Anesthesiology 2001; 94:38–46

Electrocardiographic Exercise Stress Testing for Cardiac Risk Assessment in Patients Undergoing Noncardiac Surgery

Albrecht Gauss, M.D., Hans-Jörg Röhm, M.D.,† Andreas Schäuffelen, M.D.,* Thomas Vogel, M.D.,‡ Ulrich Mohl, M.D.,* Andreas Straehle, M.D.,‡ Rainer Meierhenrich, M.D.,† Michael Georgieff, M.D.,§ Gerald Steinbach, M.D.,‖ Wolfram Schütz, M.D.**

Background: **The value of exercise electrocardiography in the prediction of perioperative cardiac risk has yet to be defined. This study was performed to determine the predictive value of exercise electrocardiography as compared with clinical parameters and resting electrocardiography.**

Methods: **A total of 204 patients at intermediate risk for cardiac complications prospectively underwent exercise electrocardiography before noncardiac surgery. Of these, 185 were included in the final evaluation. All patients underwent follow-up evaluation postoperatively by Holter monitoring for 2 days, daily 12-lead electrocardiogram, and creatine kinase, creatine kinase MB, and troponin-T measurements for 5 days. Cardiac events were defined as cardiac death, myocardial infarction, minor myocardial cell injury, unstable angina pectoris, congestive heart failure, and ventricular tachyarrhythmia. Potential risk factors for an adverse event were identified by univariate and multivariate logistic regression analysis.**

Results: **Perioperative cardiac events were observed in 16 patients. There were 6 cases of myocardial infarction and 10 cases of myocardial cell injury. The multivariate correlates of adverse cardiac events were definite coronary artery disease (odds ratio, 8.8; 95% confidence interval [CI], 1.1–73.1; P = 0.04), major surgery (odds ratio, 4.7; 95% CI, 1.3–16.3; P = 0.02), reduced left ventricular performance (odds ratio, 2.0; 95% CI, 1.1–3.8; P = 0.03), and ST-segment depression of 0.1 mV or more in the exercise electrocardiogram (odds ratio, 5.2; 95% CI, 1.5–18.5; P = 0.01). A combination of clinical variables and exercise electrocardiography improved preoperative risk stratification.**

Conclusions: **This prospective study shows that a ST-segment depression of 0.1 mV or more in the exercise electrocardiogram is an independent predictor of perioperative cardiac complications.**

CARDIAC events are a major cause of perioperative morbidity and mortality in patients undergoing noncardiac surgery.[1,2] The assessment of preoperative cardiac risk of patients at risk for or with known coronary artery disease is therefore a substantial challenge.[3,4] In addition to history and physical examination, specialized preoperative tests have been recommended for risk assessment, especially for patients with intermediate clinical risk factors, poor or unknown functional capacity, and higher risk surgery.[3–7] Although exercise electrocardiography testing has been recommended as a useful method for risk stratification,[3,5,6] other investigators have advised against it and instead favored more complicated methods such as dipyridamol-thallium imaging and stress echocardiography.[7] It has also been shown that an abnormal preoperative resting electrocardiogram has a significant predictive value.[8,9] It is still unknown whether the predictive value of exercise electrocardiography is superior to that of resting electrocardiography, and there is still no consensus as to which patients should receive which test.[6] One reason for this uncertainty is that it is difficult to assess the role of exercise electrocardiography. Only a few large prospective studies are available, providing conflicting results, and these data are predominantly from studies obtained in the 1980s.[8,10,11] To date, no prospective study has shown that exercise-induced ST-segment displacement is a statistically significant independent predictor of perioperative cardiac events. The present prospective study was therefore performed to investigate the predictive value of exercise electrocardiography compared with clinical parameters and resting electrocardiography in a group of intermediate-risk patients. Perioperative troponin-T measurements were also used to detect myocardial injury.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

* Staff Anesthesiologist, † Resident in Anesthesiology, ‡ Research Assistant, § Professor of Anesthesiology and Chairman, Department of Anesthesiology, ‖ Staff Physician, Department of Clinical Chemistry.

Received from the Department of Anesthesiology, University of Ulm, Ulm, Germany. Submitted for publication November 16, 1999. Accepted for publication July 19, 2000. Support was provided solely from institutional and/or departmental sources. Presented in part at the 45th Deutscher Anästhesiekongress, Frankfurt, Germany, June 30 – July 4, 1998.

Address reprint requests to Dr. Gauss: Department of Anesthesiology, University of Ulm, Steinhoevelstr. 9, D-89075 Ulm, Germany. Address electronic mail to: albrecht.gauss@medizin.uni-ulm.de. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

Materials and Methods

Patients

Over a 2-yr period, 204 consecutive patients with or at high risk for coronary artery disease who underwent elective noncardiac surgery requiring general anesthesia were enrolled prospectively in the study. Written informed consent was obtained, and the study protocol was approved by the Ethics Committee of the University of Ulm. Detailed criteria for entry into the study included at least one of the following: definite coronary artery disease as indicated by previous myocardial infarction, typical angina pectoris[12] or angiographically assessed significant stenosis of coronary arteries, or high risk for coronary artery disease suggested by previous or current vascular surgery, or the presence of at least three of the following cardiac risk factors: hypertension, smoking, dyslipidemia (serum cholesterol > 6.7 mM/l), or diabetes mellitus.

We defined a previous myocardial infarction as either a positive history, electrocardiographic evidence of a previous myocardial infarction, or arteriographic evidence of coronary occlusion or narrowing and corresponding ventricular asynergy or wall motion abnormalities not caused by ischemia alone.[12] Patients with left bundle-branch block or cardiac pacemakers and patients who could not perform bicycle ergometry were not eligible. A total of 19 patients were excluded from the study after performance of the exercise electrocardiography: eight because of subsequent withdrawal of consent before surgery, three because of planned surgery was canceled, and eight because of limited resources of ambulatory electrocardiographic recordings. Six of these 19 excluded patients had an abnormal electrocardiography exercise test result. The subsequent outcome of the excluded patients could not be evaluated because further investigation and data collection regarding cardiac events were not performed. The final evaluation was thus based on 185 patients.

