Dipyridamole-thallium / sestamibi before vascular surgery: A prospective blinded study in moderate-risk patients

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Purpose: This study assessed in a prospective, blinded fashion whether a reversible defect on dipyridamole-thallium (DTHAL) / sestamibi (DMIBI) can predict adverse cardiac events after elective vascular surgery in patients with one or more clinical risk factors.
Methods: Consecutive patients with one or more clinical risk factors underwent a preoperative blinded DTHAL / DMIBI. Patients with recent congestive heart failure (CHF) or myocardial infarction (MI) or severe or unstable angina were excluded.
Results: Eighty patients (78% men; mean age, 65 years) completed the study. Diabetes mellitus was the most frequent clinical risk factor (73%), followed by age older than 70 years (41%), angina (29%), Q wave on electrocardiogram (26%), history of CHF (7%), and ventricular ectopy (3%). The results of DTHAL / DMIBI were normal in 36 patients (45%); a reversible plus or minus fixed defect was demonstrated in 28 patients (36%), and a fixed defect alone was demonstrated in 15 patients (19%). Nine adverse cardiac events (11%) occurred, including three cases of CHF, and one case each of unstable angina, Q wave MI, non-Q wave MI, and cardiac arrest (successfully resuscitated). Two cardiac deaths occurred (2% overall mortality), one after a Q wave MI and one after CHF and a non-Q wave MI. The cardiac event rate was 14% for reversible defect and 9.8% without reversible defect (P = .71). The cardiac event rate was 12.5% (one of eight cases) for two or more reversible defects, versus 11.1% (eight of 72 cases) for fewer than two reversible defects (P = 1.0). The sensitivity rate of two or more areas of redistribution was 11% (95% CI, 0.3%-48%), the specificity rate was 90%, and the positive and negative predictive values were 12.5% and 89%, respectively.
Conclusion: Our study demonstrated no association between reversible defects on DTHAL / DMIBI and adverse cardiac events in moderate-risk patients undergoing elective vascular surgery. (J Vasc Surg 2000;32:77-89.)

Dipyridamole-thallium (DTHAL) and sestamibi (DMIBI) have both been shown to be useful tools for detecting coronary artery disease.[1-3] However, the predictive value of DTHAL and DMIBI for adverse cardiac events after vascular surgery remains controversial. An early report by Boucher and colleagues noted a 50% cardiac event rate when the reversible ischemia was demonstrated by means of DTHAL and a 0% event rate with a negative result of DTHAL.[4] These observations were supported by numerous subsequent studies,[5-12] including the report by Eagle and associates,[5] who found that the predictive value of DTHAL increased when it was combined with clinical risk factors (diabetes mellitus,

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Q wave on electrocardiogram, angina, history of congestive heart failure [CHF], age older than 70 years, and ventricular ectopy requiring medical therapy). Most of these studies, however, were limited by their retrospective nature, the lack of use of consecutive patients, or the results of the DTHAL not being blinded to all clinicians.

More recently, the usefulness of DTHAL and DMIBI as preoperative screening tools has come into question.[13-18] In a prospective study of consecutive patients undergoing vascular surgery, Mangano et al found no association between reversible ischemia on DTHAL and adverse cardiac events.[16] All clinicians were blinded to the DTHAL results.

We sought to determine whether the DTHAL / DMIBI was predictive of adverse cardiac events in moderate-risk patients undergoing elective vascular surgery. Similar to the study by Mangano et al, we enrolled consecutive patients, and the results of the DTHAL / DMIBI were blinded to all clinicians. Our study differs in that we specifically entered patients with one or more clinical risk factors, because these patients have been demonstrated, at our institution as well as others, to be at a higher risk for an adverse postoperative cardiac event.[5,13,14] In addition, we wanted to determine whether two or more reversible defects on DTHAL / DMIBI were predictive of adverse cardiac events.

METHODS

Eligible patients underwent a preoperative DTHAL (Veteran Affairs [VA] Greater Los Angeles Health Services Medical Center) or DMIBI (Harbor-UCLA Medical Center). The results of the scan were blinded to all clinicians. Thus, there were no alterations in medical, anesthetic, or surgical management on the basis of these scans. Our protocol was approved by the Harbor-UCLA and VA Medical Centers' Human Subjects Committees, and all patients gave informed consent.

Inclusion criteria. Consecutive patients scheduled for major vascular surgery at Harbor-UCLA Medical Center and the West Los Angeles (LA) VA Medical Center were prospectively examined by one of the investigators for potential eligibility during the 2-year study period, from June 1997 to June 1999. The study physician performed a routine history and examination and a review of medical records. To be eligible for enrollment, the patient had to have at least one clinical risk factor, as described by Eagle and associates,[5] and the planned procedure had to be elective to allow time to schedule a DTHAL / DMIBI. In addition, we limited the procedures to infrarenal aortic procedures, infrainguinal reconstructions, and extra-anatomic bypass grafting procedures. Carotid procedures were excluded because of the shorter length of the operation, the lower level of hemodynamic stress, and because adverse cardiac event rate in this procedure is considered to be lower than that of infrainguinal and aortic procedures. Suprarenal and thoracoabdominal procedures were excluded because these operations present considerably higher hemodynamic stress to the patient.

Rationale for inclusion criteria. Our two previous retrospective studies demonstrated a 0% adverse cardiac event rate after elective vascular surgery in patients with no clinical risk factors.[13,14] Conversely, in patients with one or more clinical risk factors, the cardiac event rate increased significantly, to 6.7% ($P < .05$) at the West LA VA Medical Center and to 7.5% ($P < .05$) at Harbor-UCLA Medical Center.[13-14] Eagle and colleagues similarly noted only a 3.1% event rate in patients with no clinical risk factors, a 15% event rate in patients with one or two risk factors, and a 50% event rate in patients with three or more risk factors.[5] Thus, patients with no clinical risk factors were considered to be at low cardiac risk and proceeded to vascular surgery without any preoperative cardiac evaluation.

