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Stress Testing

Prognostic Value of Dobutamine Stress Echocardiography in Predicting Cardiac Events in Patients With Known or Suspected Coronary Artery Disease

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OBJECTIVES The study sought to determine the utility of dobutamine stress echocardiography (DSE) in predicting cardiac events in the year after testing.

BACKGROUND Increasingly, DSE has been applied to risk stratification of patients.

METHODS Medical records of 1,183 consecutive patients who underwent DSE were reviewed. The cardiac events that occurred during the 12 months after DSE were tabulated: myocardial infarction (MI), cardiac death, percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass surgery (CABG). Patient exclusions included organ transplant receipt or evaluation, recent PTCA, noncardiac death, and lack of follow-up. A positive stress echocardiogram (SE) was defined as new or worsened wall-motion abnormalities (WMAs) consistent with ischemia during DSE. Classification and regression tree (CART) analysis identified variables that best predicted future cardiac events.

RESULTS The average age was 68 ± 12 years, with 338 women and 220 men. The overall cardiac event rate was 34% if SE was positive, and 10% if it was negative. The event rates for MI and death were 10% and 8%, respectively, if SE was positive, and 3% and 3%, respectively, if SE was negative. If an ischemic electrocardiogram (ECG) and a positive SE were present, the overall event rate was 42%, versus a 7% rate when ECG and SE were negative for ischemia. Rest WMA was the most useful variable in predicting future cardiac events using CART: 25% of patients with and 6% without a rest WMA had an event. Other important variables were a dobutamine EF <52.5%, a positive SE, an ischemic ECG response, history of hypertension and age.

CONCLUSIONS A positive SE provides useful prognostic information that is enhanced by also considering rest-wall motion, stress ECG response, and dobutamine EF. (J Am Coll Cardiol 1999;33: 708–16) © 1999 by the American College of Cardiology

Dobutamine stress echocardiography (DSE) continues to be widely and successfully applied to determine whether patients with and without known coronary artery disease have ischemia (1–13). In general, DSE is used when the patient is not able to exercise by treadmill or bicycle to a degree that will provide useful clinical information. Advantages of DSE are that it does not require patient cooperation, and the echocardiographer has ample time to obtain adequate imaging at all levels of stress.

Our study was designed to prospectively follow consecutive patients who underwent DSE at the UCLA School of Medicine during a five-year period and to determine what findings related to stress testing best predicted patient outcome over the ensuing 12 months. Specifically, we catalogued cardiac events, including cardiac death, myocardial infarction (MI), and revascularization by percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting surgery (CABG).

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METHODS

Patient population. A total of 1,183 patients referred to the UCLA Adult Cardiac Imaging and Hemodynamics Laboratories for DSE between March 1991 and March 1996, who gave informed consent to have their medical data reviewed, were entered into the study. If a patient had more than one DSE during that time period, only the first test was entered into the analysis. Two hundred and eight patients who were being considered for orthotopic liver

Abbreviations and Acronyms

CABG	=	coronary artery bypass grafting surgery
CART	=	classification and regression tree analysis
DSE	=	dobutamine stress echocardiography
ECG	=	electrocardiogram
EF	=	ejection fraction
MI	=	myocardial infarction
PTCA	=	percutaneous transluminal coronary angioplasty
RPP	=	rate pressure product
SE	=	stress echocardiogram
WMA	=	wall-motion abnormality

transplantation were excluded, as were 12 patients who died from noncardiac causes while hospitalized, two patients who had orthotopic heart transplantations, and 13 patients who had a PTCA within the six months prior to dobutamine stress testing. An additional 376 patients did not have either 12 months of follow-up or an event within 12 months and, therefore, were not included in the final analysis. Fourteen additional patients were excluded because one or more components of the complete data set were missing for statistical analysis. The final study population consisted of 558 patients.

Dobutamine stress echocardiography. Dobutamine was delivered intravenously using a standard metered delivery device beginning at 5 μg/kg/min for three min and proceeding by 5 μg/kg/min increments every three min to a maximum dose of 40 μg/kg/min. In the latter two years of the study, the intermediate 25- and 35-μg/kg/min doses were omitted. Atropine was given intravenously at the discretion of the clinician conducting the test when the heart rate response appeared to be inadequate.