Preoperative Resting Electrocardiogram and Exercise Stress Testing

Exercise stress testing was performed a median of 1 day before surgery without discontinuing cardioactive medication. A 12-lead resting electrocardiogram was recorded before exercise. The resting electrocardiogram was classified as abnormal if abnormal Q waves were present (≥ 0.04-s duration, ≥ 25% R wave) or if ST-segment depressions of 0.1 mV or more (60 ms after the J point) were present at rest. Exercise stress testing was performed on a supine bicycle ergometer (EL 900 B, Madaus Schwarzer, Munich, Germany).

The examination was begun at 25 W and increased in 2-min steps of 25 W. A 12-lead electrocardiogram was recorded once a minute at 50 mm/s during exercise and during the recovery period until the electrocardiogram reverted to its pre-exercise morphology, but at least 5 min after exertion. Blood pressure measurements were performed during the pretest period before exercise, at the end of each workload, and every 2 min thereafter during the recovery period. Exercise stress testing was symptom-limited.[12] The exercise electrocardiography was classified as abnormal if new horizontal or downsloping ST-segment depressions of 0.1 mV or more (60 ms after the J point, unless that point fell within the T wave, in which case it was measured at a minimum of J + 40 ms) were seen in three consecutive beats without baseline variation.[12,13] If ST-segment depression was present at rest, an increase of the depression by 0.1 mV or more was classified as pathologic.[13] ST-segment elevations of 0.2 mV or more were regarded as pathologic except if they occurred in leads with signs of previous infarctions.[13] Each rest and exercise electrocardiogram was evaluated by two independent investigators who were blinded to patient identity and clinical course. If the interpretations of the two investigators did not agree, a third investigator performed an independent evaluation, with a majority of two concordant interpretations prevailing.

Holter Monitoring

Patients were monitored with a two-channel Holter electrocardiography recorder (LRE, Technology Partner GmbH, Munich, Germany), from the evening before the operation until the morning of the second postoperative day (total recording time, 55.5 ± 10 h). Two bipolar leads (modified V_4 and V_5) were used. The data were evaluated by computer with an evaluation software (CAPS-L, LRE Technology Partner GmbH). The baseline ST-segment level was defined at the start of the monitoring period as the average ST-segment during a stable period (usually 10 min). Prolonged episodes of ischemia were defined as reversible ST-segment changes lasting more than 30 min[14] and involving a shift from baseline of either 0.1 mV or more of horizontal or downsloping ST-segment depression (60 ms after the J point, unless that point fell within the T wave, in which case it was measured at a minimum of J + 40 ms), or 0.2 mV or more elevation (at the J point), separated from a preceding episode by at least 1 min. Every computer diagnosis of an ST-segment depression was visually confirmed to exclude false-positive ST depressions associated with artifacts or abnormal QRS complexes such as ventricular ectopic beats or conduction abnormalities. Furthermore, T-wave changes that were incorrectly detected as ST changes by the computer software were identified. Holter tapes were analyzed by two independent investigators who were blinded to patient identity and clinical and any other electrocardiographic data. The interpretation of the results was performed analogously to that of resting and exercise electrocardiograms.

Perioperative Management and Measurements

For each patient, the American Society of Anesthesiologists physical status classification,[15] the original cardiac risk index,[16] and the modified multifactorial index[17] was determined.

Two-dimensional surface echocardiography with color Doppler spectral analysis was performed by an experienced cardiologist before surgery. Echocardiographic assessment included visual determination of global left ventricular performance (graded as normal or mildly, moderately, or severely reduced) and observation of valvular and wall motion abnormalities. Regional left ventricular function was assessed from parasternal short-axis and long-axis views and apical two- and four-chamber views. Motion was graded as normal, hypokinetic, akinetic, or dyskinetic. Preoperative use of any medica-

Table 1. Demographic and Clinical Data for the 185 Patients and Numbers with Cardiac Event and Variable

	No. of Subjects	Percent	No. with Event and Variable
Age (yr)*	67 (38–90)		
Age > 70 yr	66	36	8
Gender (M/F)	147/38	79/21	12/4
Definite coronary artery disease	90	49	15
Typical angina	52	28	7
Previous myocardial infarction	57	31	11
Previous coronary artery graft or angioplasty	25	14	2
Coronary risk factors			
Hypertension	117	63	9
Diabetes mellitus	35	19	1
Smoking	77	42	6
Dyslipidemia	79	43	8
ASA physical status: ASA II/III/IV[15]	10/167/8	5/90/4	0/13/3
Functional capacity: NYHA I/II/III/IV[12]	56/124/5/0	30/67/3/0	4/11/1/0
Reduced left ventricular performance[12]	28	15	7
Cardiac risk index[16]			
Class I (0–5 points)	129	70	7
Class II (6–12 points)	49	26	8
Class III (13–25 points)	7	4	1
Modified multifactorial risk index[17]			
0–5 points	135	73	7
10 points	37	20	8
>10 points	13	7	1
Preoperative medication			
Nitrates	58	31	9
β-adrenergic blockers	56	30	7
Calcium channel blockers	64	35	5
Angiotensin-converting enzyme inhibitors	67	36	4
Digitalis	27	15	3
Diuretics	43	23	3
Type of surgery			
Major vascular	43	23	6
Minor vascular	106	57	4
Major abdominal	26	14	5
Minor abdominal	10	5	1

* Median values (range in parentheses).

ASA = American Society of Anesthesiologists; NYHA = New York Heart Association.

tion and serum levels of creatinine and potassium were also analyzed (table 1).

Surgery was classified as major vascular (aortic repair, aortoiliac or iliac endarterectomy), minor vascular (carotid endarterectomy, peripheral vascular), major intraabdominal (gastric, liver, pancreatic, small bowel, colonic, or rectal) or minor abdominal (cholecystectomy, laparotomy, herniotomy).