Exclusion criteria. Some patients were excluded from the study. Patients with severe cardiac symptoms (NYHA class III angina, unstable angina, myocardial infarction (MI) within the last 6 months, and decompensated CHF were considered to be at high cardiac risk[13,14,16-19] and, thus, underwent the full preoperative cardiac examination as directed by the cardiology consultant. Other exclusion criteria included emergent (within 24 hours) surgery (ie, ruptured aortic aneurysm or acute limb ischemia) or urgent (within 72 hours) surgery (ie, progressive tissue loss or worsening rest pain), nonatherosclerotic vascular disease, procedures under strict local anesthesia, DTHAL / DMIBI within the last 6 months, and contraindications to receiving intravenous dipyridamole (allergy, severe pulmonary disease). Although patients undergoing endovascular aortic aneurysm repair were not specifically excluded, most of these patients were referred from outside institutions because of their high operative risk and, as such, had already undergone extensive cardiac testing. Patients who had undergone prior coronary artery bypass grafting (CABG) were enrolled only when the CABG procedure had been performed more than 6 months earlier, when they had not undergone a post-CABG DTHAL / DMIBI, and when, after the CABG, they still had a clinical risk factor.

Rationale for use of dipyridamole-thallium and sestamibi. Patients at the West LA VA Medical Center underwent a 1-day DTHAL, whereas patients at Harbor-UCLA Medical Center underwent a 2-day DMIBI, because these were the established nuclear cardiac imaging modalities at these institutions. The accuracy of DMIBI as a means of identifying coronary artery disease was established at Harbor-UCLA Medical Center in previous studies.[2,3] DMIBI differs from DTHAL in that technetium-99m is used as the perfusion tracer, instead of thallium-210. The shorter half-life of technetium-99m permits injection of higher doses, providing higher image count density. DMIBI undergoes minimal redistribution and has a radiation dosimetry that is superior to thallium-201. Previous studies have shown that DMIBI provides information regarding coronary artery disease that is comparable with DTHAL.

Technique of dipyridamole-thallium / sestamibi. Patients were given an intravenous injection of dipyridamole (0.56 mg / kg) in 4 minutes under the supervision of a physician. In the absence of systemic effects on blood pressure or heart rate, 3.0 to 4.0 mCi (depending on whether reinjection was necessary) of thallium-201 was given 3 minutes after the dipyridamole infusion (at the VA). Single photon emission computed tomographic (SPECT) images were obtained 15 minutes and at 3 to 4 hours after injection. At Harbor-UCLA Medical Center, 15 mCi of technetium 99m-sestamibi was given intravenously 3 minutes after the completion of the dipyridamole infusion. A rest study was performed the next day, with reinjection of technetium-99m.

Perfusion defects were classified as fixed or reversible and categorized by means of their location and the number of areas involved. Reversible defects were categorized as small, moderate, or large. The results of the study were recorded by a nuclear radiologist who was blinded to the clinical history of the patient.

Perioperative management. Perioperative management did not deviate from the standard approach at our institutions. Medical consultation was obtained preoperatively for optimization. Medical management was not altered because of the DTHAL / DMIBI, because the clinicians were blinded to the results. The addition of new medications (eg, nitrates, beta blockers) both preoperatively and postoperatively, was left to the discretion of the consulting internist with the surgical team and was based on the patient's clinical history and the results of the examination. The type of anesthetic used (general, epidural, spinal) and the use of a pulmonary artery catheter were likewise determined by the attending anesthesiologist and were based on clinical assessment. Cardiovascular medications, the use of a pulmonary artery catheter, and the anesthetic type were recorded.

A study physician assessed the patient postoperatively on a daily basis until discharge.

Data were collected prospectively by the investigator, who was blinded to the DTHAL / DMIBI results. After surgery, the patients were monitored in the intensive care unit for at least 24 hours postoperatively. Creatine phosphokinase (CPK) levels with myocardial isoenzymes were obtained every 8 hours on the first day and then every 12 hours for the next 4 days, or until discharge when the patient was sent home before 4 days. A daily electrocardiogram was obtained for the first 3 days. Additional serial CPK levels with MB were obtained for episodes of tachycardia, chest pain, hemodynamic instability, or shortness of breath that were suspected to be of cardiac origin.

Safety monitoring. An interim analysis was performed after 50 patients were enrolled to ensure patient safety. If this interim analysis demonstrated a strong association between a reversible defect on DTHAL / DMIBI and adverse cardiac events, the study would be halted. In addition, when an adverse postoperative cardiac event developed in a study patient, the results of the DTHAL / DMIBI would be unblinded at the clinicians' request.

Definitions of adverse cardiac events. An adverse outcome was noted by one of the investigators and was independently confirmed by two cardiologists blinded to the patient's DTHAL / DMIBI results. In the event of a disagreement, a consensus was used. An adverse cardiac event was defined as one occurring within 30 days of surgery or during the index hospital stay. Adverse postoperative cardiac events were defined as Q wave and non-Q wave MI, CHF, ventricular tachycardia, unstable angina, cardiac arrest, and cardiac death. MI was defined as meeting two of three criteria: (1) an elevation of the serum creatinine kinase MB isoenzyme level to more than 5%; (2) new Q wave on electrocardiogram or persistent changes in the sinus tachycardia-T wave; and (3) chest pain lasting longer than 30 minutes, or evidence of acute infarction at autopsy. CHF was defined as: (1) symptoms or signs of pulmonary congestion (shortness of breath or rales); (2) symptoms or signs of new left or right ventricular failure (cardiomegaly, S3 heart sound, jugular venous distention, or peripheral edema); (3) abnormal chest radi-

Table I. Cardiovascular risk factors (n = 80)

Risk factor	*Number of patients (%)*
Diabetes mellitus	59 (73)
History of smoking	62 (67)
Age older than 70 years	33 (41)
Currently smoking	26 (33)
Q wave on ECG	21 (26)
Angina	23 (29)
History of CHF	7 (9)
Ventricular ectopy	2 (3)

ECG, Electrocardiogram; *CHF,* congestive heart failure.

ography findings (vascular redistribution, interstitial, or alveolar edema); and (4) a change in medication involving at least diuretic treatment. Ventricular tachycardia was defined as consecutive premature ventricular contractions lasting more than 30 seconds, more than 30 beats, and resulting in hypotension less than 90 mm Hg. Unstable angina was defined as typical precordial chest pain consistent with ischemia, lasting 30 minutes or longer, unresponsive to nitroglycerin and rest, or a crescendo pattern of angina occurring at a lower threshold or higher frequency. Cardiac arrest and cardiac death were defined as arrest or death from a dysrhythmia or CHF caused by a cardiac complication.

