

## Further Observations on Perioperative Myocardial Ischemia

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In a prospective study<sup>1</sup> of 1,023 patients who underwent coronary artery bypass graft (CABG) operations, we demonstrated three perioperative characteristics that were associated with a significantly increased incidence of postoperative transmural myocardial infarction (PMI). These were: 1) new ST-segment depression between arrival in the operating room and onset of cardiopulmonary bypass; 2) the operating surgeon's estimate of the quality of distal coronary anastomosis; and 3) the duration of myocardial ischemia by aortic cross-clamping. In a subsequent identical prospective study<sup>2</sup> of 495 patients, we determined the effectiveness of cardioplegia with and without papaverine, a coronary dilator, in mitigating the contribution of global myocardial ischemia during aortic cross-clamping to the incidence of PMI. Although the study failed to show any benefit of papaverine cardioplegia on PMI incidence or postoperative cardiospecific creatinine phosphokinase (CPK-MB) spillage, analysis of the hemodynamic data incidentally collected and unreported provided an opportunity to confirm our previous observations in an additional 495 patients and to respond to questions raised concerning methods and data of our previous report.<sup>3</sup> These new data were analyzed specifically to confirm the high incidence of ischemia in the preinduction period and the high incidence of hemodynamically unrelated ischemia perioperatively.

## METHODS

*Study Design.* During an 8-month period, all patients scheduled for elective CABG by four participating surgeons were eligible for study. All data relating to preoperative characteristics and perioperative events were recorded by trained observers who did not participate in any aspect of patient care. Data relating to the perioperative experience of 495 patients were recorded, representing approximately 80% of eligible patients during

the study period. Patient selection, anesthetic and surgical management, and data acquisition and analysis were described in detail previously<sup>1,2</sup> and were identical in the two studies with two exceptions. One-half of the patients in this study were given papaverine 60 mg added to our existing cold cardioplegia regimen. This variable had no relevance to hemodynamic measurements made before onset of bypass and had no effect on outcome in terms of PMI or mortality.<sup>2</sup> In this study, hemodynamically significant tachycardia was defined as greater than 89 beats/min in contrast to 99 beats/min in the earlier study. This new definition was a response to the generally lower heart rates observed during the preinduction period, probably the result of increased use of chronic beta-adrenergic-blocker therapy during the period between the two studies.

*Death and Reoperations.* Seven patients (1.4%) died in the hospital. Myocardial infarction was considered the cause of two deaths. Both had new myocardial ischemia appearing between arrival in the operating room and institution of cardiopulmonary bypass, prolonged ischemic time, less than optimal surgical ratings, and required inotropic and intraaortic balloon pump support to wean from bypass. Before death, the electrocardiogram of each was diagnostic of new transmural infarction and the 10-h CPK-MB level exceeded 80 U/l. Of the five other postoperative deaths, two resulted from severe central nervous system dysfunction as a consequence of operation, and one patient had a fatal cerebrovascular accident 3 days after operation. A fourth patient died of sepsis three weeks postoperatively. The fifth patient had a fatal myocardial infarction 7 days after operation during an otherwise uneventful postoperative course. For the purposes of this study the two patients with intraoperative PMI were included in the group with PMI, the other five were included in the group without PMI. Six additional patients required reexploration for bleeding within 24 h of operation, and five others, all with chronic obstructive pulmonary disease, required revision of the sternum before discharge. None of these reoperated patients suffered PMI or died.

*Data Analysis.* Data were placed in a National Advanced System<sup>®</sup> Computer (AS/9000N) with an IMB<sup>®</sup> 3033 Operating System. Relationships between perioperative variables and outcome were tested by either chi square or Fisher's Exact Test as appropriate. Continuous variables were examined by Student's *t* test. Statistical signifi-

