

EDITORIAL VIEWS

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Adverse Outcomes after Surgery in the Year 2001—A Continuing Odyssey

IN the first year of the new millennium, worldwide mortality will exceed 50 million, with cardiovascular disease continuing as the leading cause for death in developed and in nondeveloped countries.¹ In that same year, 100 million patients will undergo surgery throughout the world, with one third being more than 65 yr of age or having two or more cardiovascular risk factors.² Approximately 10%, or three million, of these at-risk patients will suffer a perioperative myocardial infarction—causing a 50% or greater reduction in their 2-yr survival rate, thereby increasing aggregate world health care costs by an additional 50 billion dollars.^{3,4} Although we have learned much about the problem of cardiovascular complications after surgery, a great deal remains unknown, and a number of controversies persist—not the least of which is the appropriate methodology for detection of this adverse and costly outcome. Thus, this issue of ANESTHESIOLOGY highlights the study of Badner* *et al.*, furthering our understanding of the complex interrelationships between surrogate measures of myocardial infarction in at-risk patients undergoing non-cardiac surgery.⁵

The Odyssey⁶

Our understanding of coronary artery pathophysiology and its relationship to myocardial cell injury developed over centuries. Our journey began in earnest with Chirac, who in 1698 first related total coronary ligation to survival in his classic treatise, *De*

Motu Cordis.⁷ During the next 200 yr, investigations continued, leading to pivotal works relating coronary ligation to intraventricular hemodynamic changes (Porter, 1895)⁸ and to clinical findings—principally myocardial infarction (Herrick in 1912).⁹ During the next 30 yr, investigators continued to explore coronary pathophysiology using similar models of complete coronary ligation.¹⁰ This was a dichotomous (all or none) approach to coronary-flow pathophysiology—when, in 1935, a new course had emerged, having profound implications. The findings by Tennant and Wiggers—that even brief periods of coronary occlusion were associated with reduction in active myofibril shortening and passive lengthening—led to an appreciation of the dynamic nature of coronary occlusion and established the important relationship between reversible ischemia and regional mechanical dysfunction.¹¹

At about the same time, Dack (1936)[†] suggested that hypotension during surgery might be caused not only by hemorrhage or anesthetic overdose, but also by myocardial infarction. Fifteen years later, Wroblewski (1951) was bold enough to suggest that intraoperative myocardial infarction was a problem of some concern!¹² However, not until the late 1960s was the problem addressed seriously, with investigators attempting to discern those preoperative conditions most likely associated with perioperative infarction.² Thereafter, progress accelerated. We expanded our focus to include the intraoperative period and, more recently, the critically important postoperative period—successfully characterizing electrocardiographic and echocardiographic markers of myocardial ischemia, including incidence, time-course, and potential etiologies.² In parallel, important concepts emerged from general cardiology investigations, such as: postischemic dysfunction (the stunned myocardium), persistent-but reversible-ischemic dysfunction (the hibernating myocardium), coronary endothelial dysfunction, and atherosclerotic plaque pathodynamics.¹⁰ We have come to appreciate perioperative excitotoxic and inflammatory phenomena, specifically as they may relate to the development of postoperative ischemia. Perhaps

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* Please note that the principal investigator of this study, Richard Knill, is recently deceased. In recognition, this Editorial View is dedicated to his family.

† Personal communication.

most importantly, we have been able to discern that a significant association exists between postoperative ischemia and in-hospital morbidity and long-term survival rates,^{3,13,14} thereby allowing design of therapeutic trials aimed at mitigating adverse outcome.¹⁵

The Problem

Given this wealth of information delineating the phenomenon of *reversible* ischemia after surgery, surely we also must have definitively determined the characteristics of perioperative ischemia's *irreversible* consequence—myocardial infarction. As we approach the year 2001, can there be any confusion, for example, regarding the incidence, timing, or sequelae of perioperative infarction? Unfortunately, our odyssey is destined to continue because a number of questions remain unanswered, including several fundamental questions regarding the definition of—and diagnostic criteria for—perioperative myocardial infarction! The following table, which summarizes the findings of a number of investigations, illustrates our conundrum.^{16,17}

These studies included tens-of-thousands of patients and used nearly every marker, or combination of markers, for assessment of myocardial infarction and quantification of its incidence. We have accumulated a great deal of data, but unfortunately, we are not able to infer a consistent pathophysiologic model for perioperative infarction. Perhaps the only consistency found among these “definitive” studies is that the methodology for detection of infarction was *consistently-inconsistent*, as documented by the large variability in reported outcome rates (table 1). Even adjusting for risk—using patient-specific, surgery-specific, or center-specific factors—does not resolve these disparities. Moreover, these disturbing outcome-rate inconsistencies also exist for studies performed within the same institution over similar time periods and even for studies performed over identical time periods using identical patient populations!‡

At the core of our problem is the observation that a clinician would be technically correct if he or she prospectively chose any of the following criteria for assessment of “myocardial infarction (MI):”

$MI = M_JI$, defined as—death of ≥ 1 myocardial cell; or

$= M_{cs}I$, defined as—death of \geq one batch of myocardial cells; or

$= M_qI$, defined as—a new ECG Q-wave; or

$= M_{cI}$, defined as—an increase in a myocardial enzyme; or

$= M_rI$, defined as—a decrease in regional/global function; or

$= M_{is}I$, defined as—a “deleterious” change in your favorite surrogate;

... et cetera.