Statistical analysis. Potential univariate correlates of adverse cardiac outcome were identified by using the chi-square or Fisher exact tests when appropriate. Continuous variables were compared with the use of the Wilcoxon rank-sum test. Other factors compared included sex, history of smoking, history of CABG, Eagle risk factors, type of vascular procedure (aortic versus nonaortic), findings on DTHAL/DMIBI (normal, fixed or reversible defect), the presence of two or more reversible defects on DTHAL/DMIBI, the number of reversible defects, serum creatinine levels, use of perioperative nitrates and/or beta blockers, type of anesthetic (general, spinal, epidural), and the intraoperative use of a pulmonary artery catheter. A *P* value of less than .05 was considered statistically significant. No adjustment was made for multiple comparisons. All statistical comparisons were performed with the SAS statistical software package (SAS Institute, Cary, NC).

RESULTS

Ninety-one patients were enrolled in the study. Of these, 11 patients were excluded before the completion of the DTHAL/DMIBI, leaving 80 patients (50 at Harbor-UCLA Medical Center and 30 at the West LA VA Medical Center). In four cases, a new cardiac event developed in the patient (CHF in two patients, and one patient each with unstable angina and non-Q wave MI) after they signed the consent but before the DTHAL/DMIBI was performed. In four cases, patients either failed to keep the appointment for the DTHAL/DMIBI or decided after signing the consent that they no longer wanted to participate in the study. In two cases, the patient was deemed to be at high cardiac risk at the time of preoperative evaluation by internal medicine (one patient) or by anesthesiology (one patient), because the patients' symptoms of angina were more severe than originally appreciated. Wheezing developed in one patient after injection of dipyridamole, and the study was, therefore, cancelled.

Results of dipyridamole-thallium/sestamibi. Chest tightness developed in one patient during DTHAL, but the study was successfully completed. No other patient had a complication from DTHAL or DMIBI. The results of DTHAL/DMIBI were normal in 36 patients (45%) and demonstrated a reversible defect plus or minus fixed defect in 29 patients (36%) and a fixed defect alone in 15 patients (19%). Of the 29 patients with a reversible defect, 21 patients had one area of reversible defect, seven patients had two areas of reversible defects, and one patient had three areas of reversible defects.

The mean age of the 80 patients was 65 years. Seventy-eight percent of the patients were men. Cardiovascular risk factors are listed in Table I. The mean number of clinical risk factors per patient was 1.8 (range, 1-4). There were 65 infrainguinal procedures (femoropopliteal, tibial, or pedal), seven procedures for aortoiliac occlusive disease, six infrarenal aortic aneurysms, one iliofemoral bypass grafting procedure, and one axillofemoral bypass grafting procedure. Sixty patients (75%) underwent general anesthesia, 18 patients (22%) underwent epidural anesthesia, and five patients (6%) underwent spinal anesthesia (some patients had both general and epidural anesthesia).

There were nine (11.2%) adverse postoperative cardiac events, including three in patients with CHF and one each in patients with unstable angina, Q wave MI, non-Q wave MI, or cardiac arrest (successfully resuscitated). Two additional patients died of a cardiac etiology (overall cardiac mortality rate, 2.5%). CHF and a non-Q wave MI developed in one patient. The other patient had a Q wave MI.

Primary analysis. The adverse cardiac event rate was 9.8% for patients without a reversible defect on DTHAL/DMIBI and 13.8% for patients with a

Table II. Dipyridamole-thallium / sestamibi results in patients with adverse cardiac events

Event	*DTHAL results*	*DMIBI results*
1. Unstable angina		Normal
2. CHF	Moderate inferior reversible defect Small anteroapical reversible defect Small inferior fixed defect	
3. Q wave MI		Small anterospetal fixed defect Moderate apical fixed defect
4. CHF		Moderate apical fixed defect Large inferior / posterior fixed defect
5. Non-Q wave MI, CHF, death	Moderate inferior reversible defect	
6. Cardiac arrest	Small to moderate inferior reversible defect	
7. Non-Q wave MI		Normal
8. CHF	Normal	
9. Q wave MI, death		Small inferior reversible defect

DTHAL, Dipyridamole-thallium; *DMIBI,* sestamibi; *CHF,* congestive heart failure; *MI,* myocardial infarction.

reversible defect (P = .75; odds ratio [OR], 1.5; 95% CI, 0.4-5.9). The event rate was 8.3% for patients with normal DTHAL / DMIBI results and 13.3% for those with a fixed defect alone (P = .7). There was also no difference in event rate between patients with normal scan results (8.3%) and those with abnormal results (fixed or reversible) on the DTHAL / DMIBI (13.6%; P = .5; OR, 1.7; 95% CI, 0.4-7.5). The cardiac event rate was 14.2% (three of 21) for patients with one reversible defect, 14.3% (one of seven) for patients with two reversible defects, and 0% for patients with three reversible defects (one patient; P = 0.5). The cardiac event rate was 12.5% (one of eight) for patients with two or more reversible defects, versus 11.1% (eight of 72) for fewer than two reversible defects (P = 1.0; OR, 1.1; 95% CI, 0.1-10.5; Tables II and III). Both cases of cardiac death occurred in patients with one area of reversible defect. Thus, the cardiac death rate was 0% for patients with no reversible defects, versus 6.8% for patients with a reversible defect (P = .13). The cardiac death rate was 2.7% for patients with one or no reversible defects, versus 0% for patients with two or more reversible defects (P = 1.0). The sensitivity rate, specificity rate, and positive and negative predictive values (with 95% CIs) for a normal study and for one and two reversible defects are listed in Table IV. Of the three patients with completely normal DTHAL / DMIBI results, two underwent infrainguinal reconstruction, and one underwent aortic surgery. There was no correlation between intraoperative adverse events (hypotension, bleeding) and the subsequent development of adverse cardiac events.

Secondary analysis. We also performed analysis for adverse cardiac events, excluding CHF (n = 6) as an adverse event (because some may argue that CHF is not ischemic event). For this analysis, there was no difference in adverse events between patients with normal DTHAL / DMIBI results (5.5%) and abnormal (fixed or reversible) scan results (9.1%; P = .6; OR, 0.6; 95% CI, 0.1-3.4), and there was no difference in adverse events between patients with reversible ischemia (10.3%) and patients with no reversible ischemia (normal or fixed; 5.9%; P = .7; OR, 0.5; 95% CI, 0.1-2.9). There was no difference in the cardiac event rate between patients with one or no reversible defects on DTHAL / DMIBI (8.3%) and patients with two or more reversible defects (0%; P = 1.0).