Balanced anesthesia was used with induction of anesthesia by 0.3 mg/kg etomidate combined with 0.003–0.01 μg/kg fentanyl. Intubation was performed after application of succinylcholine (1.5 mg/kg) or vecuronium bromide (0.1 mg/kg). Bolus injections of fentanyl (0.1–0.2 mg), nitrous oxide, and volatile anesthetics (enflurane or isoflurane) were used for maintenance of narcosis. Postoperative pain control was managed with nonopioid and opioid analgesics, without the use of regional anesthesia.

A history and a physical examination were performed by one of the authors every day from the first to the fifth postoperative day and on the day of discharge. Approximately 30 days after the operation, a telephone interview was performed to obtain the cardiac history. A 12-lead electrocardiogram was obtained on the day before surgery, just before induction of anesthesia, after surgery, daily for the first 5 days after surgery, and on the day of discharge.

Twelve-lead electrocardiograms were analyzed by two independent investigators who were blinded to patient identity, clinical data, Holter electrocardiography, as well as creatine kinase and troponin-T data. The interpretation of results was performed analogously to the evaluation of the resting and exercise electrocardiograms.

Serum creatine kinase, creatine kinase isoenzyme MB, cardiac troponin-T, and creatinine levels were measured before surgery and daily for the first 5 days after surgery. For the troponin-T measurement, serum was frozen at −18°C and analyzed some weeks later. Troponin-T (reference range, 0–0.1 ng/ml) was measured by an enzyme-linked immunosorbent assay (ELISA Troponin-T, Boehringer Mannheim, Germany). Because the cause of elevated troponin-T in patients with chronic renal failure is not clarified[18,19] and the ability of troponin-T to predict cardiac risk is reduced in the presence of renal insufficiency,[20] troponin-T concentration more than 0.1 ng/ml was only classified as positive if renal insufficiency was excluded.

The physicians caring for the patients had access to the preoperative resting and exercise electrocardiogram and were aware of the clinical findings and any preoperative cardiac evaluation. They had no access to the final evaluation of the preoperative resting and exercise electrocardiogram, the results of Holter electrocardiography, and troponin-T measurements.

Analysis of Outcome

The major analyzed outcome variables were cardiac mortality and cardiac morbidity during the first 30 postoperative days. Adverse events noted by the study physicians during research visits and the abnormal findings of the 12-lead electrocardiograms, Holter electrocardiograms, and the creatine kinase and troponin-T analysis were validated separately by two investigators. These investigators were blinded to the patients' preoperative clinical and electrocardiography data; disagreements were resolved by a third investigator.

Cardiac death was diagnosed if the patient died from a myocardial infarction, dysrhythmia, or congestive heart failure caused primarily by a cardiac condition. Perioperative cardiac morbidity was defined as the appearance of perioperative myocardial infarction or myocardial injury, unstable angina pectoris,[12] congestive heart failure, or ventricular tachyarrhythmia.

The diagnosis of perioperative myocardial infarction required one of the following criteria:

- new large Q waves ($\geq$ 0.04-s duration, $\geq$ 25% R wave), even in the absence of symptoms or abnormalities in serum enzymes or troponin-T levels (Q-wave infarction)[12]
- compatible history and characteristic enzyme or troponin-T changes without electrocardiography abnormalities, provided that new wall motion abnormalities are identified on echocardiography (non–Q-wave infarction)[12]
- S-T–segment and/or T-wave changes in two consecutive 12-lead electrocardiograms or an episode of new 0.1-mV or more horizontal or downsloping ST segment depression in the Holter electrocardiography more than 30 min in duration without abnormal Q waves, each of them coupled with specific enzyme or troponin-T alterations (creatine kinase MB $>$ 20 U/l and $>$ 6% of the creatine kinase or troponin-T $>$ 0.1 ng/ml on at least 2 successive days). All T-wave changes in the 12-lead electrocardiogram had to be localized and not widespread (non–Q-wave infarction).

Minor perioperative myocardial cell injury was defined as troponin-T elevation more than 0.1 ng/ml on at least 2 successive days in the absence of symptoms or electrocardiography abnormalities.

Congestive heart failure was defined as the need for sympathomimetic support associated with hemodynamic and pulmonary findings consistent with the diagnosis or at least the need for diuretics because of signs or symptoms of pulmonary congestion. Ventricular tachyarrhythmia was defined as a documented ventricular tachycardia or fibrillation with hemodynamic compromise.

Statistical Analysis

Sample size calculation was based on the estimated event rate of meaningful cardiac events of approximately 10% for the selected study population.[21,22] The sample size was chosen in a way that the limits of the 95% confidence interval for this rate were in a range of $\pm$ 5% around the 10% mark. For a sample size of 200 subjects, the 95% confidence interval will be 6.22–15. Another reason for choosing the sample size of approximately 200 subjects was the fact that in the planned study duration of 2 yr this size would be manageable because of our clinical experience.

Potential risk factors for an adverse event were identified by univariate and multivariate logistic regression analysis. To avoid overadjustment by using too many variables in the multivariate model, all variables were subjected to univariate analysis in a first step. Variables with a P value less than 0.1 in the likelihood ratio test were considered as potential risk factors in the multivariate model. To avoid multicollinearity, only one variable in a set of variables with a correlation coefficient greater than 0.7 was used for to the multivariate analysis. Multivariate analysis was performed by multiple logistic regression, including backward selection. Stopping criterion was a P value of 10%. Odds ratios and their 95% confidence intervals were calculated from the model. Sensitivity, specificity, and predictive values were calculated by contingency table analysis. All analysis was performed using SAS software 6.12 (SAS Institute, Cary, NC).