Review of studies and surveys reveals that nearly all of these plausible criteria have been used, resulting in disparate estimates for the incidence of perioperative myocardial infarction, as characterized in figure 1.

Complicating this further, is the intrinsic illusory nature of myocardial damage precipitated by perisurgical events—for, as we can best guess, the large majority of such infarctions are believed to be asymptomatic, unaccompanied by a Q-wave, and not associated with ventricular failure.² Most likely, such injury reflects perioperative coronary atherosclerotic plaque transformation and rupture acutely precipitated by any one of a number of excitotoxic or

Table 1. Summary of Rates of Perioperative Complications*

Risk Factor	No. of Patients	Myocardial Infarction or Cardiac Death (%)	
		Range	Pooled Average
Unselected patients (age >40 yr)	6,237	2.0–3.7	2.5
Some selection criteria	2,654	2.7–5.8	4.6
Vascular patients	3,306	2.2–19.0	6.2
Patients undergoing preoperative thallium scintigraphy	1,586	5.2–19.0	8.6
Present study ⁵ (some selection criteria)	323	5.6	5.6

* Adapted from Mangano DT: Assessment of the patient with cardiac disease. *Curr Opin Cardiol* 10:530–542, 1995; and Mangano DT, Goldman L, McSPI Research Group: Preoperative assessment of the patient with known or suspected coronary disease. *N Engl J Med* 333:1750–1756, 1995.

‡ One example is the disparate nonfatal cardiac morbidity rates as reported in HCFA, *versus* State-regulatory agencies, *versus* medical society surveys.