Table III. Adverse cardiac event rate with dipyridamole-thallium / sestamibi results

DTHAL/DMIBI result	*Cardiac event rate*
Normal	3 / 36 (8.3%)
Normal or fixed	5 / 51 (9.8%)
Fixed alone	2 / 15 (13.3%)
Reversible defect ± fixed	4 / 29 (13.8%)
≥ 2 reversible defects	1 / 8 (12.5%)
≥ 3 reversible defects	0.1 (0%)

DTHAL, Dipyridamole-thallium; *DMIBI,* sestamibi.

The adverse cardiac event rate was significantly higher for aortic procedures (four of 13, 31%) than for infrainguinal / extra-anatomic procedures (five of 67, 7.5%; P = .03). Because the event rate was higher in the aortic procedure group, we analyzed the predictive value of DTHAL / DMIBI in this subgroup. The cardiac event rate was 33% (three of nine) for patients with reversible ischemia and 25% (one of four) for patients without reversible ischemia

Table IV. Predictive value of dipyridamole-thallium / sestamibi (with 95% CIs)

DTHAL/DMIBI result	*Sensitivity*	*Specificity*	*(+) Predictive value*	*(–) Predictive value*	P *value*
Normal	33% (7% to 70%)	53% (41% to 65%)	8% (2% to 22%)	86% (73% to 95%)	.5
≥1 reversible defect	44% (14% to 79%)	65% (53% to 76%)	14% (4% to 32%)	90% (79% to 97%)	.72
≥2 reversible defects	11% (0.3% to 48%)	90% (81% to 96%)	12.5% (0.3% to 53%)	89% (79% to 95%)	1.0

DTHAL, Dipyridamole-thallium; *DMIBI,* sestamibi.

Table V. Univariate analysis for adverse cardiac event

Factor	*Cardiac event (n = 9)*	*No cardiac event (n = 71)*	P *value*
Male sex	7 (78%)	55 (77%)	1.0
History of smoking	7 (78%)	46 (66%)	.7
Current smoker	4 (44%)	22 (31%)	.5
Prior coronary artery bypass graft	2 (22%)	8 (11%)	.4
Harbor-UCLA patient	5 (56%)	45 (63%)	.7
West LA VA patient	4 (44%)	26 (37%)	.7
Aortic procedure	4 (44%)	9 (13%)	.03
Perioperative nitrate	1 (11%)	8 (11%)	1.0
Perioperative beta-blocker	3 (33%)	26 (37%)	1.0
General anesthesia	7 (78%)	54 (76%)	1.0
Spinal anesthesia	0	5 (8%)	1.0
Epidural anesthesia	3 (33%)	15 (21%)	.4
Pulmonary artery catheter	2 (22%)	16 (22%)	1.0
Intraoperative nitrate	3 (33%)	14 (20%)	.4

(*P* = 1.0; OR, 1.5; 95% CI, 0.1-21).

No statistically significant associations was revealed by means of the univariate analysis of other clinical factors (Table V). Because all patients had at least one clinical risk factor, the univariate analysis of individual clinical risk factors is not reported. The mean number of clinical risk factors per patient in patients with an adverse cardiac event was 1.4, versus 1.9 for patients without an event (*P* = .18). The mean operative time for patients with a cardiac event was 314 minutes versus 311 minutes for patients without a cardiac event (*P* = .9).

DISCUSSION

This study demonstrated no association between a reversible defect on DTHAL / DMIBI and adverse postoperative cardiac events in moderate-risk patients undergoing elective major vascular surgery. A reversible defect had a sensitivity rate of 44% and a positive predictive value of only 14% for an adverse cardiac event. Two or more reversible defects had a sensitivity rate of only 11% (95% CI, 0.3-48), a specificity rate of 90%, a positive predictive value of 12.5%, and a negative predictive value of 89%. Of the nine adverse cardiac events, 56% occurred in patients with normal results on DTHAL / DMIBI or with a fixed defect. In fact, the adverse cardiac event rate was 8.3% in patients with normal DTHAL / DMIBI scan results, which was not significantly different from the event rate in patients with a fixed defect (13.3%) or in patients with a reversible defect (13.8%). There was also no difference in event rates between patients with normal scan results (8.3%) and patients with abnormal (fixed or reversible) scan results (13.6%; *P* = .5). The OR was 1.7 (95% CI, 0.4-7.5). Whether this OR is clinically significant is debatable. Although some authors have noted a correlation between a fixed defect and an adverse cardiac event, most cardiologists would not recommend canceling surgery, coronary arteriography, or additional cardiac testing because of a fixed defect. When excluding CHF as an adverse event, there was still no relationship between adverse events and abnormal scan results or reversible ischemia. The overall adverse cardiac event rate of 11.2% is comparable with what we and others have previously observed in patients with one or more clinical risk factors. However, the adverse cardiac event rate was significantly higher in patients who underwent aortic surgery (31%) than in patients undergoing nonaortic surgery (7.5%; *P* = .03). The analysis of the aortic subgroup also showed no cor-

Table VI. Selected studies demonstrating association between dipyridamole-thallium redistribution and adverse cardiac events

Author (y)	*DTHAL blinded*	*Prospective*	*Consecutive patients*	*Sensitivity*	*Specificity*	*(+) Predictive value*	*(–) Predictive value*	P *value*
Boucher et al (1985)[2]	No	No	No	100%	80%	50%	100%	.0001
Cutler, Leppo (1987)[4]	No	Yes	Yes (aortic)	100%	69%	23%	100%	.001
Eagle et al (1989)[3]	No	No	Yes*	83%	66%	30%	96%	< .0001
Vanzetto et al (1996)[9]	Yes	Yes	Yes† (aortic)	80%	77%	50%	93%	< .0001

*Study reviewed consecutive patients referred to cardiology for DTHAL, not consecutive patients scheduled for surgery.
†Study enrolled consecutive patients with two or more clinical risk factors.
DTHAL, Dipyridamole-thallium.

relation between a reversible defect on DTHAL / DMIBI (P = 1.0) and an adverse cardiac event. Although there is no evidence in the present study of a correlation between a reversible defect and a cardiac event in the aortic subgroup, the small number of aortic surgery patients enrolled (n = 13) and the wide 95% CI for the OR (0.1-21) raise the possibility of a type-II error.