The test was symptom limited and was stopped if the patient developed >2 mm ST depression, severe wall-motion abnormalities (WMAs), frequent ventricular or supraventricular ectopy, ventricular tachycardia, supraventricular tachycardia, systolic blood pressure >220 mm Hg, systolic blood pressure decrease to >20 mm Hg below baseline systolic blood pressure or to a systolic blood pressure below 80 mm Hg, nausea, moderate to severe chest pain, or moderate to severe dyspnea. An ST depression of ≥1 mm flat or downsloping ST depression was considered positive for ischemia. Lesser degrees of ST depression or ST changes in the presence of baseline repolarization abnormalities, left bundle branch block, or therapy with digoxin were considered equivocal for ischemia.

Echocardiography was performed at rest and at each stage of dobutamine infusion with the patient in the left lateral decubitus position. Images were recorded on ½-inch videotape using a commercially available VHS video recorder for each stage of stress. In addition, digitized images were obtained of the apical 4-chamber, apical 2-chamber, apical long axis, and parasternal short axis views at rest, and at 5 μg/kg/min, 10 μg/kg/min, and peak dobutamine. The views with the best definition of myocardium were then displayed as cineloops in a quad-screen format with the baseline, 5 μg/kg/min, 10 μg/kg/min, and peak dobutamine images for each view appearing in sequence on the same quad-screen.

The myocardium was divided into equal segments for grading of wall motion. Each of the six walls (anterior, anterior interventricular septum, lateral, inferior interventricular septum, inferior medial, and inferior lateral) on the three apical views was divided into three segments: basal, mid, and apical. The mid short-axis view was divided into six equal segments and was used for corroboration of wall motion noted on apical views. Wall motion was graded for each segment as hyperkinetic, normal, mildly hypokinetic, moderately to severely hypokinetic, or akinetic/dyskinetic. If the wall motion in at least one segment deteriorated by at least one grade compared to the rest wall motion, the SE was considered positive for ischemia. Akinesis and dyskinesis were considered to be the same grade of dysfunction. The interpretations used for wall motion in the final clinical report read by an experienced echocardiographer were used for the purposes of this study in order to duplicate the usual clinical setting.

Left ventricular ejection fraction (EF) was either estimated visually or measured at baseline and at peak dobutamine dosage using a commercially available software program that applied Simpson's rule on the two-chamber and four-chamber views.

Twelve-month follow-up. In all patients, the medical record was reviewed to determine the occurrence either before the index DSE or in the ensuing 12 months of any of the following: MI, CABG, PTCA, death, hypertension, or diabetes. Only patients with at least 12 months of follow-up or a cardiac event defined as death, MI, PTCA, or CABG within the first 12 months were included in the analysis.

Statistical analysis. Summary statistics for continuous data are reported as mean ± 1 SD. The Student *t* test was used to identify significant differences in numerical variables; categorical variables were analyzed by chi-square tests. A p value of <0.05 was chosen to define statistical significance. Multiple comparisons were made; therefore, we corrected p values by using the Bonferroni method and divided 0.05 by the number of pair-wise tests performed (n = 36). A final p value of <0.00138 was used to define significance for the multiple comparisons.

Bivariate logistic regression analyses, as well as standard forward and backward stepwise multiple logistic regressions (14), were performed to identify predictors of subsequent cardiac events from clinical and demographic variables available for each patient studied. Independent variables evaluated were: history of hypertension, diabetes mellitus, MI, CABG, or PTCA; age; gender; peak dose of dobutamine; rest and peak dobutamine heart rate, blood pressure, and rate pressure product (RPP); percent of achieved

Table 1. Rest and Exercise Characteristics of Study Group

Criteria	N	Age (yrs)	SD	Dob Dose	SD	Rest RPP	SD	Dob RPP	SD	Rest EF%	SD	Dob EF%	SD
A. All patients	558	67	12	34	8	10181	2580	17634	5220	56	10	65	12
Men	220	68	12	35	8	9723	2313	17396	4655	53	12	62	13
Women	338	67	12	33	8	10479	2702	17789	5559	58	9*	67	10*
B. Cardiac events													
Any event in <12 months	89	69	10	33	9	10398	2830	16508	5036	50	13	58	15
No event in <12 months	469	67	12	34	8	10140	2531	17848	5232	57	9*	67	10*
C. Stress Echocardiogram Results													
SE-positive	136	70	10	33	8	10151	2557	17808	4900	53	12	61	13
SE-negative	422	67	12	34	8	10191	2590	17578	5324	56	10	67	11*
D. History of MI or CABG/PTCA													
No MI/CABG/PTCA	359	66	12	33	8	10305	2657	18085	5449	58	8	68	10
Prior MI	154	70	11*	35	7	9888	2473	16346	4492*	50	12*	59	14*
Prior PTCA	41	71	10	35	7	9315	2187	17089	4954	52	13	60	13*
Prior CABG	88	70	10	35	8	9893	2619	16908	4830	50	12*	59	13*