Results

Characteristics of the Patients and Preoperative Electrocardiographic Data

Demographic and clinical data for the 185 patients and the numbers with cardiac event and variable are shown in table 1. Forty-nine percent of the patients presented with definite coronary artery disease. Vascular surgery was performed in more than 80% of the patients (23% aortic or iliac operations, 45% carotid endarterectomy). Eighty-three percent displayed at least one of Eagle's clinical markers.[6] All 185 patients had at least an intermediate risk according to the American College of Cardiology–American Heart Association guidelines for preoperative clinical risk assessment.[5] With respect to the original cardiac risk index,[16] approximately 70% of our patients were classified as class I. The preoperative rest-

Table 2. Preoperative Electrocardiographic Data

	No. of Subjects	Percent	No. with Event and Variable
Abnormal 12-lead electrocardiographic results at rest	40	22	9
Exercise electrocardiographic stress test			
ST segment depression ≥ 0.1 mV	56	30	11
ST segment depression ≥ 0.2 mV	16	9	3
Angina pectoris during stress test	23	12	2
Shortness of breath during stress test	94	51	8
Maximum heart rate < 100 beats/min*	36	19	3
< 85% PMHR†	141	76	13
ST segment depression ≥ 0.1 mV during exercise before achieving 85% of PMHR	43	23	9
Maximal workload < 100 W	101	55	7
ST segment depression ≥ 0.1 mV during exercise before achieving a workload of 100 W	38	21	7
Drop in exercise systolic blood pressure below resting values[12,13]	8	4	1
Blunted systolic blood pressure response (< 20 mmHg increase at peak exercise)[12]	25	14	4
Sustained decrease in systolic blood pressure > 10 mmHg after an initial increase[13]	6	3	1

* Maximal achieved heart rate less than 100 beats/min during exercise. † Inability to achieve 85% of the predicted maximal heart rate during exercise.
PMHR = predicted maximal heart rate.

ing electrocardiography was abnormal in 22% of patients, and the exercise stress electrocardiography was abnormal in 30%. Twenty-four percent of patients achieved 85% of their predicted maximal heart rate (table 2).

Adverse Cardiac Events

Sixteen patients (9%) had perioperative adverse cardiac events (table 3). Six patients (3%) developed a perioperative myocardial infarction; in two of these patients, the myocardial infarction was combined with acute congestive heart failure. One patient presented with acute heart failure and pulmonary edema combined with troponin-T elevation. Another nine patients had troponin-T elevations more than 0.1 ng/ml on 2 consecutive days without symptoms or electrocardiographic abnormalities. Three patients showed prolonged ischemia more than 30 min in the Holter electrocardiography. All of these three patients had troponin-T elevations more than 0.1 ng/ml on 2 consecutive days, and one of them developed a Q-wave infarction. There were two deaths within the first 30 postoperative days, but in each case, there was a noncardiac cause.

Table 3. Perioperative Cardiac Events

	No. of Subjects	Percent
Myocardial infarction	6	3
Q-wave infarction	(2)	
Non–Q-wave infarction	(4)	
Combined with congestive heart failure	(2)	
Myocardial cell injury combined with congestive heart failure	1	0.5
Minor myocardial cell injury*	9	5
Total	16	9

* Troponin-T increase > 0.1 ng/ml on at least two successive days in the absence of symptoms or electrocardiographic abnormalities.

Variables Associated with Adverse Cardiac Events

The preoperative variables significantly associated with an adverse cardiac event in the univariate analysis at *P* less than 0.1 are presented in table 4. Other exercise test parameters such as abnormal blood pressure responses or shortness of breath proved to be nonpredictive in the univariate analysis. The multivariate correlates of adverse cardiac events were definite coronary artery disease, major vascular or visceral surgery, reduced left ventricular performance, and ST-segment depression of 0.1 mV or more in the exercise electrocardiography (table 5). ST-segment depression of 0.1 mV or more during exercise and ST-segment depression of 0.1 mV or more before achieving 85% of the predicted maximal heart rate, as well as ST-segment depression of 0.1 mV or more before achieving a workload of 100 W were highly correlated. Therefore, only the variable with the lowest *P* value (ST-segment depression ≥ 0.1 mV during exercise) was included in the main multivariate model. Given the fact that previous studies[11,23] had found that the combined variable (ST-segment depression ≥ 0.1 mV before achieving a certain percentage of the predicted maximal heart rate) was predictive of cardiac complications, we also conducted a secondary multivariate analysis including the combined variable instead of the single variable (ST-segment depression ≥ 0.1 mV during exercise). However, the results were comparable with the main model: independent predictors of outcomes were coronary artery disease, major surgery, reduced left ventricular performance, and the combined exercise stress test variable.

Risk stratification was possible with use of the two clinical independent risk factors of coronary artery disease and major surgery. Sixty-three patients without any risk factor had a risk of 0% for cardiac complications.

Table 4. Variables Associated with Perioperative Cardiac Events: Sensitivity, Specificity, Predictive Values, Odds Ratios and P Values of the Univariate Analysis

			Predictive Value			
	Sensitivity	Specificity	Positive	Negative	OR	*P* Value
Definite CAD	94%	56%	17%	99%	18.8 (2.4–146)	0.005
Preoperative myocardial infarction	69%	73%	19%	96%	5.9 (1.9–17.9)	0.002
Preoperative intake of nitrates	56%	71%	16%	94%	3.1 (1.1–8.9)	0.03
Major surgery	69%	66%	16%	96%	4.2 (1.4–12.7)	0.01
ASA physical status > 3[15]	19%	97%	37%	93%	7.6 (1.6–35.3)	0.01
Cardiac risk index > 5 points[16]	56%	72%	16%	95%	3.3 (1.2–9.5)	0.02
Modified multifactorial risk index > 5 points[17]	56%	76%	18%	95%	4.0 (1.4–11.5)	0.009
Reduced left ventricular performance[12]	44%	88%	25%	94%	5.5 (1.8–16.3)	0.002
Abnormal 12-lead electrocardiographic results at rest	56%	82%	22%	95%	5.7 (2.0–16.6)	0.001
ST segment depression ≥ 0.1 mV during exercise	69%	73%	20%	96%	6.1 (2.0–18.4)	0.001
ST segment depression ≥ 0.1 mV during exercise before achieving 85% of the PMHR	56%	80%	21%	95%	5.1 (1.8–14.7)	0.002
ST segment depression ≥ 0.1 mV during exercise before achieving a workload of 100 W	44%	82%	18%	94%	3.5 (1.2–10.0)	0.02

Values in parentheses are 95% confidence intervals.