The lack of predictive value of DTHAL / DMIBI in the present study contradicts earlier reports (Table VI). However, in most instances, these reports were either retrospective, did not involve consecutive patients, or the results of the DTHAL were not blinded.[4-11] In a retrospective review of 254 vascular patients referred to a nuclear cardiology laboratory, Eagle and colleagues[5] noted that DTHAL results were best used when combined with the clinical risk factors. In patients with one or two clinical risk factors, Eagle et al noted a 29.6% cardiac event rate in patients with a reversible defect on DTHAL, versus only a 3.2% event rate in patients with no reversible defect. Because the DTHAL results were not blinded, 44 patients had the surgery cancelled or postponed because of abnormal DTHAL results and were not included in the analysis.[5] In a prospective study of 116 consecutive patients undergoing aortic surgery, Cutler and Leppo[6] noted that all postoperative MIs and deaths occurred in the 54 patients with a reversible defect on DTHAL. However, because the results of the DTHAL were not blinded, 20 patients with abnormal DTHAL results underwent preoperative cardiac catheterization. One patient sustained a cerebrovascular accident after catheterization. Another patient died of a ruptured abdominal aortic aneurysm while awaiting coronary revascularization. Six patients underwent CABG. One of these patients died 3 days later of hemorrhagic pancreatitis.[6] Vanzetto et al[12] prospectively studied 134 consecutive high-risk patients (those with two or more clinical risk factors) undergoing aortic surgery. The DTHAL results were blinded. The major cardiac event rate (MI and cardiac death) was 23% in patients with a reversible defect and 1% in patients without a reversible defect (P < .01), and the overall cardiac event rate (including CHF, unstable angina, and ventricular arrhythmias) was 50% in patients with a reversible defect and 7% in patients without a reversible defect (P < .0001).[12] The percentage of patients with reversible ischemia (36%) in the present study is identical to that noted by Vanzetto et al.[12]

Our findings are supported by several recent studies (Table VII). In a prospective study of 60 consecutive patients, Mangano and colleagues[16] found no association between DTHAL redistribution and adverse cardiac outcome. Similar to the current study, they noted that 58% of severe perioperative cardiac ischemic episodes occurred in patients without redistribution defects. The sensitivity of DTHAL for adverse cardiac outcome was only 46%, and the positive predictive value was only 27%.[16] Because the DTHAL results were blinded, vascular surgery was neither delayed nor modified, preoperative cardiac catheterization was not obtained, and medical and anesthetic care were not changed by the DTHAL results.[16] In two retrospective studies, de Virgilio and associates found that DTHAL and DMIBI redistribution were not predictive of adverse cardiac events in patients without severe cardiac symptoms (recent MI, unstable angina, decompensated CHF).[13-14] The positive predictive values of DTHAL and DMIBI for adverse cardiac events were 6% and 10%, respectively.[13-14] In a prospective study of 457 consecutive patients undergoing abdominal aortic surgery, Baron et al also found that DTHAL results did not accurately predict adverse cardiac outcomes.[15] The best correlates of cardiac complications were definite clinical evi-

Table VII. Studies demonstrating no association between dipyridamole-thallium / sestamibi redistribution and adverse cardiac events

Author (y)	*DTHAL blinded*	*Prospective*	*Consecutive patients*	*Sensitivity*	*Specificity*	*(+) Predictive value*	*(–) Predictive value*	P *value*
Mangano et al (1991)[12]	Yes	Yes	Yes	46%	66%	27%	82%	.43
Seeger et al (1994)[14]	No	Yes	Yes (aortic)	40%	50%	11%	84%	.47
Baron et al (1994)[11]	No	Yes	Yes (aortic)	36%	65%	19%	81%	.9
Stratmann et al (1995)[13]	No	Yes	Yes*	33%	73%	6%	96%	.7
de Virgilio et al (1996)[10]	No	No	No	25%	80%	10%	92%	1.0
de Virgilio et al (1996)[11]	No	No	No	40%	43%	6%	89%	.64
Present study	Yes	Yes	Yes†	44%	65%	14%	90%	.72

*Enrolled consecutive patients with either stable angina or one or more risk factors for coronary artery disease.
†Enrolled consecutive patients with one or more Eagle risk factors, aortic or infrainguinal surgery.
DTHAL, Dipyridamole-thallium.

dence of coronary artery disease and an age older than 65 years.[15] Stratmann et al noted a 3% cardiac event rate in 87 patients with normal DMIBI results and a 5% event rate in the 110 patients with abnormal DMIBI results (*P* = not significant).[17] Of the 110 patients with abnormal DMIBI results, 53 had reversible defects, and the cardiac event rate in this subgroup of patients was only 6% (*P* = not significant versus normal or fixed defect).

Similar to the study of Mangano et al, the current study was prospective, the DTHAL / DMIBI results were blinded, and consecutive patients were enrolled. However, the present study differed in several respects. First, to try to optimize the results of the DTHAL / DMIBI, we only included patients with clinical (Eagle) risk factors, because these patients are at moderately increased risk for an adverse cardiac event. Second, we enrolled patients at two institutions to get a broader patient population with varied cardiac risk factors. On the basis of our previous studies, we noted that diabetes mellitus was more prevalent in patients undergoing vascular surgery at Harbor-UCLA Medical Center (50%) than at the West LA VA Medical Center (33%), whereas more patients at the West LA VA Medical Center were older than 70 years (32% vs 14%), had a Q wave on EKG (31% vs 14%), and had a history of CHF (12% vs 6%).[13,14] Third, we used SPECT imaging for the DTHAL / DMIBI, which is thought to increase the sensitivity for reversible defects.[20] We used DTHAL at Harbor-UCLA and DMIBI at the West LA VA Medical Center, because these were the established nuclear cardiac imaging modalities at these respective institutions. Although this is a potential weakness of our study, the similarity of these two imaging techniques for detecting coronary artery disease has been previously established. Finally, we analyzed our results both by means of the presence of a reversible defect and by using the number of reversible defects. Despite these differences, the results from the present study are similar to those of Mangano et al.