Values are listed as means ± 1 SD. Any event, one or more cardiac events during first one year of follow-up (some patients had more than one cardiac event); CABG = coronary artery bypass surgery; Dob = dobutamine; Dob dose = maximum dose of dobutamine delivered in μg/kg/min; EF = ejection fraction in %; MI = myocardial infarction prior to stress echocardiogram; N, number of patients; PTCA, percutaneous transluminal coronary angioplasty; RPP = rate pressure product in beats/min/mm Hg; SE = stress echocardiogram. Statistical differences are reported as *$p < 0.05$ (using the Bonferroni correction = $p < 0.00138$) for comparisons in values of women versus men, no event versus event, SE-negative versus SE-positive, and history of prior MI, PTCA, CABG each versus no MI/CABG/PTCA.

maximum predicted heart rate; rest and peak dobutamine EF; presence of induced chest pain; negative, equivocal or ischemic electrocardiogram (ECG); rest wall-motion abnormality (WMA), and a positive stress echocardiogram (SE). Chi-square testing was used for the bivariate analyses.

Additional multivariate analyses were performed using Classification and Regression Trees (15). The CART model identified variables that allowed patients to be successively split into subsets which best predicted future cardiac events. Subgrouping was curtailed at the point that further splitting could not be justified.

RESULTS

Study population. The final patient population included 220 men and 338 women (Table 1). The average age was 67 ± 12 years (range 26 to 93 years). There was no significant difference between the ages of the men and women. In addition, the age of this group of patients was not significantly different from those patients who did not have 12 months of follow-up.

The average dose of dobutamine received by the patient population was 34 ± 8 μg/kg/min, and was similar for men and women. The average rest and peak dobutamine RPPs were also similar for men and women. The rest and dobutamine EFs were significantly higher ($p < 0.05$) for women than for men: rest 58 ± 9% and dobutamine 67 ± 10% for women versus 53 ± 12% and 62 ± 13%, respectively, for men.

Cardiac events. Events occurred in 89 of the 558 patients, an event rate of 16%. Characteristics of patients with and without a cardiac event are listed in Table 2. Characteristics that were significantly different between the two groups according to bivariate testing were: history of MI, hypertension, or diabetes mellitus; ischemic ECG with dobutamine, rest WMAs, and positive SE.

Myocardial infarctions occurred in 28 patients (5%), PTCA in 27 patients (5%), CABG in 33 patients (6%), and death in 24 patients (4%) (Table 3). Fourteen patients had more than one event. The average age was not significantly different between the group of patients with an event versus the group with no event within 12 months of follow-up (Table 1). However, the rest EF (50 ± 13 vs. 57 ± 9%) ($p < 0.001$) and the dobutamine EF (58 ± 15 vs. 67 ± 10%) ($p < 0.001$) were significantly less in the patients with an event. The change in EF with dobutamine was also statistically significantly lower ($p < 0.01$) in patients with an event (8 ± 6%) versus those without an event (10 ± 5%); however, the difference was not clinically relevant and was not analyzed further.

DSE results. Positive SEs were present in 136 of 558 patients (24%). The average dobutamine peak dose, rest and dobutamine RPPs were not significantly different between those patients with a positive versus negative SE (Table 1). However, the average peak dobutamine EF (61 ± 13 vs. 67 ± 11%) ($p < 0.001$) was significantly less in patients with a positive SE.