OR = odds ratio; CAD = coronary artery disease; ASA = American Society of Anesthesiologists; PMHR = predicted maximal heart rate.

Eighty-five patients with one of the two risk factors had a risk of 7%. The remaining 37 patients with both risk factors had an aggregated risk of 27% for cardiac complications. These latter groups were further differentiated by the findings of exercise stress electrocardiography (fig. 1). In particular, risk stratification of the group presenting with both clinical risk factors was improved: 20 of these patients who had normal exercise electrocardiographic findings had a risk of 10%, whereas 17 patients with abnormal exercise electrocardiographic findings had a risk of 47%.

Discussion

The present study is the first prospective investigation to show that the occurrence of an ST-segment depression of 0.1 mV or more in a preoperative exercise stress electrocardiography is a statistically significant independent predictor of perioperative cardiac events. This finding is significant, because 76% of the patients were not able to reach 85% of their maximal predicted heart rate, and 80% of our patients received vascular surgery. This result should be emphasized because it has been assumed up to now that exercise stress electrocardiography is of little value for the preoperative risk stratification for such patients.[6,7,24]

Table 5. Multivariate Analysis: Variables Significantly Associated with Cardiac Events

	OR	*P* Value
Definite coronary artery disease	8.8 (1.1–73.1)	0.04
Major vascular or visceral surgery	4.7 (1.3–16.3)	0.02
Reduced left ventricular performance	2.0 (1.1–3.8)	0.03
ST segment depression ≥ 0.1 mV during exercise stress electrocardiographic test	5.2 (1.5–18.5)	0.01

Values in parentheses are 95% confidence intervals.

OR = odds ratio.

Review articles with discussions of the role of preoperative exercise stress electrocardiography generally cite many studies[3,5,6]; however, the majority of the investigations are retrospective or have an unclear study design.[23,25–31] In addition, in some studies only a part of the patients were evaluated perioperatively[26,29,31,32] or only a small number of patients were investigated.[25,29,31–34] In one of the largest studies with unclear study design, Cutler *et al.*[23] investigated 130 patients and found the highest rate of cardiac complications in patients who had an ischemic response on their exercise electrocardiography at less than 75% of their predicted maximal heart rate.

To date, only three large prospective studies have been published on the role of preoperative exercise stress electrocardiography.[8,10,11] Carliner *et al.*[8] investigated 198 patients, von Knorring and Lepäntalo[10] investigated 105 patients, and McPhail *et al.*[11] investigated 100 patients. In two of these studies, several different types of exercise stress testing were used,[8,11] and in one study only a single modified V_4-electrocardiography lead was recorded.[10] None of these studies[8,10,11] involved the evaluation of the exercise stress electrocardiography by two independent investigators blinded to patient identity and clinical course,[35] and perioperative Holter monitoring and newer biochemical markers were not used for the detection of cardiac complications.[8,10,11] Two of these prospective studies demonstrated that preoperative stress-induced ischemia is a significant predictor in univariate analysis[8,10]; in the study by Knorring and Lepäntalo's,[10] only univariate analysis was performed. McPhail *et al.*[11] found that patients who had a positive stress test (ST depression ≥ 1 mm) and impaired exercise tolerance indicated by their inability to achieve less

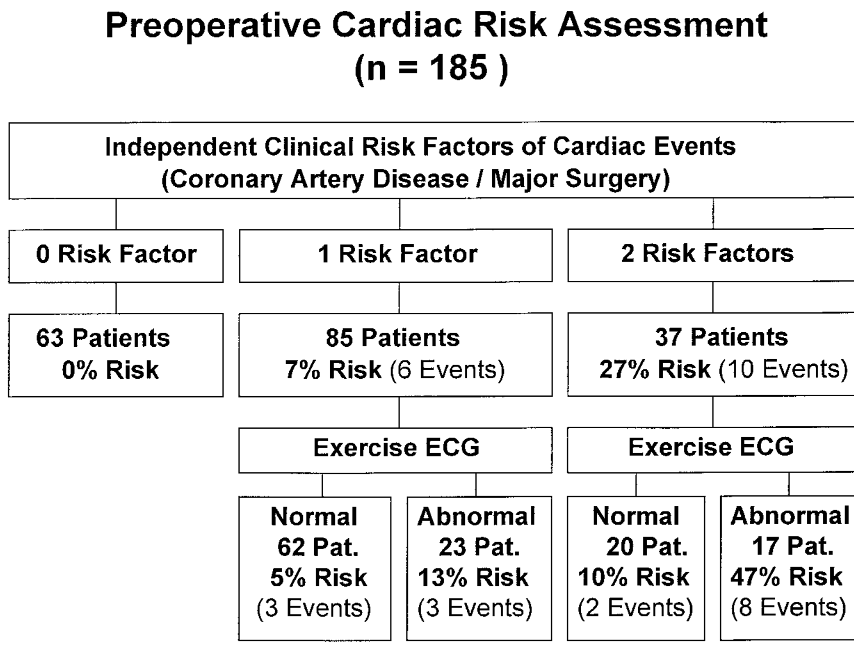

Fig. 1. Risk stratification using in retrospect the two independent clinical risk factors followed by further differentiation of the findings of the exercise electrocardiography. ECG = electrocardiogram; Pat. = patients.

than 85% of their predicted maximal heart rate had a significantly higher rate of cardiac complications than patients with a positive stress test who achieved more than 85% of their predicted maximal heart rate. Multivariate analysis of the data from the study by Carliner *et al.*[8] showed only preoperative resting electrocardiography as a significant predictor of risk. In contrast, the study by McPhail *et al.*[11] showed that the ability to reach a high maximal heart rate and a high cardiac work load maximal oxygen uptake was an independent predictor of a low rate of cardiac complications.[11] Gerson *et al.*[27,28] reported similar results in two retrospective studies. By multivariate analysis, inability to perform 2 min of supine bicycle exercise increasing the heart rate to greater than 99 beats/min was the best predictor of perioperative cardiac complications.[27,28] Contrary to these previous studies,[11,27,28] our study did not show that inability to reach a certain heart rate is predictive. This could be a result of the large proportion of vascular surgery patients with limited exercise capacity in our study, and the fact that 30% of our patients were receiving treatment with β blockers. However, consistent with the results of Cutler *et al.*[23] and McPhail *et al.*,[11] we also found that ST-segment depression of 0.1 mV or more during exercise before achieving a specified percentage of the predicted maximal heart rate was predictive.