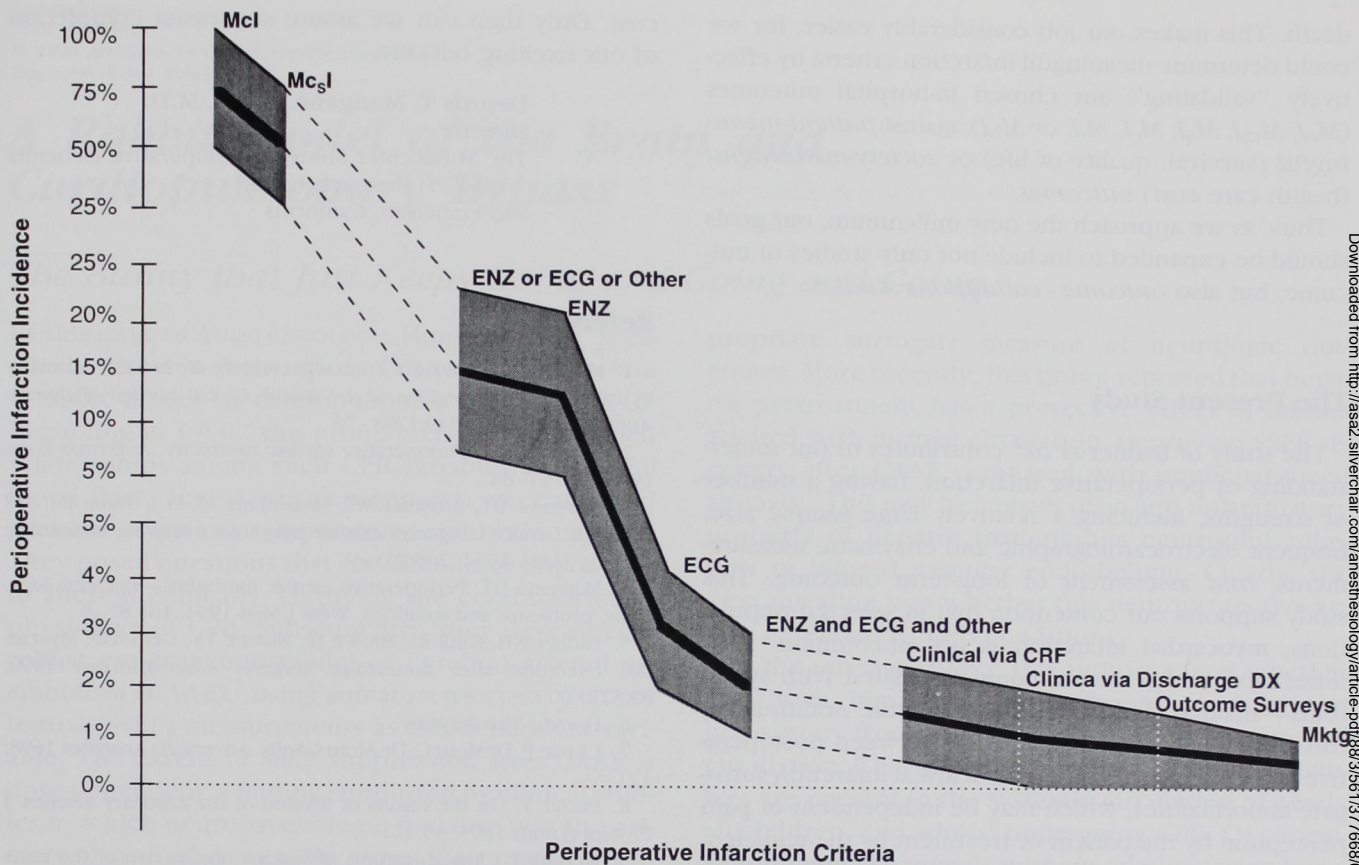


Fig. 1. Reported incidence of "myocardial infarction" for various criteria. MCI = single-cell infarction; McI = multiple-cell infarction; ENZ = positive cardiac enzymes; ECG = new Q wave; Other = clinical or radionuclear or echocardiographic evidence of infarction; CRF = diagnosis of myocardial infarction reported on a case report form; Discharge Dx = diagnosis of myocardial infarction reported on the discharge note; Outcome Survey = data reported by individual hospitals or groups of hospitals, governments, medical societies; Mktg = publicized rates of myocardial infarction (to the media).

inflammatory stimuli.² The resulting injury patterns are neither predictable nor readily measurable, lasting from days to months—further thwarting our efforts to definitively diagnose perioperative myocardial infarction. Consequently, we should expect that at the turn of the millennium, in the year 2001, our conclusions will be no less definitive than they are today—namely, that the incidence of perioperative myocardial infarction is exactly: "Somewhere between 0% and 30%"—"Or more."

Consequently, unless the problem of methodologic inconsistency is addressed, we will continue to debate the findings of outcome studies, surveys, therapeutic trials, and clinical assessments, including their economic implications—leading us to confusing, if not conflicting, judgments regarding care

assessment, paradigm development, therapeutic efficacy, and health care cost.

One Solution: Outcome-Validation Studies

Given this rather insurmountable problem, how do we decide whether a perioperative myocardial infarction has occurred? Which criterion(ia) is(are) most "accurate"—electrocardiographic, enzymatic, pathologic? Probably during our lifetimes, no one will discern the answers to these formidable questions. However, our real goal is its identification of perioperative adverse outcome because "outcome" is a harbinger (associative or causal) for subsequent events,^{3,14,18} which are universally considered to be important—such as premature

death. This makes our job considerably easier, for we could determine meaningful infarction criteria by effectively "validating" our chosen in-hospital outcomes (M_{CI} , M_{CSI} , M_{qI} , M_{eI} , M_{pI} , or M_{isI}) against *patient-meaningful* (survival, quality of life) or *society-meaningful* (health care cost) *outcomes*.

Thus, as we approach the new millennium, our goals should be expanded to include not only studies of outcome, but also *outcome-validation studies*.

The Present Study

The study of Badner *et al.*⁵ contributes to our understanding of perioperative infarction, having a number of strengths, including a relatively large sample size, frequent electrocardiographic and enzymatic measurements, and assessment of long-term outcome. This study supports our contention that in selected populations, myocardial infarction is not uncommon, is at times fatal, and is uncommonly associated with symptoms—making clinical detection difficult. Additionally, this study indicates an association between postoperative heart rate increases and myocardial infarction surrogate abnormalities, which may be independent of pain perception by the patient or treatment by the clinician. Importantly, the results indicate substantial disparity among estimates for perioperative infarction based on differing criteria, supporting the inferences suggested in figure 1. Finally, Badner *et al.*'s study makes a valid attempt to address the important question of outcome-validity.

Conclusions

We now accept that assessment of adverse perioperative outcome is critical for evolution of patient care, including effective development of practice paradigms, objective assessment of physician and center performance, comprehensive evaluation of new therapeutics, and realistic accounting of health care costs. However, we also now appreciate the difficulties in accurately and reproducibly assessing perioperative outcomes. Therefore, our mandate is to once again redirect our efforts—expanding our focus to include the critical post-hospital discharge period—thereby allowing assessment of perioperative diagnostic and therapeutic paradigms *vis a vis* their longer-term implications for quality of life, event-free survival, and extended-care

cost. Only then can we assure successful completion of our exciting odyssey.

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