Patients with a positive SE had a 34% cardiac event rate within the ensuing 12 months (Table 3) versus an event rate of only 10% in patients with a negative SE ($p < 0.001$). The specific events for each subcategory of patients are listed in Table 3. The incidences of the hard cardiac events MI and death were 10% and 8%, respectively, for those patients with

Table 2. Characteristics of Patients With and Without a Cardiac Event (Bivariate Analysis)

Characteristics	Total	% of Total	Cardiac Event N	Cardiac Event (%)	No Cardiac Event N	No Cardiac Event (%)	p
Total patients	558		89	16	469	84	
Men	220	39	43	20	177	80	0.63
Women	338	61	46	14	292	86	0.63
Hx CABG	88	16	20	23	68	77	0.07
Hx PTCA	41	7	9	22	32	78	0.30
Hx MI	154	28	41	27	113	73	< 0.001
History of HTN	393	70	73	19	320	81	0.006
History of DM	206	37	44	21	162	79	0.008
ECG+	71	13	23	32	48	68	0.002
Rest wall-motion abn	301	54	74	25	227	75	< 0.001
≤20 μg/kg/min	77	14	15	19	62	81	0.37
SE-positive	136	24	46	34	90	66	< 0.001

abn, abnormality; Cardiac event, one or more cardiac events (some patients had more than one cardiac event); CABG, coronary artery bypass graft surgery; DM, diabetes mellitus; ECG+, ischemic stress ECG; HTN, hypertension; Hx, history of; MI, myocardial infarction; N, number of patients; PTCA, percutaneous transluminal coronary angioplasty; SE, stress echocardiogram.

a positive SE, and only 3% ($p < 0.01$) and 3% ($p < 0.05$), respectively, for those patients with a negative SE.

Combined stress echocardiography and ECG results. The frequencies of cardiac events for patients with an ischemic, equivocal, and a nonischemic ECG were 32%, 18%, and 11%, respectively. Further stratification was possible by combining the data regarding a positive or negative SE with the presence or absence of an ischemic ECG response to dobutamine (Table 3). Patients with a positive SE and an ischemic ECG had a 42% event rate versus a 7% event rate in patients with both a negative SE and a negative ECG. Patients with a positive SE and a negative ECG for ischemia had a 35% event rate versus a 23% event rate in

Table 3. Summary of Cardiac Events Within First Year of Follow-Up

Total in Category	Patients N	Patients (%)	MI N	MI (%)	PTCA N	PTCA (%)	CABG N	CABG (%)	Death N	Death (%)	Any Event N	Any Event (%)
All patients	558		28	5	27	5	33	6	24	4	89	16
Men	220	39	12	5	11	5	21	10	9	4	43	20
Women	338	61	16	5	16	5	12	4	15	4	46	14
Hx CABG	88	16	6	7	8	9	7	8	3	5	20	23
Hx PTCA	41	7	1	2	7	17	3	7	1	2	9	22
Hx MI	154	28	14	9	17	11	12	8	9	6	41	27
No prior MI/CABG/PTCA	359	64	13	4	7	2	18	5	15	4	42	12
ECG+	71	13	3	4	7	2	13	4	2	1	23	32
ECG±	172	32	14	8	12	7	9	5	7	4	31	18
ECG−	311	56	11	4	8	3	11	4	15	5	35	11
Rest WMA	301	54	24	8	22	11	30	10	18	6	74	25
SE-positive												
All patients	136	24	14	10	13	10	21	15	11	8	46	34
ECG+	36	6	1	3	3	8	10	28	2	6	15	42
ECG±	57	10	9	16	5	9	5	9	4	7	16	28
ECG−	43	8	4	9	5	12	6	14	5	12	15	35
Rest WMA	122	22	13	11	11	9	20	16	11	9	42	34
SE-negative												
All patients	422	76	14	3†	14	3†	12	3†	13	3*	43	10‡
ECG+	35	6	2	6	4	11	3	9	0	0	8	23
ECG±	119	21	5	4	7	6	4	4	3	3	15	13
ECG−	268	48	7	3	3	1	5	2	10	4	20	7
Rest WMA	179	32	11	6	11	6	10	6	7	4	32	18

Abbreviations as in Tables 1 and 2. *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

Table 4. Rest Wall Motion and Incidence of Positive Stress Echocardiograms, Myocardial Infarctions, and Cardiac Events