The discrepancy between the present study and earlier studies that show a favorable predictive value for DTHAL / DMIBI may be explained as follows. In earlier studies showing DTHAL benefits (other than the study by Vanzetto et al), the DTHAL / DMIBI results were not blinded. As such, medical, surgical, and anesthetic treatment may have been altered in patients with reversible defects. In some instances, surgery was cancelled, or the surgery was postponed to obtain coronary arteriography. In several earlier studies, the data were not collected prospectively, and therefore, some adverse cardiac events may have been missed. Patients enrolled in most earlier studies were not consecutive patients, but rather select patients who were referred for nuclear cardiac imaging. Consequently, a selection bias may have occurred. Most prior studies did not specifically enroll moderate-risk patients, but rather included patients without a clinical risk factor. An exception was the study by Vanzetto et al, which enrolled patients with at least two cardiac risk factors similar to the risk factors described by Eagle and colleagues. In fact, in their study, patients had a mean of 4.1 risk factors, which may explain the high reported cardiac event rate (22%).[12] Another difference is that most prior studies used planar imaging, whereas SPECT imaging was used in the present study. However, the inclusion of only moderate-risk patients and the use of SPECT in the current study should have increased the positive predictive value and the sensitivity of DTHAL, which was not the case. The type of vascular operation studied differs

between series. Many earlier studies have focused solely on aortic cases, whereas the current study included both aortic and infrainguinal procedures. We believed this was justified, because Krupski et al[21] showed that the adverse cardiac event rates for infrainguinal procedures are at least as high as those for aortic procedures. As noted in our results, however, we detected a statistically higher adverse cardiac event rate in the patients undergoing aortic procedures. Although no predictive value of DTHAL / DMIBI was detected by means of our analysis in the small subgroup of aortic patients, the OR was 1.5, with a 95% CI of 0.1 to 21. Another difference between studies involves the definition of adverse end points. In the present study, we used CHF as one of the adverse end points, as has been done in numerous other studies.[15,16,18] Other authors have argued that CHF may occur because of iatrogenic fluid overload and have thus not included CHF as an end point.[5-7] Nevertheless, in the present study, there was still no correlation between reversible ischemia on DTHAL / DMIBI and adverse cardiac events when CHF was excluded. The lack of predictive value of DTHAL / DMIBI may be explained by the unexpected physiologic changes during the perioperative period (eg, sudden hypoxia, excessive blood loss) that are not necessarily predictable by means of preoperative criteria.

Over and above the question of whether DTHAL / DMIBI is a sensitive test for predicting adverse cardiac events, one must consider the risks of extended cardiac evaluation and the cost. de Virgilio et al[14] reported that obtaining a DTHAL delayed time to surgery from 12 days to 18 days ($P = .0003$) without altering the cardiac event rate. In patients undergoing CABG before peripheral vascular surgery, Hertzer et al noted a mortality rate after CABG of 5.3%, and in the subset of patients with aortic aneurysms, 2.9% sustained a rupture of the aortic aneurysm after CABG and died.[22]

Massie et al noted that the risks of extended cardiac evaluation and treatment did not produce any improvement in either the perioperative or long-term survival rate.[23] This latter study is particularly noteworthy because the authors previously advocated the use of DTHAL. Taylor et al noted no operative deaths and no fatal MIs in 285 consecutive elective major vascular procedures performed over 1 year.[19] In their study, only patients with severe cardiac symptoms (unstable angina, severe CHF, uncontrolled arrhythmia), who represented only 5.8% of the study group, underwent extended cardiac testing, which consisted of proceeding directly to coronary angiography. We have previously advocated a similar approach.[13,14] Finally, the cost of DTHAL is an important issue. Bry et al[24] estimated an average cost of $3092 per patient for DTHAL screening and cardiac intervention, and a cost of $181,000 per MI prevented. They further noted that most postoperative MIs were clinically insignificant.

Potential weaknesses of the present study should be noted. The number of patients enrolled was fewer (80 patients) than the study by Vanzetto et al (134 patients). Nevertheless, the present study is the second largest prospective blinded study in moderate-risk patients. For one or more areas of reversible ischemia, the OR for an adverse cardiac event was 1.5, with a 95% CI ranging from 0.1 to 5.9. For two or more areas of ischemia, the OR was 1.1 (95% CI, 0.1-10.5). This finding is important, because most cardiologists would only recommend coronary angiography for patients with two or more areas of reversible ischemia. The low sensitivity rate (11%) of two or more reversible defects for adverse cardiac events in the present study (with a 95% CI of 0.3 to 48) makes it highly unlikely that adding more patients to the study would increase the sensitivity rate of the test to more than 50%. Another study weakness is that we did not control for the use of perioperative medications or intraoperative monitoring with pulmonary artery catheters, although these variables did not affect the cardiac event rate on univariate analysis. Finally, 11 patients were excluded from the study before obtaining the DTHAL / DMIBI; four of these patients sustained an adverse cardiac event before obtaining the scan. It is unknown whether the addition of these patients would have altered our results.

In summary, our findings support other recent studies that demonstrate no correlation between a reversible defect on DTHAL / DMIBI and an adverse cardiac event after elective vascular surgery. Given the added time and expense incurred in obtaining a preoperative DTHAL / DMIBI and its lack of predictive value, we would recommend reassessing its use as a tool for preoperative cardiac assessment before elective major vascular surgery. Studies are now underway that will help us to determine whether preoperative coronary revascularization will lower perioperative cardiac morbidity and mortality.

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DISCUSSION

Dr William C. Krupski (Denver, Colo). I would like to thank the Program Committee for asking me to discuss Dr de Virgilio's presentation this morning, and I compliment him on a wonderful job. Moreover, he forwarded the manuscript to me well in advance of this meeting, so I had plenty of time to study it. The manuscript is particularly well written, and I commend it to you all when it appears in print, as I am sure it will.

