of the data. Although the *data collection* in Group 2 was prospective, the choice of which of the multitude of possible comparisons should be emphasized chiefly was not fully planned in advance. Differences in subgroups identified retrospectively generally should be viewed as hypotheses requiring testing in future studies, rather than as proven conclusions.

Despite these caveats, this report contains several noteworthy findings that should be investigated further. Virtually all the reinfarctions in Groups 1 and 2 occurred in patients with intraoperative "hemodynamic aberrations." This suggests that prevention of these changes is beneficial. The astoundingly low incidence of 7% in Group 2 is considerably less than the 55% incidence in Group 1. When Group 2 patients did have these problems develop (presumably despite aggressive treatment), they appeared more likely than Group 1 patients to sustain a recurrent myocardial infarction. This further strengthens the possibility of a causal link between intraoperative hemodynamic aberration and reinfarction. This hypothesis needs to be tested prospectively in humans.

Another important observation in this study is that the major reduction in mortality is dependent upon the prevention of reinfarction rather than a decreased mortality following reinfarction. This further emphasizes the importance of identification and subsequent modification of factors predisposing to reinfarction.

Lastly, although the investigators claim to have demonstrated that the duration of monitoring and intensive care alters outcome, this claim is not substantiated by their data, despite a P value of less than 0.05. The authors decided to extend the period of ICU monitoring from 24 to 96 h in selected patients because of the occurrence of five late infarctions after cessation of monitoring in their first 210 patients. It is not correct then to use Standard Statistical P value calculations to compare these 210 patients (who, *because* of their unfortunate experience, became "historic controls") with subsequent patients. Methodologically, the moral is that the investigators should have begun a randomized prospective study before they had convinced themselves that they were saving lives by extending the period of intensive care. This is not merely an arcane, academic issue. Provision of the recommended degree of intensive care to all such patients would have major implications for the entire health care system. If it is, in fact, of no material benefit, then its widespread use not only will waste money, but also may divert attention from other, possibly more effective, interventions. Conversely, if it is of substantial benefit, then it should be used widely and the lack of clearly trustworthy evidence for it may delay this happening.

Intuitively it appears logical that prolongation of monitoring and prompt recognition and therapy of hemodynamic abnormalities throughout the perioperative period in which the patient is at greatest risk should decrease the incidence of reinfarction. At present, the data of Rao *et al.* provide only a hypothesis that this is so. We submit that the data are not sufficiently compelling to recommend prolonged monitoring and ICU care for all such patients. It is highly desirable that such a study be performed to test this hypothesis before extended postoperative intensive care becomes the accepted standard.

EDWARD LOWENSTEIN, M.D.
SALIM YUSUF, M.D.
RICHARD S. TEPLICK, M.D.

Department of Anesthesia
Massachusetts General Hospital
Harvard Medical School, Boston, and International Study of Infarct Survival
Oxford, England

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