	Patients	Normal Rest Wall Motion		Abnormal Rest Wall Motion	
	N	N	(%)	N	(%)
Total in category	558	257	46	301	54
Any cardiac event	89	15	17	74	83
No cardiac events	469	242	52	227	48
SE-positive	136	14	10	122	90
SE-negative	422	243	58	179	42
SE +; with cardiac event	46	4	9	42	91
SE−; no cardiac event	379	232	61	147	39
Prior MI	154	27	18	127	82
No prior MI	404	230	57	174	43
Prior CABG	88	9	10	79	90
No prior CABG	470	248	53	222	47
Prior PTCA	41	8	20	33	80
No prior PTCA	517	249	48	268	52

Abbreviations as in Tables 1 and 2.

patients with a negative SE but an ischemic ECG. In patients with an equivocal ECG due to baseline abnormalities, drugs, or left bundle branch block, those with a positive SE had a 28% event rate versus a 12% event rate in those with a negative SE.

Rest wall-motion abnormalities. Fifty-four percent of patients had abnormal wall motion at rest, which was a significant independent predictor of a cardiac event (Table 4). The prevalence of abnormal rest wall motion was 82% in patients with a known prior MI. However, 43% of patients without a history of a prior MI also had a rest WMA. Of patients with a cardiac event, 83% had abnormal rest wall motion. Similarly, 90% of patients with a positive SE had abnormal wall motion at rest.

If a rest WMA was present, the incidence of any cardiac event was 25%. The presence of a rest WMA in combination with a positive SE resulted in a 34% incidence of any cardiac event, versus an incidence of 18% when the SE was negative. Patients with a rest WMA, positive ECG for ischemia, and positive SE for ischemia had a cardiac event rate of 41%, in contrast to a cardiac event rate of 5% in those 171 patients with normal wall motion at rest and with dobutamine plus a normal stress ECG.

Logistic regression analysis. Each one of the possible predictor variables was tested for association with the outcome "cardiac event." Predictors that were significantly related to the outcome included rest EF, dobutamine EF, positive ECG, rest WMA, positive SE, and history of MI. We then attempted to include these variables in a (forward) stepwise multiple logistic regression but the stepping was extremely unstable, as variables moved dramatically into and out of significance as other variables were included or excluded. Moreover, the result was unsatisfactory: the Hosmer/Lemeshow "goodness of fit" test (14) indicated an inadequate fit, even after interaction terms were included. Backward stepwise regression also failed to converge.

CART results. Classification and regression tree analysis (CART) indicated that the best single predictor of a cardiac event was a rest WMA (Fig. 1). Thus, the presence or absence of rest WMA is the first branch of the tree used to predict future cardiac events. For those 301 patients with a rest WMA (the left branch of the tree) the next most useful predictor was a peak dobutamine EF of <52.5%. The third branch on this side of the tree was a history of hypertension. Fifty-five patients had a rest WMA, a peak dobutamine EF <52.5%, and a history of hypertension. Of these 55 patients, 51% had a cardiac event compared with the 16% event rate of the entire patient population.

The right-sided branch of the CART tree revealed that the second best predictor of a cardiac event, after it was known that rest wall motion was normal, was the patient's age. For patients in this category who were ≤66.5 years, only 1 of 120 patients had an event, an event rate of 0.8%. The event rate was 10% for the 137 patients who were >66.5 years.

A positive SE was the next best predictive factor for an event in the 225 patients with abnormal rest wall motion and a dobutamine EF% of >52.5%. In this category 29% had an event if they had a positive SE, versus a 12% event rate if the SE was negative.

A second CART tree was generated leaving out the EF variables to allow prediction of events when these values are not available (Fig. 2). Rest WMA remained the initial branch point, and the right side of the tree remained unchanged. However, a positive SE replaced the peak dobutamine EF of <52.5% as the secondary branch point on the left side of the tree. The next two branches were "age <77.5 years," followed by an "ischemic ECG."

