Anesthesiology
1998; 88:1233–9

Dobutamine Stress Echocardiography to Detect Inducible Demand Ischemia in Anesthetized Patients with Coronary Artery Disease

Manfred D. Seeberger, M.D., Karl Skarvan, M.D.,† Peter Buser, M.D.,‡ Wolfgang Brett, M.D.,§ Reinhard Rohlfs, R.N.,‖ Jean-Jacques Erne, R.N.,‖ Cyril Rosenthaler, M.D.,# Matthias Pfisterer, M.D.,** Dan Atar, M.D. ‡*

Background: **A cardiac risk stratification test that can be performed during operation would be expected to give valuable information for the therapeutic management of patients who need urgent noncardiac surgery. This study was designed to evaluate the feasibility and safety of a dobutamine–atropine stress protocol to detect inducible demand ischemia in anesthetized patients.**

Methods: **A standard dobutamine–atropine stress protocol was performed in 80 patients with severe coronary artery disease during fentanyl–isoflurane anesthesia. Biplane transesophageal echocardiography and 12-lead electrocardiography were used to detect induced ischemia. After dobutamine testing, esmolol, nitroglycerin, or both were used to revert ischemia and any hemodynamic changes, as appropriate.**

Results: **The protocol detected inducible ischemia or achieved the target heart rate in 75 of the 80 (94%) patients. None of the prospectively defined adverse outcomes, such as cardiovascular collapse, severe ventricular arrhythmia, persistent (≥5 min) ischemia, or hemodynamic instability, occurred in any of the patients. Ischemia was induced and detected in 73 of the 80 (91%) patients.**

Conclusion: **Dobutamine stress echocardiography is feasible in anesthetized patients with severe coronary artery disease. The lack of serious complications and the high sensitivity to detect inducible ischemia in this patient population provide the basis for further evaluation of the safety and diagnostic value of dobutamine stress echocardiography during general anesthesia in larger studies of patients at risk for coronary artery disease undergoing noncardiac surgery. (Key words: Atropine; electrocardiography; myocardial ischemia.)**

COMPLICATIONS resulting from underlying coronary artery disease (CAD) continue to be a major cause of death and complications in patients having surgery.[1] Various strategies have been developed to assess and decrease cardiac risk in patients scheduled for noncardiac surgery,[2–5] and guidelines for perioperative cardiovascular evaluation have been established.[6] Unfortunately, situations in which surgical care is urgent or semielective do not permit appropriate cardiac evaluation.[6] Strategies to assess and decrease cardiac risk in these patients are especially important because patients undergoing urgent surgery have a markedly higher incidence of cardiac complications compared with patients having elective surgery.[7] For these patients, the guidelines suggest postoperative risk stratification.[6] Such a strategy may determine long-term risk and future therapy but cannot address the risk of acute perioperative myocardial infarction, which has a high mortality rate.[8] Based on evidence that intensive care significantly reduces mortality rates in patients with myocardial infarction who are not having surgery,[9] intensive postoperative monitoring and treatment have been recommended for patients having surgery who are at high risk for cardiac complications.[10] However, as many as one third of surgical procedures in high-risk populations, such as patients with vascular disease, is performed on an urgent basis,[11] and the cost of intensive postoperative care in all of these patients would be prohibitively high. Thus an intraoperative cardiac risk stratification test might provide valuable information

* Staff Anesthesiologist.

† Professor of Anesthesia.

‡ Assistant Professor of Cardiology.

§ Staff Cardiac Surgeon.

‖ Research Associate, Department of Anesthesia.

Resident in Anesthesia.

** Professor of Cardiology.

Received from the Departments of Anesthesia, Internal Medicine (Division of Cardiology), and Surgery (Division of Cardiothoracic Surgery), University of Basel, Basel, Switzerland. Submitted for publication September 22, 1997. Accepted for publication January 14, 1998. Supported in part by a grant from the International Anesthesia Research Society. Presented in part at the American Society of Anesthesiologists annual meeting, October 21–25, 1995, Atlanta, Georgia, and at the International Anesthesia Research Society's 71st Clinical and Scientific Congress, March 14–18, 1997, San Francisco, California.