Dr de Virgilio has followed an important principle of clinical research. He and his colleagues at Harbor-UCLA developed a hypothesis regarding the utility of preoperative dipyridamole-thallium / sestamibi scans to assess cardiac risk before vascular surgery based on two retrospective studies that have already appeared in the literature (De Virgilio et al. Ann Vasc Surg 1996;10;325-9 and de Virgilio et al. J Vasc Surg 1998;32:275-80). However, as we know, retrospective studies—like post hoc analyses of prospective trials—are hypothesis seeking, not hypothesis proving. Today, he has presented the "second-best" way to prove a hypothesis; namely, a prospective, blinded study of consecutive patients. The only better method of obtaining such proof is the large, (often multicenter) *randomized* prospective trial, showing the benefit (or lack thereof) of an intervention in groups of matched patients. In brief, the Harbor-

UCLA group has shown that DTS was essentially ineffective in accurately predicting postoperative adverse cardiac events. A "negative" study was somewhat helpful, but the negative predictive value was only 89%, so as many as one in 10 of our patients with a "normal" scan may experience an adverse postoperative cardiac event. Even worse, the positive predictive value was only 12.5%, so a positive scan is next to useless for identification of patients at most risk for untoward outcomes. Think of the money and effort wasted if all patients with positive scans had gone on to have additional tests, such as cardiac catheterizations!

I have very few criticisms of Dr de Virgilio's study. Obvious concerns arise about the potential for Type II statistical errors because of the relatively small number of patients. It is not clearly stated whether *all* treating physicians (including anesthesiologists) were blinded to scan results. A uniform anesthetic technique, perhaps including the routine use of perioperative beta blockers, might have made this a "cleaner" study. Routine ECGs and enzymes were obtained for only the first three postoperative days, whereas we have previously shown that many MIs occur on days 5 through 7 (Krupski et al. J Vasc Surg 1992;15:354-65). Finally, some might denounce excluding the highest risk patients and combining results of two different tests performed by different individuals at two different institutions. Personally, I think these are all minor weaknesses.

Enthusiasm for DTS peaked in the last decade, when groups (mostly from Boston schools) showed favorable results of preoperative stress scans. However, there is an informative table in the manuscript, indicating that no fewer than seven published studies from the 1990s showed no predictive value of redistribution on stress scans. It is always delightful to discuss a paper that confirms one's own biases, and I was fortunate to participate in one of the earliest doubting reports cited by Dr de Virgilio when I had the pleasure of working at the San Francisco VAMC. Like today's presentation, in that study, treating physicians were blinded to scan results, and over half of postoperative ischemic cardiac events occurred in patients *without* redistribution defects (Mangano et al. Circulation 1991;84:493-502). Since our publication, the number of reports and patients showing that scans are of little benefit has increased dramatically, including one trial in Paris involving 457 patients. (Baron et al. N Engl J Med 1994;330:663-9).

Despite all this overwhelming evidence—including today's results—that DTS is not what it was initially cracked up to be, referring physicians, consulting cardiologists, anesthesiologists, and others continue to demand these tests. Dr de Virgilio, how do we reverse this behavior? How do we convince our colleagues that stress scanning is neither accurate nor cost-effective? Do you plan to perform a randomized controlled trial comparing the outcomes of patients having scans with those managed without them, or are your present data sufficiently persuasive? Finally, what is your current practice with respect to preoperative cardiac evaluation; are there still patients who warrant scans or do you recommend cardiac angiography as a primary investigation in the highest risk group?

I enjoyed this presentation very much, and I hope the excellent manuscript makes as important an impact as it deserves.

Dr Christian de Virgilio. First of all, I wanted to thank Dr Krupski for his comments, and I wanted to say that he and the perioperative ischemia group have been a source of inspiration for me as they laid the foundation for this work back in 1990.

The first question was how do we reverse the behavior of our colleagues in cardiology. That was sort of my initial intent because despite your study and the study of others, the cardiologists still insisted on obtaining a DTHAL or DMIBI prior to approval of the patient going to the OR. The kicker that was thrown in by cardiology was that Eagle and colleagues indicated that the DTHAL was useful in patients with one or more Eagle risk factors.

So in the design of the study we added the element of including only patients who we have previously demonstrated to be at higher cardiac risk. That is, in our own institution patients without an Eagle risk factor had essentially a 0% adverse cardiac event rate, whereas those with one or more had an increased cardiac event rate.

The second thing was that our study used SPECT scanning instead of planar imaging, and SPECT has been reported to have a much greater sensitivity for picking up areas of ischemia. So by including patients with only one or more risk factors and including SPECT scanning as the basis of our study, we were hoping to improve both the sensitivity and the positive predictive value of the test, neither of which proved true in this study.

So to answer your question, I think it is a matter of going to cardiologists at your individual institution and educating them with regard to what is out there in the literature. We have done that ourselves at Harbor UCLA in the form of multidisciplinary conferences. We now have a better ability to convince them not to obtain this test.

As far as performing a randomized controlled trial, I personally feel convinced at this point that the DTHAL and the DMIBI really do not have any value as far as predicting adverse events. There is literature, particularly the group of Stratmann and colleagues, that demonstrated that the dipyridamole Sestamibi is useful in predicting who is going to have a cardiac event long term. So there may be some utility in that respect.

The thing to point out is that even though our study was a small number, when one looked statistically at the 95% CI for the sensitivity of two or more areas of ischemia, that 95% CI interval went from 0.3% to only 48%. So we felt fairly confident that at best, two or more areas of ischemia were a coin toss as far as the sensitivity.

We await your future studies, that is, the CARP trial, as far as looking at whether preoperative cardiac revascularization will, in fact, benefit these patients. As far as my own current practice, we basically have adopted the policy of the group in Oregon in which only patients who have severe obvious cardiac symptoms undergo preoperative evaluation, and in those instances basically I would recommend going directly to catheterization.

In other patients who do not have any overt symptoms, my feeling is the event rate is too low and that putting patients through three interventions, that is, a cardiac catheterization, a PTCA, and/or a coronary bypass followed by a vascular surgery, is going to be a greater risk than simply proceeding with the vascular operation.

Thank you again, and I want to thank my colleagues as well as the American Heart Association, who sponsored this study.

Dr Kraiss. Very nice study, and I applaud you on going to all the work to actually conduct a prospective study. However, if you look at your raw numbers, your patients who had some abnormality on DTHAL had almost a 60% to 100% increase in cardiac events compared with the patients who had normal scans in a larger study that is likely to become statistically significant.