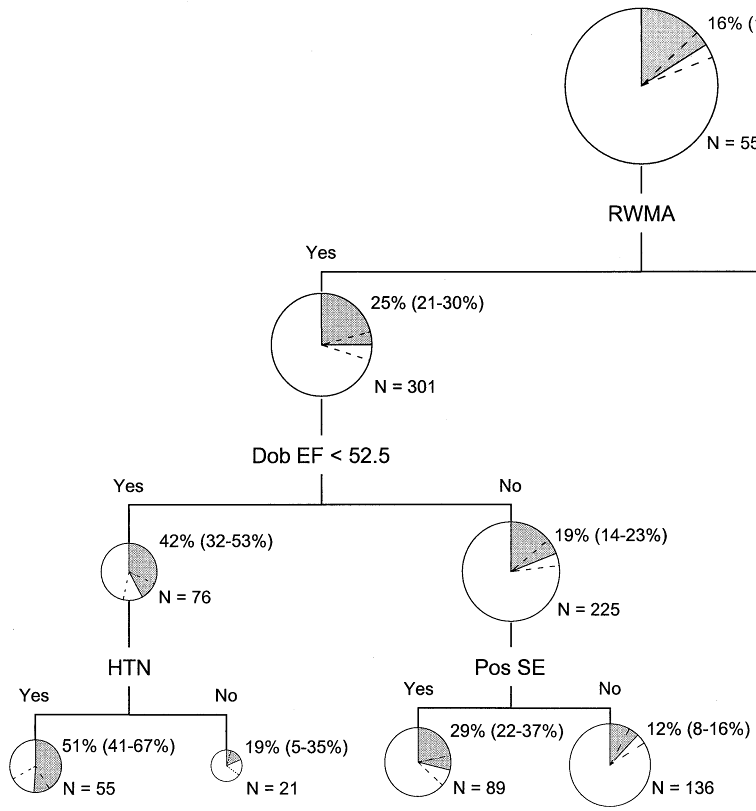

Figure 1. CART model illustrating likelihood of a patient having a cardiac event in the 12 months after DSE. The total number of patients, N = 558, is represented by the large pie circle **(top).** The area of each pie is proportional to the number of patients (N) in each group or subgroup. The **shaded area** of each pie is equal to the percentage of patients in that group who had a cardiac event in the 12 months after DSE. The actual percentage of patients with an event appears next to the shaded portion of each pie, and is followed in parentheses by the 95% confidence limits for the calculated event percentage. Dob EF = dobutamine ejection fraction in %; HTN = hypertension; Pos SE = positive stress echocardiogram; RWMA = rest wall-motion abnormality.

DISCUSSION

This large database of consecutive patients is unusual in that women are well represented and, in fact, comprise the majority of the patients (61%). This is in contrast to most studies done on unselected cardiovascular patients in which the majority of patients are men. Although women in general develop cardiac disease a decade later than do men, it is of interest that the average ages of the men and women were similar in this study. Dobutamine stress echocardiography (DSE) selected a patient population that was 6 years older than that found in our previous study of exercise stress echocardiography in which the average age of all patients was 62 ± 13 years, with similar ages for men and women (16). In the exercise study, however, 66% of the patients were men. Thus, DSE selects a patient population that is older and has a higher representation of women than does exercise stress echocardiography.

Gender itself was not a variable that was predictive of a cardiac event by logistic regression analysis or by the CART method in this sample of older patients, in contrast to the male gender being predictive of an event with treadmill stress echocardiography (16).

Variables predictive of future cardiac events. The cardiac event rate was 16% for the group as a whole, which is similar to the 14% event rate observed using exercise SE (16). A history of MI, hypertension, or diabetes mellitus were all significant bivariate variables for predicting a cardiac event, and event rates for patients with these individual variables were, respectively, 27%, 19%, and 21%. These results corroborate the known value of these risk factors in predicting future cardiac events.

The presence of WMAs at rest, an ischemic ECG response, and a positive SE were the other significant bivariate variables for predicting a cardiac event, with event rates, respectively, of 25%, 32%, and 34%. These results show that either an ischemic ECG or a positive SE are equally good by themselves in selecting patients with a twofold increased likelihood of having an event when compared to the average event rate of 16% when all patients are considered. It is important to emphasize that when an ECG clearly shows ischemia, it is as good as a positive SE in predicting subsequent events when considered by itself.