Address reprint requests to Dr. Seeberger: Department of Anesthesia, University of Basel, Kantonsspital, CH-4031 Basel, Switzerland. Address electronic mail to: seeberger@ubaclu.unibas.ch

Table 1. Characteristics of 80 Patients with Severe Coronary Artery Disease Undergoing Intraoperative Dobutamine–Atropine Stress Echocardiography

Characteristic	Value
Previous myocardial infarction	24 (30%)
Hypercholesterolemia	63 (79%)
Smoking history	50 (63%)
Hypertension	49 (61%)
Diabetes mellitus	18 (23%)
History of exertional angina	80 (100%)
Evidence of ischemia at preoperative stress test* (n = 55)	50 (91%)
Coronary angiography and left ventricular catheterization	
2- or 3-vessel coronary artery disease	78 (98%)
Preexisting segmental wall motion abnormalities	51 (64%)
Ejection fraction (%)	64 ± 11
Left ventricular end-diastolic pressure (mmHg)	14 ± 6
Medications	
β-Adrenergic antagonists	59 (74%)
Calcium antagonists	45 (56%)
Nitrates	36 (45%)
Laboratory findings and anesthesia at study baseline	
Hemoglobin (g/L)	138 ± 14
Calcium (mM)	2.22 ± 0.53
Fentanyl (μg/kg)	7 ± 4
Flunitrazepam (μg/kg)	5 ± 4
Isoflurane (% inspiratory concentration)	0.5 ± 0.2

Data are no. (%) of patients or mean ± SD.

* Exercise ECG or dipyridamole-thallium-201 scintigraphy.

for identifying patients who could benefit most from postoperative intensive care and for guiding perioperative management.

We hypothesized that dobutamine stress echocardiography (DSE) would be as feasible and safe to detect inducible demand ischemia in anesthetized patients as it is in awake patients,[12,13] and thus we tested this hypothesis in patients with severe CAD.

Methods

Study Population and Anesthetic Technique

The study protocol was approved by our institutional review board. Eighty patients (67 men, 13 women) with proved CAD (≥70% stenosis) who were scheduled for elective coronary artery bypass graft surgery gave written informed consent and were included in the study (table 1). All patients had a history of stable exertional angina; preoperative exercise electrocardiography (ECG) or dipyridamole-thallium-201 scintigraphy was performed in 55 of the 80 patients and was positive in 50 (91%) of them. The patients had no hemodynamic instability, no severely depressed left ventricular function (ejection fraction >30% in all patients), no hemodynamically relevant valvular heart disease, and no preexisting ECG abnormalities precluding analysis of the S-T segment. On the day of surgery, no patient had signs of myocardial ischemia before the study. Anti-ischemic medication (table 1) was not discontinued before the study.

Anesthesia was induced and maintained with thiopentone or etomidate, fentanyl, pancuronium, flunitrazepam, and isoflurane (table 1). Controlled mechanical ventilation with 50% oxygen was provided to achieve normoventilation. During DSE, anesthesia and ventilation were maintained at stable levels.

Dobutamine Stress Echocardiography

Dobutamine stress echocardiography was performed as soon as central venous access had been achieved and hemodynamics were stable after induction of anesthesia. Dobutamine was infused for 3 min each at 10, 20, and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 1 mg atropine was added intravenously if dobutamine alone did not increase the heart rate to the age-adjusted maximum (≥0.85 [220 minus the patient's age in years]) or induce ≥1 mm S-T segment depression or new segmental wall motion abnormalities (as we will define here). Other parameters resulting in premature termination of DSE were defined as significant ventricular arrhythmia (>6 beats/min or >3 consecutive beats), development of severe hypertension (systolic arterial pressure >220 mmHg or diastolic arterial pressure >120 mmHg), and severe arterial hypotension (>20% decrease to <50 mmHg mean arterial pressure). After termination of DSE, esmolol, nitroglycerin, or both were administered to quickly reverse ischemia and induced hemodynamic changes before surgery started. During the subsequent intraoperative course, the occurrence of ischemia was assessed by continuous two-lead ECG (leads II and V5) and repeated transesophageal echocardiography (TEE) analyses. Postoperative patient follow-up examination included 12-lead ECGs on arrival in the ICU and on the first postoperative morning and measurements of cardiac enzymes at the discretion of the treating physicians.

For off-line study evaluation, synchronized recordings of 12-lead ECG and biplane TEE were performed, and hemodynamic variables were measured immediately be-

fore dobutamine administration, at the end of each infusion rate, and 5 and 10 min after stopping dobutamine administration. ECG data were printed on paper at a speed of 25 mm/s and a calibration of 1 mV = 10 mm (Personal C3; ESAOTE Biomedica, Florence, Italy); TEE recordings included transgastric midpapillary short-axis and long-axis cross sections (Sonos 2500 and biplane 5-MHz probe; Hewlett-Packard, Andover, MA); and hemodynamic recordings included systemic arterial and central venous pressures (PCMS Workstation 19845-15-03; Spacelabs Inc., Chatsworth, CA).