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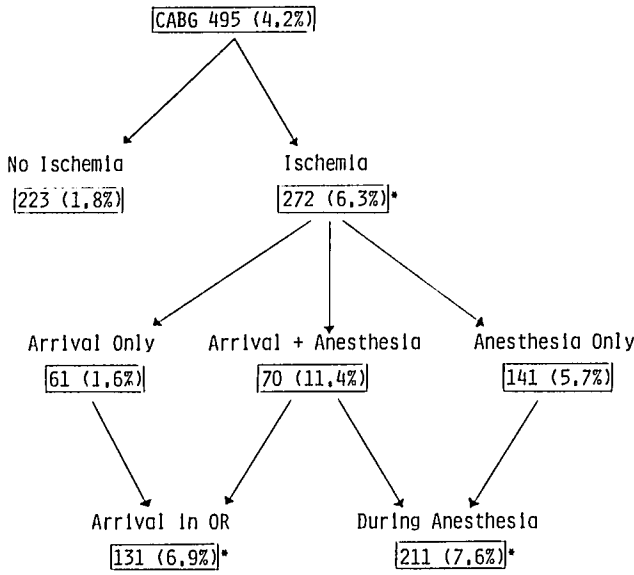


FIG. 1. Incidence of myocardial ischemia and PMI in 495 patients undergoing CABG. Numbers in boxes represent number of patients; numbers in parentheses represent per cent of subgroup who suffered PMI. \*  $P < 0.05$  vs. PMI rate for "no ischemia."

importance of the roles of increasing severity of ischemia and multiple risk factors on PMI incidence was tested by the Wilcoxon-Mann-Whitney test for graded responses.

RESULTS

The outcomes in these 495 patients were strikingly similar to those in the previous study of 1023 patients.<sup>1</sup> Mortality was identical (1.4%) with PMI, accounting for 29% of the deaths (vs. 36% in the earlier study). PMI occurred in 4.2% of patients (vs. 4.1%). New perioperative ischemia appeared in 55% of patients (vs. 37%) (fig. 1). PMI occurred in 6.3% of patients with new ischemia (vs. 6.9%) compared with 1.8% of patients without new ischemia (vs. 2.5%). The relationship between degree of ST-segment depression and rate of PMI was confirmed (table 1).

Aortic cross-clamping exceeded 40 min in 17% of patients (vs. 18%) and was associated with a three-fold increase in PMI. Less-than-optimal surgical ratings were

TABLE 1. Relationship Between Degree of ST-Segment Depression and Incidence of Postoperative Myocardial Infarction (PMI)

	Perioperative ST Segment Depression		
	None	0.10-0.19 mV	≥0.2 mV
Number of patients	223	224	48
PMI rate (%) <sup>*</sup>	1.8	5.4	10.4

\* Differences among degrees of ST-segment depression significant at  $P < 0.006$ .

TABLE 2. Relationship of Predisposing Perioperative Factors to Incidence of Postoperative Myocardial Infarction (PMI)

	Predisposing Factors Present <sup>*</sup>			
	None	One	Two	Three
Patients	150	239	84	22
PMI rate (%) <sup>†</sup>	1.3	3.8	7.1	18.2

\* The three predisposing perioperative factors were: 1) appearance of new ST-segment depression in Lead II or V5 before onset of cardiopulmonary bypass; 2) less-than-optimal rating by the surgeon as to the quality of distal anastomosis and vein graft; and 3) cross clamping of the aorta for more than 40 min.

† Differences in rates significant at  $P < 0.002$ .

given to 23% of patients (vs. 25%) and were associated with a two-fold increase in PMI. Both these observations confirm those of the earlier study, as well as the relationship of all three predisposing factors to PMI (table 2).

New myocardial ischemia was considered hemodynamically related when its appearance was associated with systolic arterial blood pressure  $\geq 180$  mmHg or  $\leq 90$  mmHg and/or heart rate  $\geq 90$  beats/min. Values outside these limits are also referred to as hemodynamic abnormalities. New ischemia was present on arrival to the operating room, determined by comparison with the preoperative ECG, in 26% of patients (vs. 18%). Of 131 patients with new ischemia on arrival, only 39% were hemodynamically related (vs. 34%). From induction of anesthesia to onset of cardiopulmonary bypass, 211 patients had new myocardial ischemia (43% vs. 28% in prior study). Of these, 30 patients (14%) had no hemodynamic abnormality during anesthesia (vs. 17%). The remaining 181 patients (86%) had at least one hemodynamic abnormality after induction of anesthesia (vs. 83%). The hemodynamic abnormality, however, did not occur within the 5 min preceding nor coincide with the appearance of ischemia in 52% of these episodes (vs. 51%). When ischemia was temporally related to a hemodynamic abnormality, tachycardia was twice as frequent as hypertension or hypotension.