Stress echocardiography was added to stress ECG testing to improve the predictive value of the testing. It is a

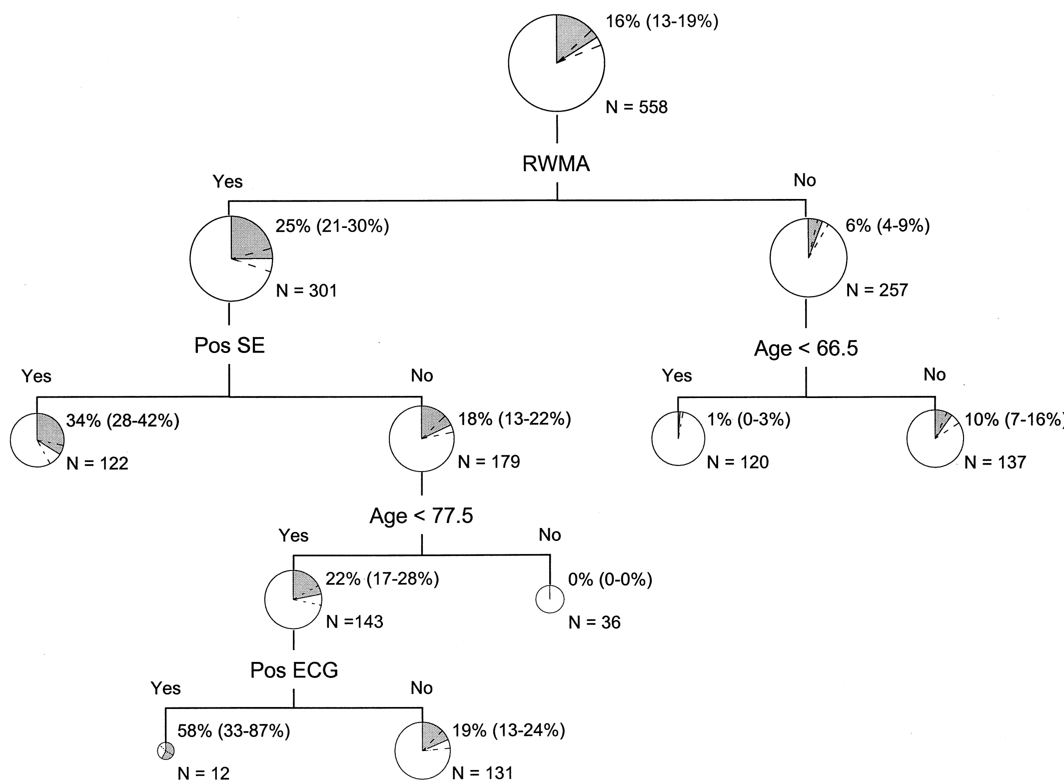

Figure 2. CART model similar to Figure 1 but with exclusion of Dob EF as a variable. Abbreviations are same as Figure 1; Pos ECG = ischemic ECG with dobutamine.

complement to, not a replacement for, the information available from ECG testing. Combining the information available from both the ECG and the SE enhanced the risk stratification of our patients (Table 3). As expected, the risk of an event was highest in patients with both a positive SE and an ischemic ECG (42%), and lowest in patients with both a nonischemic ECG and a negative SE (7%), a sixfold difference in risk of having an event. Thus, DSE is useful in identifying both those patients at high and low risk for developing future cardiac events. Intermediate results were obtained for the other combinations of findings (Table 3).

Our attempt at multiple logistic regression gave an inadequate fit. We attribute this failure to the presence of strong interactions beyond the bilinear terms we tested and to the failure of various other assumptions, such as equal variances (homoskedasticity). In logistic regression, linear combinations of predictor variables are evaluated synchronously to predict each patient's probability of suffering a cardiac event. In CART, by contrast, predictor variables are evaluated sequentially, and the choice of the next variable depends on the results with previous variables. The CART produces a flow chart of branching categories that splits patients into subgroups with differing probabilities of having a cardiac event. It is particularly effective in dealing with interaction terms.

In the initial CART tree (Fig. 1), the dobutamine EF% was more helpful in subgrouping patients into risk categories than was the presence of a positive SE, although these two variables tend to track together as patients with a positive SE also have lower dobutamine EF%s than do those patients with a negative SE. Many echocardiographic laboratories may not routinely report rest and dobutamine EFs. Therefore, CART was used to create a second tree of probabilities to apply when the dobutamine EF is not available.

Rest wall-motion abnormalities. The single variable that was the most predictive of a future cardiac event for both CART trees was the presence of a resting WMA; the event rate was 25% for those with resting WMA versus 6% ($p < 0.001$) for those with normal wall motion. This result was not surprising in light of the fact that the presence of resting WMA selects patients more likely to have underlying coronary artery disease, and 54% of our patient population had a resting WMA.