Study Interpretation

Electrocardigraphic and TEE recordings were analyzed separately off-line by two experienced, independent investigators who were blinded to all other patient data during each analysis.

For ECG analysis, S-T segments at each study period were compared with the patient's own baseline measurements. Evidence of myocardial ischemia was defined as ≥1 mm horizontal or downsloping S-T segment depression or horizontal S-T segment elevation at 60 ms after the J point; if baseline S-T segment changes were present, an additional ≥2 mm S-T segment shift was required to diagnose ischemia.

Echocardiographic images were digitally converted to rate-synchronized cine loops (Sonos 2500; Hewlett-Packard). Quad screens were used to analyze segmental wall motion by comparing randomized cine loops of study periods during dobutamine infusion and recovery to an identified baseline cycle, as previously reported.[14] Briefly, the midpapillary short-axis cross-section was divided into four and the long-axis cross-section into six segments, and each segment was evaluated for inward endocardial motion and myocardial thickening. Five classes of wall motion and thickening patterns were defined: normal, mild hypokinesis, severe hypokinesis, akinesis, and dyskinesis.[14] Myocardial ischemia was diagnosed if segmental function showed either worsening (motion and thickening) by at least one class during increasing dobutamine doses or a biphasic response.[15] A random sample representing 25% of the cycles was submitted twice for analysis to test intrareader variability.

Based on the midpapillary short-axis cross-section, end-diastolic endocardial area, area ejection fraction, and systolic wall stress were determined for cycles at baseline, peak dobutamine infusion rate, and 10 min after stopping dobutamine administration (Sonos 2500; Hewlett-Packard).[16,17]

Dobutamine stress echocardiography was considered feasible if it achieved the target heart rate (≥0.85 [220 minus the patient's age in years]) or induced and detected ischemia at any dobutamine infusion stage. Dobutamine stress echocardiography was considered safe if it did not cause cardiovascular collapse, ventricular fibrillation, or ventricular tachycardia, and if it did not induce persistent (≥5 min after cessation of dobutamine administration) ischemia or hemodynamic instability (mean arterial pressure <60 mmHg). Dobutamine stress echocardiography was considered sensitive if dobutamine combined with 12-lead ECG and biplane TEE induced and detected ischemia in the study patients.

Statistical Analysis

McNemar's test was used to compare the sensitivity of ECG and biplane TEE to detect myocardial ischemia. Fisher's exact test or the chi-square test, as appropriate, was used to analyze dichotomous variables. Unpaired or paired Student's *t* test was used to analyze continuous variables. Probability values <0.05 were considered significant. Continuous variables are reported as means ± SD.

Results

Tables 1 and 2 show patient characteristics and hemodynamic findings. The peak dobutamine dose was 37 ± 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$; 1 mg atropine was administered intravenously in 52 of the 80 (65%) patients.

Feasibility and Safety

Dobutamine stress echocardiography was feasible because it either induced and detected ischemia or achieved the target heart rate in 75 of the 80 (94%) patients. None of the prospectively defined adverse outcomes occurred in any of the study patients. Side effects during DSE consisted of premature atrial contractions in 11 (14%) patients, premature, ventricular contractions in 6 (8%) patients, and three consecutive premature ventricular contractions in 1 (1%) patient. Rate-dependent left bundle-branch block developed in 1 patient; 13 (16%) patients had a peak systolic arterial pressure >220 mmHg. After stopping dobutamine infusion and intravenous administration of incremental doses of esmolol in 79 of the 80 (99%) patients (mean total dose, 145 ± 66 mg) and nitroglycerin in 44 (55%) patients (mean total dose, 233 ± 262 μg), these side effects resolved within 2 min. Induced ischemia resolved

Table 2. Hemodynamic Findings at Baseline and at Peak Dobutamine Dose in the 80 Study Patients

	Baseline	Peak Dobutamine	*P* Value
Heart rate (beats/min)	57 ± 9	107 ± 22	<0.05
Systolic arterial pressure (mmHg)	97 ± 15	175 ± 52	<0.05
Double product (beats/min × mmHg)	5,542 ± 1,247	18,355 ± 6,126	<0.05
Mean arterial pressure (mmHg)	70 ± 10	112 ± 31	<0.05
Central venous pressure (mmHg)	8 ± 3	9 ± 4	<0.05
Left ventricular end-diastolic area (cm^2)	18.6 ± 4.7	19.3 ± 6.4	NS
Area ejection fraction (%)	49 ± 12	53 ± 12	<0.05
Systolic wall stress (g/cm^2)	56 ± 25	103 ± 55	<0.05

Data are mean ± SD.