To examine the possibility that ischemia would be more frequently related to hemodynamic abnormality if our definition of hemodynamic abnormality was less severe, we also analyzed heart rate and systolic arterial blood pressure changes by criteria referenced to usual rather than absolute values. For each patient, "resting in-hospital normal" blood pressure and heart rate were determined as the means of four to more than 20 measurements routinely recorded by floor nurses during preoperative hospitalization. Any change  $>20\%$  in systolic arterial pressure and  $>10$  beats/min in heart rate was now considered a hemodynamic abnormality.

By our original absolute criteria, 364 patients arrived in the operating room without any hemodynamic abnormality.

mality. Of these 80 (22%) demonstrated new myocardial ischemia. Deviations of arrival systolic arterial pressure and heart rate from their "resting in-hospital normal" permitted nine categories of hemodynamic change (table 3). The distribution of all patients (row A) and distribution of all new ischemia (row C) by category of hemodynamic change is strikingly similar, both within categories and by rows or columns. Heart rate increases >10 beats/min and systolic arterial blood pressure 20% less than criterion were in fact infrequent, and most patients tended toward bradycardia and hypertension on arrival in the operating room. Frequency of ischemia (row B) did not differ significantly among categories. No relationship between new ischemia on arrival and these lesser degrees of hemodynamic change could be identified.

The arterial blood pressure and heart rate data of 107 of 149 patients considered by the original definition to have hemodynamically unrelated myocardial ischemia after induction of anesthesia were also examined. Because ST-segment depression is considered a late manifestation of myocardial ischemia, hemodynamic changes 5 min before and at the onset of ST-segment depression were categorized in the same fashion (table 4). Data of 42 of 149 patients were excluded because ischemia appeared less than 5 min after induction of anesthesia or a hemodynamic abnormality without ischemia preceded the ischemic event by more than 5 min. In 79% of patients, heart rate remained within 10/min or more than 10 beats/min lower than their resting in-hospital heart rate at the onset of ischemia. Systolic arterial blood pressure remained within the 20% range in 72% of patients at the onset of ischemia. Tachycardia and hypotension were relatively infrequent. The data recorded 5 min before onset of ischemia were in the same pattern. Small increases in heart rate or changes in systolic arterial blood pressure did not correlate well with new intraoperative ischemia.

DISCUSSION

These data of an additional 495 patients confirm all the major conclusions of an earlier study of 1,023 patients regarding the relationship of perioperative new ST-segment depression to postoperative myocardial infarction. Prolonged global myocardial ischemia by aortic cross-clamping and the surgeon's estimate of the technical quality of his operation were also confirmed as significant determinants of PMI. We have no ready explanation for the higher overall rate of new ischemia in this group compared with the earlier one (55% vs. 37%).

These new data provided the opportunity to clarify an issue raised<sup>3</sup> concerning the definition of hemodynamically unrelated ischemia in our earlier report. Lowenstein<sup>3</sup> suggested that our requirement for hemodynamic abnormality was so severe that an inappropriately large pro-

TABLE 3. Relationship of New Myocardial Ischemia to Heart Rate and Systolic Arterial Blood Pressure of 364 Patients\* on Arrival to Operating Room Compared with Their Mean Resting In-hospital Values

Systolic Arterial Blood Pressure	Heart Rate		
	Increased ≥10/min	Within 10/min	Decreased ≥10/min
Increased > 20%			
(A) % of all patients	2	24	18
(B) % with ischemia	14	21	24
(C) % of all ischemia	1	22	20
Within 20%			
(A) % of all patients	2	31	20
(B) % with ischemia	14	26	18
(C) % of all ischemia	1	38	15
Decreased > 20%			
(A) % of all patients	0.3	2	1
(B) % with ischemia	0	14	25
(C) % of all ischemia	0	1	1

\* Patients with systolic arterial blood pressure ≥180 mmHg or ≤90 mmHg and/or heart rate ≥90/min were excluded from this tabulation.

portion of observed ischemic episodes was classified as hemodynamically unrelated. Our purpose in initially selecting those limits was to discover the association of clearly abnormal and clinically important hemodynamic events to the appearance of new ischemia. As a consequence, both our earlier and current data clearly define a relationship between clinically important tachycardia but not anesthetic-related hypertension and hypotension and the appearance of ST-segment depression. Our newer data allowed examination of the relationship between appearance of new ischemia and less severe hemodynamic changes as possibly reducing the frequency of ischemia not attributed to hemodynamically altered myocardial oxygen supply or demand.