The emphasis CART places on the importance of rest WMAs is especially pertinent because the results of the resting wall motion are often ignored in favor of whether there was a change in the wall motion with stress (i.e., a positive SE). The fact that a WMA is present at rest is especially important when the patient has no history of a MI. A resting WMA can represent either ischemia (e.g., hibernating or stunned myocardium) or infarction. Patients may have a WMA at rest, which represents ischemia, yet the WMA does not detectably worsen with stress. In this case, by the standard definition of "no new or worsened wall motion" with stress, the SE is negative, although the rest WMA may represent ischemia. This is a known limitation of SE reading in the presence of resting wall-motion abnormalities.

Normal rest wall motion. The results from CART are provocative because they suggest that for patients with normal rest wall motion who are less than age 66.5, the probability of having an event in the next 12 months is so low (<1%) that a SE is not necessary for further prognostication. This, however, does not mean that the SE would not be useful for diagnostic purposes in defining whether or not the patient has coronary artery disease, which would affect treatment plans.

The prognostic trees generated from this database predict the likelihood that an individual patient will have an event within the 12 months after DSE. It is most helpful when the tree limbs predict high or low, rather than intermediate, probabilities. For example, in Figure 1, a patient with a rest WMA, a dobutamine EF of <52.5% and a history of hypertension should definitely have further evaluation and/or treatment to address a 51% likelihood of a cardiac event. In Figure 2, the patients at highest risk for an event (58%) are those with a rest WMA, a negative SE, age <77.5 years, and a positive ECG. This reemphasizes the point that the presence of a rest WMA alone, without further deterioration of wall motion with dobutamine, should alert the clinician that resting ischemia may be present, especially when the ECG is consistent with ischemia.

Revascularization procedures, which resulted indirectly from the results of stress testing, were the significant cardiac events tabulated in many patients. Patients with positive or nondiagnostic tests were more likely to undergo further investigation with angiography. This process, as expected, often resulted in revascularization, which was, therefore, not truly independent of the SE results. However, if only the hard events of new MI or death are examined, those patients with a positive SE had statistically higher event rates of 10% ($p < 0.01$) and 8% ($p < 0.05$) for MIs and death, respectively, compared with a rate of 3% for both MIs and death in those patients with a negative SE (Table 3). Thus, the SE result alone predicts an approximate threefold increase in MIs and deaths, further highlighting the prognostic value of DSE.

Previous studies. Other investigators have reported a similar prognostic value of DSE in predicting subsequent cardiac events for smaller patient populations (17–20). Geleijnse et al. (18) found the single most important independent predictor for hard cardiac events was any abnormal imaging pattern, either at rest or with stress. An ischemic pattern provided additional, independent prognostic information. Marcovitz et al. (20) reported that the risk of hard cardiac events during follow-up was highest in those patients with both abnormal rest wall motion and an ischemic response to dobutamine. This study emphasized that having WMAs at rest, in addition to dobutamine-induced ischemia, was a more powerful predictor of future hard cardiac events than either finding alone. These studies in combination with our own provide strong evidence for highlighting the presence of rest WMAs in any schemata used to predict prognosis in patients with known or suspected coronary artery disease.

The DSE has also proved to be useful in various subsets of patients to predict future cardiac events: for example, noncardiac vascular disease patients who are scheduled for surgery (3,6,21–23), patients with a recent MI (24–26) or with left ventricular dysfunction (27). Ballal et al. (28) reported a high event rate in patients with "chronotropic incompetence" who had a submaximal dobutamine stress test irrespective of whether stress-induced wall-motion abnormalities were detected. We reported similar findings in patients with submaximal exercise SEs (16). In the current study, however, neither the achieved maximum predicted heart rate nor the achieved maximal double product was a significant independent variable for predicting cardiac events.

Conclusions. We demonstrated the prognostic power of DSE for predicting future cardiac events in routine clinical practice in a large population of patients, the majority of whom were women. We emphasized using all clinical and stress echocardiographic data available in assessing risk in an individual patient. The importance of rest wall-motion abnormalities in predicting future cardiac events was highlighted. The CART analysis, employed to develop branching trees of probability that can easily be applied to an individual patient, can be used to generate a decision tree for predicting cardiac outcomes.

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