NS = not signifciant.

within 5 min in all patients. After the study, no patient had TEE or ECG evidence of any ischemic episode before onset of cardiopulmonary bypass. In addition, no patient had any intraoperative cardiac instability or complications, except for one patient who experienced an asystole lasting 8 s that began 4 min after stopping dobutamine and after intravenous administration of 30 mg esmolol and 100 μg nitroglycerin. Normal sinus rhythm resumed after a precordial blow and intravenous administration of 0.5 mg atropine. In this patient, DSE had been prematurely stopped after 3 min at the lowest dobutamine infusion rate of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Postoperative patient follow-up examination revealed nonfatal perioperative myocardial infarction of the lateral wall in one patient who had echocardiographic evidence of transient ischemia in the septum at 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Subsequently this patient had dissection of the obtuse marginal branch of the left circumflex coronary artery during surgical preparation.

Sensitivity

Dobutamine stress echocardiography combining biplane TEE and 12-lead ECG during administration of dobutamine and atropine induced and detected myocardial ischemia in 73 of the 80 (91%) patients. New segmental wall motion abnormalities were found in 59 (74%) patients and diagnosed S-T segment changes in 49 (61%) patients. TEE and ECG results were positive in 35 patients, and the location of detected ischemia corresponded in 32 (91%) of them. The most sensitive ECG lead, V4, detected ischemia in 38 of the 49 (78%) patients with evidence of ischemia in any of the 12 standard ECG leads. The two-lead combination of V4 and V5 detected ischemia in 41 of the 49 (84%) patients with any ECG evidence of ischemia, the combination of V4 and II detected ischemia in 40 (82%) patients, and the combination of leads II and V5 detected it in only 30 (61%) patients. None of the 14 patients who had ECG but not TEE evidence of ischemia fulfilled ECG criteria of left ventricular hypertrophy, but 5 of them had a history of arterial hypertension.

Analysis of factors that may have influenced sensitivity is limited by the small number (n = 9) of patients who did not show TEE and/or ECG evidence of ischemia during DSE. Compared with patients who showed evidence of ischemia, patients with negative DSE were younger, more of them also had a negative preoperative stress test (exercise ECG or dipyridamole-thallium-201 scintigraphy), and their peak systolic wall stress was smaller (each $P < 0.05$; data not presented in detail). Ongoing medication with β-adrenergic antagonists was significantly correlated with failure to achieve the target heart rate (4 of 59 *vs.* 9 of 21; $P < 0.01$) but not with reduced sensitivity.

In the TEE short-axis cross-section, image quality was adequate for analysis in 315 of the 320 (98%) segments. In the long-axis cross section, image quality was adequate for analysis in only 367 (76%) of the 480 segments because the anterior and inferior apical segments could not be imaged adequately in most patients. Intraobserver variability of the two readers was 6% and 11%, and interobserver variability was 9% (in 61 segments). The consensus readings were confirmed by the independent third reader in 41 of the 61 (67%) segments, and the remaining 20 segments were excluded from analysis.

The quality of the ECGs was adequate for analysis in 79 of the 80 patients. Interreader variability was 4%, requiring consensus readings in three patients. In one of these patients, the ECG was regarded as equivocal

and excluded from analysis. None of the 14 patients who gave ECG evidence of ischemia in the absence of new segmental wall motion abnormalities had preexisting Q waves in leads diagnostic of ischemia.

Discussion

This study shows that a DSE protocol combining biplane TEE and 12-lead ECG during administration of dobutamine and atropine is feasible in anesthetized patients with severe CAD because it induced and detected ischemia or achieved the target heart rate in 75 of the 80 (94%) study patients. The protocol was regarded as safe in all study patients because no severe complications occurred. In addition, the sensitivity of the protocol to detect inducible demand ischemia was high (91%). However, the sample size of 80 patients was too small to allow definitive conclusions regarding the safety of DSE in anesthetized patients, and the diagnostic value of DSE in anesthetized patients can be determined only after assessing both sensitivity and specificity in a population of patients with and without CAD.

This study exclusively evaluated patients with severe CAD who subsequently underwent coronary artery bypass graft surgery. One reason for this is that cardiopulmonary bypass was continuously available to ensure patient safety in the event that persistent ischemia or cardiovascular instability occurred during stress testing. As cardiopulmonary bypass backup was available, we wanted to evaluate patients with most severe CAD because this group would be the most likely to experience serious adverse effects caused by DSE. Another reason is that a stress test that is not highly sensitive for detecting inducible demand ischemia in patients with severe CAD would not be clinically useful and the test's evaluation could be discontinued before additional resources are wasted. The current study tested the feasibility of DSE in anesthetized patients with severe CAD, and its findings, therefore, justify further evaluation of the safety and diagnostic value of this test during general anesthesia in larger studies of patients with high and low risk of CAD.