The second important result of our study is the definition of the role of exercise stress electrocardiography: in contrast to the preoperative resting electrocardiography, the exercise electrocardiography was found to be an independent predictor and represented a significant enhancement for risk stratification. The independent predictive value of resting electrocardiography was demonstrated by Carliner *et al.*[8] and confirmed in recent studies.[9,36] Our study is the first to demonstrate the superiority of preoperative exercise stress electrocardiography over resting electrocardiography.

Palda and Detsky[7] advised against the use of exercise stress electrocardiography for preoperative risk stratification and instead recommended myocardial imaging or stress echocardiography; therefore, a direct comparison of these methods would be interesting. To our knowledge, there were only two smaller studies, in which dipyridamole-thallium scintigraphy was compared with exercise electrocardiography.[34,37] In the study by McPhail *et al.*,[37] sensitivity of scintigraphy was significantly higher than that of exercise electrocardiography, whereas specificity was lower. Regarding the predictive value, there was no difference between both tests.[37] In the regression analysis of the study by Leppo *et al.*,[34] only the presence of thallium redistribution was significant. However, the predictive value of thallium imaging has been questioned in two newer prospective studies.[38,39] The positive predictive value of dipyridamole-thallium scintigraphy ranges from 4% to 20%[5,6,40] and that of stress echocardiography from 7% to 38%,[5,6,40–42] so that the two methods are comparable.[40] The predictive value of exercise stress electrocardiography in our study was 20%, and published values range from 5% to 25%[5,8,11]; however, it should be noted that the predictive value is dependent not only on the incidence of cardiac complications, which is influenced by the special risk of the investigated study population, but also on the definitions of adverse outcome. In contrast to other studies, we have included myocardial cell injury as an outcome parameter in addition to myocardial infarction and death. Thus, comparisons of the predictive values from different studies must be interpreted with care. Myocardial perfusion imaging and stress echocardiography have the disadvantage of limited availability, in addition to being expensive and time-consuming. Stress echocardiography also requires very experienced medical staff. In contrast, exercise stress electrocardiography is simple, widely available, and has become a well-standardized technique. Especially if a clinical parameter (definite coronary artery disease) and the operative risk are combined with the results of the exercise stress electrocardiography, preoperative risk stratification is possible and seems comparable to scintigraphy-based risk stratification[24] with the advantage of a more cost-effective and easy accessible approach.[3] It is unclear if patients who cannot perform bicycle ergometry or treadmill stress testing can be evaluated with arm ergometry[13,29,33] as an alternative to scintigraphy or stress echocardiography. Exercise electrocardiography is not useful for patients with left bundle branch block or paced ventricular rhythm.[43]

Consistent with previously published data, definite coronary artery disease[39,44–46] and major surgery[16,44,46] proved to be independent predictors.

Although, because of the clinical markers and the type of operation performed, all 185 patients had at least an intermediate risk,[5] approximately 70% of our patients were classified as relatively healthy given their classical risk classifications.[16,17] The main reason for this discrepancy is that in contrast to the American College of Cardiology–American Heart Association guidelines,[5] the risk indices[16,17] do not contain mild angina pectoris, diabetes, compensated congestive heart failure, peripheral vascular surgery, and carotid endarterectomy as risk factors. Nonetheless, our population was not a particularly sick one, and this might be one reason why we found risk indices not to be independent predictors.

Limitations

First, the major limitation of our study is the relatively small sample size and thus the low number of severe cardiac complications. In anticipation of this, we had defined the occurrence of troponin-T elevation more than 0.1 ng/ml on at least 2 successive days without electrocardiographic abnormalities or symptoms as a cardiac event, even though this is a relatively "soft" outcome parameter compared with myocardial infarction or cardiac death. However, the definition of minor postoperative myocardial injury as a perioperative event is supported by data from the last 10 yr, which show that postoperative myocardial ischemia,[47–49] especially if prolonged,[14,21] is significantly associated with perioperative complications and can influence late outcome.[49] Abnormal postoperative troponin-T levels are also a predictor of 6-month prognosis.[50] In addition, reduction of perioperative myocardial ischemia by medical treatment can influence early and late mortality.[49,51] Second, in the period between the sixth postoperative day and the telephone interview 30 days after surgery, minor myocardial injury and even myocardial infarction could have been missed. Third, the physicians caring for the patients were not blinded to the preoperative resting and exercise electrocardiography. This could have influenced anesthetic management and postoperative care. However, in patients with an obvious abnormal stress test, this fact should have rather reduced than increased adverse outcome. Fourth, our finding that preoperative reduced left ventricular performance is an independent predictor of perioperative cardiac complications should be interpreted cautiously as echocardiography was performed by one unblinded cardiologist only. In contrast, studies especially evaluating this issue have shown that preoperative assessment of left ventricular performance by echocardiography or radionuclide angiography have only limited prognostic value.[39,52]

In conclusion, this prospective study shows that a ST-segment depression of 0.1 mV or more in the exercise stress electrocardiogram is an independent predictor of perioperative cardiac complications in intermediate-risk patients undergoing noncardiac surgery, whereas an abnormal resting electrocardiogram did not prove to be an independent predictor. A combination of a clinical parameter (definite coronary artery disease) with the type of surgery proposed and the results of the exercise stress electrocardiography allowed sufficient risk stratification.