I would like to propose to you another use of the scan: that is using the scan to help decide whether to do an otherwise completely elective operation and to counsel the patient. We take a patient with a 5-cm aneurysm, for instance, and we quote the patient a less than 5% morbidity and mortality based on many other studies. On the other hand, your patients who had a defect on deep DTHAL had between a 10% and 15% incidence of cardiac event rate.

So I would propose to you that the DTHAL might actually help you counsel the patient, and in a patient who has a 5-cm aneurysm who has a fixed or reversible defect on dipyridamole-thallium scan, that patient might be the one for whom you say we need to wait. We may let this aneurysm grow because the risk-benefit analysis of doing a completely elective operation does not favor intervention at this point. I think the same thing would apply to patients who are being considered for elective operations for claudication.

So I think there is some utility in this test. Even if you decide not to aggressively pursue coronary intervention to make the patient a better candidate for surgery, I think it can help you in counseling the patient about whether or not to even do the surgery.

Dr de Virgilio. I appreciate your comments, and I would agree with you if we had found that the negative predictive value of our test was worthwhile, but as I pointed out in our data, five of the nine adverse events occurred in patients with a fixed defect or a normal defect. The negative predictive value was 89%, which means that basically, our cardiac event rate in patients without redistribution was 11%.

So I really do not know what to tell a patient because even with a normal scan I do not feel reassured; in fact, as a case in point, last week we had a patient with a renal artery reconstruction. The patient himself had read about the DTHAL and insisted that one be done. It was normal, and then intraoperatively, the patient dropped his ST segments and had a positive troponin.

So I agree with you that in theory that would be good, but the study just does not bear it out as far as the negative predictive value.

Dr Dalman. That was a nicely designed study. It was well presented. I just do not believe that the data as described support the conclusion that preoperative cardiac "stress" testing should be abandoned. That conclusion seems a little premature based on this presentation.

You combined different cardiac risks in your relatively modest series (leg bypass and aortic aneurysm patients). Bill Krupski has previously shown us (before this meeting) that the leg bypass patient is clearly at greater risk for perioperative cardiac events that the AAA patient. So in mixing these patients together you may have obscured the value of testing for the truly "high-risk" patient. In addition, you used two different testing modalities at two different medical centers to reach your conclusions about the "at risk" vascular patient. Several potential sources of error are inherent in mixing such testing procedures and venues. In extrapolating these data for our own practice, I also note that the mean age of your patients (65 years) is significantly younger than ours for any type of arterial reconstructive procedure.

So in our particular case, where we have one colleague in nuclear medicine with an interest in this area reviews all of our studies, I believe our experience supports a different conclusion. That is, we find stress testing provides useful information regarding surgical decision making in our high-risk patient population. We believe that despite the results of this well-designed and carefully analyzed study, it remains to be proven whether this type of preoperative testing should "abandoned" at the current time.

Dr de Virgilio. I thank you for your comments. My response to that would be the following: as Dr Krupski has looked at in the past, patients who undergo infrainguinal reconstruction have at least as high a perioperative cardiac event rate as do patients with aortic surgery, and for that reason we included both of them. We did not include carotid patients because there is evidence in the literature that they may have a lower event rate.

As far as the mixing of the patients, I recognize that that is certainly a weakness of the study. However, our institution at Harbor UCLA was one of the early participants in the cardiolite study that established our center as a center of excellence for the use of the dipyridamole Sestamibi.

So I understand that there are some reservations; nevertheless, in our patients and in our population, this test has not been shown to benefit.

I would further add that ours is not the first study, but one of several studies now including the study by Mangano et al and the study by Baron and colleagues in the *New England Journal of Medicine* that included 457 patients who underwent aortic surgery in which the dipyridamole-thallium had no predictive value.

Dr Mitchell. I congratulate you on your presentation and your persistence in trying to educate us about which patients need a cardiac evaluation. One of the acknowledged problems with these perfusion scans is if you have patients who have homogenous malperfusion, and the lesions that can be frequently missed are left proximal, left main disease, and diffuse three-vessel disease.

So my question is, first, if in your reporting they looked at the ejection fraction before and after administration of the drug because some scanners can actually show that if you get global hypocontractility that in spite of fairly diffuse perfusion suggests that there is diffuse disease.

Then second, of the patients with normal scans who had cardiac events, how many of those had left main disease? Those are the patients that I really worry that we will miss.

Dr de Virgilio. To answer your question, we did not specifically look at whether there was a change in ejection fraction in our study.

Second, as part of the study protocol, if a patient developed a cardiac event after the event occurred, we allowed the cardiologists, if they so desired, to "unblind" the results of the study in case that would help them, but in no instance did any of these nine patients subsequently undergo an immediate cardiac revascularization.

So I do not really have the data to tell you whether they had left main disease, but I think the important thing of note is, again, the issue that five of the nine had a normal scan or a fixed defect. And, in fact, one of the cardiac deaths had a very small reversible defect on the scan. In talking to the cardiologists in a post hoc review, they would never have intended to perform a coronary revascularization or coronary angiography on this patient based on that scan, and yet within 24 hours of the aortic surgery the patient had a massive MI and expired.

Dr Joseph Rapp (San Francisco, Calf). At the risk of preaching to the choir, all patients are at risk. The problem with these tests is that they do not do what they profess to do. They do not differentiate the risk in our patients. I think there may be certain patients who do fall out with a Persantine-thallium, but basically to apply that test to all patients, I totally agree, is appropriate.

It is much more important, I believe, to exercise these patients and see what happens to them when they are actually stressed rather than to do this chemical vasodilation of the coronaries. In part that may be helpful, but you do not get the idea from that test of coronary reserve, which is really critical in these patients postoperatively.

Finally, I would like to ask a question and that is, in our institution we are very careful about postoperative tachycardia and feel that that is the single most dangerous event for these patients after vascular surgery or any other surgical procedure. Did you aggressively treat tachycardia, and if you did, at what level and with what drugs?

Dr de Virgilio. I think that is a very good question, and as you all know, as a result of the work again by the Oregon group, it has been demonstrated that the use of beta blockade perioperatively does lower the adverse cardiac event rate. That is certainly one of the potential weaknesses of the study.

We did, yes, aggressively attempt to treat tachycardia, but there was not a set protocol for treatment of tachycardia. The one thing I can counter to that is that there was no significant difference in the adverse cardiac event rate with respect to the use of beta blockade in this study. Certainly a study where that is specifically included in the protocol would be ideal.