A safe and accurate cardiac stress test that can be performed during general anesthesia would have several uses. First, in patients needing urgent noncardiac surgery, such a test might identify those who have an increased risk for cardiac complications and might benefit from more intensive postoperative care, thus guiding perioperative management and facilitating selective use of expensive resources.[18] No appropriate cardiac risk stratification is feasible in these patients,[6] although they have a markedly higher incidence of cardiac complications compared with patients undergoing elective surgery.[7] Intraoperative risk stratification based on ECG and TEE monitoring for ischemia is not a realistic alternative because spontaneous intraoperative ischemia is relatively rare[19] and plays a minimal role in perioperative cardiac complications.[20] Second, in patients needing semielective noncardiac surgery, cost-effectiveness and patient acceptance of DSE should be higher when performed during general anesthesia than in awake patients in the emergency room.[21] Cost-effectiveness should be higher because surgical patients with suspected cardiac risk obtain invasive cardiac monitoring by anesthesiologists as part of their anesthetic care, and high-quality TEE images can be obtained readily in anesthetized and tracheally intubated patients. To fully achieve these advantages, close cooperation between anesthesiologists and cardiologists experienced in DSE as well as the availability of an anesthesia induction room for performing DSE are required. Performing DSE after induction of anesthesia should make it more acceptable to patients,†† especially if they are in pain and experiencing psychological stress because of acutely needed surgery. Third, in patients undergoing cardiac surgery, a safe and accurate risk stratification test that can be performed during general anesthesia would also be valuable because evaluation of coronary reserve within a few hours after coronary artery bypass graft surgery would facilitate therapeutic management.[22]

Several limitations of DSE exist during general anesthesia: Imaging of apical segments is more difficult with TEE than with transthoracic echocardiography, even if multiple views are studied;[23] some protection from myocardial ischemia may be provided by the effects of anesthetic drugs[24] and ongoing medication with β-adrenergic antagonists;[25] and DSE immediately before surgery is not an option in patients needing elective surgery and who might benefit from previous coronary angioplasty or bypass surgery.

Limitations of the present study were its inability to assess the diagnostic value of the protocol because only patients with severe CAD were studied and the size of the study is insufficient to draw definitive conclusions regarding the safety of the protocol in anesthetized patients.

†† Wagner S, Mohr-Kahaly S, Nixdorff U, Kölsch B, Menzel T: Patients acceptance concerning dobutamine stress echocardiography [Abstract]. Circulation 1995; 92(Supp I):70

Three modifications of our DSE protocol might improve its utility. First, additional echocardiographic views should be obtained to provide a more inclusive view of the heart (*i.e.*, four-chamber and two-chamber views). Limiting the views to the midpapillary short- and long-axis views in the present study prevented us from imaging the apical segments of the heart in most patients. This limited echocardiographic imaging, together with a more extensive ECG monitoring, may have contributed to the finding that TEE sensitivity to detect ischemia was only slightly higher than ECG sensitivity, which contrasts with results from a previous study in awake patients.[26] Second, the dobutamine infusion protocol should be adjusted to standard protocols that use incremental dobutamine doses of 10, 20, 30, and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In the current study, we omitted the 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dose to limit study duration and prolongation of anesthesia. Given the slightly lower sensitivity of DSE to detect ischemia in the present study compared with previous studies in awake patients,[15] shortening of the dobutamine protocol may not be advisable in patients who may receive some protection from myocardial ischemia elicited by the effects of anesthetic drugs[24] and ongoing medication with β-adrenergic antagonists.[25] In contrast, prolonging the peak dobutamine dose may be considered if patients do not reach either the target heart rate or ischemia at the end of a standard dobutamine protocol.[27] Third, assessment of adverse outcomes of DSE during general anesthesia should be performed more comprehensively in future studies, such as by Holter ECG monitoring during a 2-day period, repeated sampling of cardiac enzymes, or daily transthoracic echocardiography.

The study shows that DSE is feasible in anesthetized patients with severe CAD. The lack of serious complications and the high sensitivity to detect inducible ischemia in this patient population provide a basis for further evaluation of the safety and diagnostic value of DSE in larger studies of patients with and without CAD.

The authors thank Olivia Dergeloo, R.N., for help with data collection and analysis, and Joan Etlinger for editorial assistance.

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