The authors thank the Department for Biometry and Documentation, University of Ulm (Prof. Dr. Gaus and Dr. R. Muche), for advice and assistance in the statistical analysis of the data.

References

1. Badner NH, Knill RL, Brown JE, Novick TV, Gelb AW: Myocardial infarction after noncardiac surgery. Anesthesiology 1998; 88:572–8

2. Mangano DT: Perioperative cardiac morbidity. Anesthesiology 1990; 72:153–84

3. Mangano DT: Preoperative assessment of the patient with cardiac disease. Curr Opin Cardiol 1995; 10:530–42

4. Mangano DT, Goldman L: Preoperative assessment of patients with known or suspected coronary disease. N Engl J Med 1995; 333:1750–6

5. Eagle KA, Brundage BH, Chaitman BR, Ewy GA, Fleisher LA, Hertzer NR, Leppo JA, Ryan T, Schlant RC, Spencer III WH, Spittell JA, Twiss RD: Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 1996; 93:1278–317

6. Coley CM, Eagle KA: Preoperative assessment and perioperative management of cardiac ischemic risk in noncardiac surgery. Curr Probl Cardiol 1996; 21:291–382

7. Palda AV, Detsky AS: Clinical Guideline, Part I. Guidelines for assessing and managing the perioperative risk from coronary artery disease associated with major noncardiac surgery. Ann Intern Med 1997; 127:309–12

8. Carliner NH, Fisher ML, Plotnick GD, Garbart H, Rapoport A, Kelemen MH, Moran GW, Gadacz T, Peters RW: Routine preoperative exercise testing in patients undergoing major noncardiac surgery. Am J Cardiol 1985; 56:51–8

9. Landesberg G, Einav S, Christopherson R, Beattie C, Berlatzky Y, Rosenfeld B, Eidelman LA, Norris E, Anner H, Mosseri M, Cotev S, Luria MH: Perioperative ischemia and cardiac complications in major vascular surgery: importance of the preoperative twelve-lead electrocardiogram. J Vasc Surg 1997; 26:570–8

10. von Knorring J, Lepäntalo M: Prediction of perioperative cardiac complications by electrocardiographic monitoring during treadmill exercise testing before peripheral vascular surgery. Surgery 1986; 99:610–3

11. McPhail N, Calvin JE, Shariatmadar A, Scoble TK, Barber GG, Scobie TK: The use of preoperative exercise testing to predict cardiac complications after arterial reconstruction. J Vasc Surg 1988; 7:60–8

12. The Criteria Committee of the New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th Edition. Boston. Little, Brown and Company, 1994, pp 48–319

13. Chaitman BR: Exercise stress testing, Heart Disease: A Textbook of Cardiovascular Medicine, 5th Edition. Edited by Braunwald E. Philadelphia, Saunders, 1997, pp 153–76

14. Fleisher LA, Nelson AH, Rosenbaum SH: Postoperative myocardial ischemia: Etiology of cardiac morbidity or manifestation of underlying disease? J Clin Anesth 1995; 7:97–102

15. Dripps RD, Lamont A, Eckenhoff JE: The role of anesthesia in surgical mortality. JAMA 1961; 178:261–6

16. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B, Burke DS, O'Malley TA, Goroll AH, Caplan CH, Nolan J, Carabello B, Slater EE: Multifactorial index of cardiac risk in non-cardiac surgical procedures. N Engl J Med 1977; 297:845–50

17. Detsky AS, Abrams HB, McLaughlin JR, Drucker DJ, Sasson Z, Johnston N, Scott JG, Forbath N, Hilliard JR: Predicting cardiac complications in patients undergoing non-cardiac-surgery. J Gen Intern Med 1986; 1:211–9

18. Frankel WL, Herold DA, Ziegler TW, Fitzgerald RL: Cardiac troponin T is elevated in asymptomatic patients with chronic renal failure. Am J Clin Pathol 1996; 106:118–23

19. Ooi DS, House AA: Cardiac troponin T in hemodialyzed patients. Clin Chem 1998; 44:1410–6

20. van Lente F, McErlean ES, DeLuca SA, Peacock WF, Rao JS, Nissen SE: Ability of troponins to predict adverse outcomes in patients with renal insufficiency and suspected acute coronary syndromes: A case-matched study. J Am Coll Cardiol 1999; 33:471–8

21. Landesberg G, Luria MH, Cotev S, Eidelman LA, Anner H, Mosseri M, Schechter D, Assaf J, Erel J, Berlatzky Y: Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. Lancet 1993; 341:715–9

22. Raby KE, Barry J, Creager MA, Cook EF, Weisberg MC, Goldman L: Detection and significance of intraoperative and postoperative myocardial ischemia in peripheral vascular surgery. JAMA 1992; 268:222–7

23. Cutler BS, Wheeler HB, Paraskos JA, Cardullo PA: Applicability and interpretation of electrocardiographic stress testing in patients with peripheral vascular disease. Am J Surg 1981; 141:501–6

24. Eagle KA, Coley CM, Newell JB, Brewster DC, Darling C, Strauss HW, Guiney TE, Boucher CA: Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. Ann Intern Med 1989; 110:859–66

25. Cutler BS, Wheeler HB, Paraskos JA, Cardullo PA: Assessment of operative risk with electrocardiographic exercise testing in patients with peripheral vascular disease. Am J Surg 1979; 137:484–90

26. Arous EJ, Baum PL, Cutler BS: The ischemic exercise test in patients with peripheral vascular disease. Arch Surg 1984; 119:780–3

27. Gerson MC, Hurst JM, Hertzberg VS, Doogan PA, Cochran MB, Lim SP, McCall N, Adolph RJ: Cardiac prognosis in noncardiac geriatric surgery. Ann Intern Med 1985; 103:832–7