TABLE 4. Relationship of Heart Rate and Systolic Arterial Blood Pressure to Mean Resting In-hospital Values in 107 Patients with New Myocardial Ischemia during Anesthesia Unrelated to a Hemodynamic Abnormality\*

Systolic Arterial Pressure	Heart Rate		
	Increased ≥10/min	Within 10/min	Decreased ≥10/min
At onset of ischemia (% of patients)			
Increased >20%	8	8	3
Within 20%	12	33	27
Decreased >20%	1	3	5
5 min before ischemia (% of patients)			
Increased >20%	7	6	16
Within 20%	7	26	23
Decreased >20%	1	5	9

\* Patients with systolic arterial blood pressure ≥180 mmHg or ≤90 mmHg and/or heart rate ≥90/min were considered to have a hemodynamic abnormality.

Using lenient limits of hemodynamic abnormality, a 20% change in systolic arterial blood pressure and 10 beats/min change in heart rate, we could not identify a hemodynamic pattern for 80 episodes of new ischemia on arrival in the operating room. An increase in heart rate >10 beats/min above their resting rate occurred in only two of the 80 patients. Similarly, of 107 episodes of new myocardial ischemia during anesthesia, less than 20% were associated with a heart rate increase of more than 10 beats/min. Hypotension by our new criterion was rare. It seems highly unlikely that "small but relevant" increases in heart rate could account for this new ischemia we have designated as hemodynamically unrelated. We have, in fact, reaffirmed the observation that approximately one-half of the new ischemic episodes observed in the perioperative period before cardiopulmonary bypass are not preceded by nor associated with a marked change in arterial blood pressure or heart rate. This observation is in complete accord with a growing body of data documenting the high incidence of silent ischemia attributed to reduction in regional coronary perfusion without tachycardia or change in arterial blood pressure during normal daily activity of patients with coronary artery disease with or without stable angina.<sup>4-6</sup> In anesthetized patients, reduction of coronary perfusion in response to tracheal intubation in the absence of hemodynamic change was documented by thallium scan in 45% of 22 patients undergoing CABG.<sup>7</sup> This recent finding is remarkable in view of our earlier observation of hemodynamically unrelated ischemia in response to tracheal intubation in 43% of 47 patients.<sup>1</sup>

Clearly, as many as one-half of all episodes of perioperative ischemia may not be preventable by providing optimal hemodynamic indices of myocardial oxygen supply and demand. These unrelated episodes during anesthesia may be identical to those occurring in these same patients during their daily lives unassociated with angina or hemodynamic change and may be a manifestation of coronary artery disease completely unrelated to anesthesia and operation. In view of this observation, anesthesiologists should reappraise their role in the genesis of PMI, a complication that they have generously accepted as their own.<sup>8,9</sup> The relationship of silent ischemia during daily living to sudden death and to prognosis for infarction is just now under investigation.<sup>4,5</sup> While tachycardia with its adverse effects on both myocardial oxygen supply and demand clearly is predictably related to intraoperative ischemia, perhaps tachycardia during anesthesia and op-

eration may serve only as a stress test provoking potential ischemia, without any causal relationship to subsequent PMI. Similarly, new intraoperative ischemia both hemodynamically related and unrelated may only identify a subset of patients more likely to have PMI without any causal relationship between ischemic episodes and PMI. This hypothesis would equally well explain the significant relationship we observed between new perioperative ST-segment depression and PMI.

Much recent research effort in the anesthetic management of patients with coronary artery disease is directed toward improved methods for earlier diagnosis of intraoperative ischemia, particularly with wall motion studies. Our data and those of Kleinman *et al.*<sup>7</sup> indicate that only a portion of these ischemic episodes, however diagnosed, will be prevented by careful control of hemodynamics. Those not hemodynamically related are likely a manifestation of the disease process and carry the same risk of PMI as those hemodynamically related, a risk not reduced by earlier diagnosis. Efforts would seem better spent in exploring methods of preventing perioperative ischemic episodes of both types, however diagnosed, and learning if prevention reduces the incidence of PMI.

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