28. Gerson MC, Hurst JM, Hertzberg VS, Baughman R, Rouan GW, Ellis K, Fischer EE, Colthar MS, Burwinkle BM: Prediction of cardiac and pulmonary complications related to elective abdominal and noncardiac thoracic surgery in geriatric patients. Am J Med 1990; 88:101–7

29. Hanson P, Pease M, Berkoff H, Turnipseed W, Detmer D: Arm exercise testing for coronary artery disease in patients with peripheral vascular disease. Clin Cardiol 1988; 11:70–4

30. Urbinati S, Di Pasquale G, Andreoli A, Lusa AM, Carini G, Grazi P, Labanti G, Passarelli P, Corbelli C, Pinelli G: Preoperative noninvasive coronary risk stratification in candidates for carotid endarterectomy. Stroke 1994; 25:2022–7

31. Gardine RL, McBride K, Greenberg H, Mulcare RJ: The value of cardiac monitoring during peripheral arterial stress testing in the surgical management of peripheral vascular disease. J Cardiovasc Surg (Torino) 1985; 26:258–61

32. McCabe JC, Reidy NC, Abbott WM, Fulchino DM, Brewster DC: The value of electrocardiogram monitoring during treadmill testing for peripheral vascular disease. Surgery 1981; 89:183–6

33. Kaaja R, Sell H, Erkola O, Harjula A: Predictive value of manual ECG-monitored exercise test before abdominal aortic or peripheral vascular surgery. Angiology 1993; 44:11–5

34. Leppo J, Plaja J, Gionet M, Tumolo J, Paraskos JA, Cutler BS: Noninvasive evaluation of cardiac risk before elective vascular surgery. J Am Coll Cardiol 1987; 9:269–76

35. Gianrossi R, Detrano R, Mulvihill D, Lehmann K, Dubach P, Colombo A, McArthur D, Froelicher V: Exercise-induced ST depression in the diagnosis of coronary artery disease: A meta-analysis. Circulation 1989; 80:87–98

36. Vanzetto G, Machecourt J, Blendea D, Fagret D, Borrel E, Magne JL, Gattaz F, Guidicelli H: Additive value of thallium single-photon emission computed tomography myocardial imaging for prediction of perioperative events in clinically selected high cardiac risk patients having abdominal aortic surgery. Am J Cardiol 1996; 77:143–8

37. McPhail NV, Ruddy TD, Calvin JE, Davies RA, Barber GG: A comparison of dipyridamole-thallium imaging and exercise testing in the prediction of postoperative cardiac complications in patients requiring arterial reconstruction. J Vasc Surg 1989; 10:51–6

38. Mangano DT, London MJ, Tubau JF, Browner WS, Hollenberg M, Krupski W, Layug EL, Massie B: Dipyridamole thallium-201 scintigraphy as a preoperative screening test: A reexamination of its predictive potential. Circulation 1991; 84:493–502

39. Baron J-F, Mundler O, Bertrand M, Vicaut E, Barré E, Godet G, Samama CM, Coriat P, Kieffer E, Viars P: Dipyridamole-thallium scintigraphy and gated radionuclide angiography to assess cardiac risk before abdominal aortic surgery. N Engl J Med 1994; 330:663–9

40. Shaw LJ, Eagle KA, Gersh BJ, Miller DD: Meta-analysis of intravenous dipyridamole-thallium-201 imaging (1985 to 1994) and dobutamine echocardiography (1991 to 1994) for risk stratification before vascular surgery. J Am Coll Cardiol 1996; 27:787–98

41. Poldermans D, Arnese M, Fioretti PM, Salustri A, Boersma E, Thomson IR, Roelandt JRTC, van Urk H: Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. J Am Coll Cardiol 1995; 26:648–53

42. Rossi E, Citterio F, Vescio MF, Penestri F, Lombardo A, Loperfido F, Maseri A: Risk stratification of patients undergoing peripheral vascular revascularization by combined resting and dipyridamole echocardiography. Am J Cardiol 1998; 82:306–10

43. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WFC, Froelicher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD, Winters WL, Yanowitz FG: ACC/AHA Guidelines for exercise testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 1997; 30:260–311

44. Frey Larsen S, Olesen KH, Jacobsen E, Nielsen H, Lynge Nielsen A, Pietersen A, Jensen OJ, Pedersen F, Waaben J, Kehlet H, Fischer Hansen J, Dalgaard P, Nyboe J: Prediction of cardiac risk in non-cardiac surgery. Eur Heart J 1987; 8:179–85

45. Ashton CM, Petersen NJ, Wray NP, Kiefe CI, Dunn JK, Wu L, Thomas JM: The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. Ann Intern Med 1993; 118:504–10

46. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KKL, Ludwig LE, Pedan A, Goldman L: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100:1043–9

47. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM: Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. N Engl J Med 1990; 323:1781–8

48. Mangano DT, Hollenberg M, Fegert G, Meyer ML, London MJ, Tubau JF, Krupski WC: Perioperative myocardial ischemia in patients undergoing noncardiac surgery-I: Incidence and severity during the 4 day perioperative period. J Am Coll Cardiol 1991; 17:843–50

49. Wallace A, Layug B, Tateo I, Li J, Hollenberg M, Browner W, Miller D, Mangano DT, McSPI Res Grp: Prophylactic atenolol reduces postoperative myocardial ischemia. ANESTHESIOLOGY 1998; 88:7–17

50. Lopez-Jimenez F, Goldman L, Sacks DB, Thomas EJ, Johnson PA, Cook EF, Lee TH: Prognostic value of cardiac troponin T after noncardiac surgery: 6-month follow-up data. J Am Coll Cardiol 1997; 29:1241–5

51. Mangano DT, Layug EL, Wallace A, Tateo I: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. N Engl J Med 1996; 335:1713–20

52. Halm EA, Browner WS, Tubau JF, Tateo IM, Mangano DT: Echocardiography for assessing cardiac risk in patients having noncardiac surgery. Ann Intern Med 1996; 125:433–41