Observer Bias in the Interpretation of Dobutamine Stress Echocardiography

JOHN F. TIGHE, JR., M.D., DAVID M. STEIMAN, M.D., MARINA N. VERNALIS, D.O., ALLEN J. TAYLOR, M.D.

Cardiology Service, Department of Medicine, Walter Reed Army Medical Center, Washington, D.C., USA

Summary

Background and hypothesis: Blinded image analysis is typically utilized in published studies evaluating the accuracy of dobutamine stress echocardiography (DSE). However, in clinical settings, practical considerations may limit the use of blinded interpretations and thus the potential for observer bias arises. This study evaluated the relationships between clinical and blinded interpretations of DSE.

Methods: Wall motion analysis from clinical and blinded DSE interpretations were compared and factors associated with their concordance were investigated in 115 consecutive patients with known or suspected coronary artery disease.

Results: Clinical and blinded interpretations agreed on the presence or absence of inducible ischemia in 102 of 115 cases (88.7%; $\kappa = 0.76$, $p < 0.00001$). In studies in which the clinical and blinded interpretations were in agreement, there was greater ST-segment depression (STD) in echocardiographically positive compared with negative studies (mean STD 0.73 ± 0.65 vs. 0.42 ± 0.67 mm; $p = 0.008$). In contrast, studies in which there was disagreement had significantly less ST-segment changes (mean STD 0.19 ± 0.56 mm; $p = 0.012$) despite comparable results on blinded wall motion analysis. Multiple logistic regression for factors related to the results of clinical and blinded wall motion analysis disclosed that angina pectoris and ST-segment changes were related to clinical interpretations, whereas only angina pectoris was related to the findings on blinded analysis.

Conclusions: Clinical interpretations of echocardiographic images during DSE overall demonstrate good agreement with the results of blinded analysis. Ancillary testing data may influence the analysis of wall motion abnormalities, and thus the potential for observer bias exists unless these interpretations are performed blinded to other clinical data.

Key words: dobutamine stress echocardiography, coronary artery disease, ST-segment changes, interpreter bias

Introduction

Wall motion analysis of echocardiographic images during dobutamine stress echocardiography (DSE) contributes to the enhanced accuracy of this test over electrocardiographic (ECG) stress testing alone.^{1–4} In published studies evaluating the accuracy of DSE, wall motion analysis is typically conducted without knowledge of other clinical stress testing data such as the clinical circumstances of the test, or of any other testing parameters such as the symptomatic, hemodynamic, or ECG response to stress. Thus, to ensure comparability in clinical applications of DSE to published results, the evaluation of wall motion changes indicating inducible ischemia is optimally conducted in a blinded fashion. In clinical settings where the performing physician is often also responsible for the test interpretation, a blinded analysis may be impractical, although access to clinical information creates the potential for the introduction of bias in the subjective analysis of the wall motion response to stress.

Observer bias can arise from a variety of causes and may potentially alter physician judgments of subjective data.^{5,6} For example, past studies on probability estimates of coronary artery disease have indicated these to be more accurate when they were derived from objective data, without knowledge of the clinical condition of the patient.^{7,8} In this study, we compare the results of clinical and blinded wall motion analysis during DSE in an effort to assess the magnitude of any information bias arising from the availability of clinical data. We hypothesized that, since the interpretation of DSE relies entirely on the subjective interpretation of wall motion for the identification of inducible ischemia, blinded and clinical assessments of wall motion would systematically differ. Furthermore, we sought to identify which factors contributed to these differences.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

Address for reprints:

Allen J. Taylor, M.D., MAJ, MC
Director of Clinical Cardiovascular Research
Room 4A, Heaton Pavilion
Walter Reed Army Medical Center
Washington, D.C., 20307-5001, USA

Received: September 25, 1996

Accepted with revision: February 4, 1997

Methods

Patients

We performed a retrospective analysis of 115 consecutive patients without left bundle-branch block or on digoxin therapy who underwent DSE at Walter Reed Army Medical Center from September 1994 to May 1995. Patient characteristics are displayed in Table I. Discontinuation of medications prior to DSE was at the discretion of the ordering physician. Anti-anginal medications were in use in 69.6% of the study group and included a beta-receptor antagonist in 45.2%.

Dobutamine Stress Echocardiography Protocol

Dobutamine stress echocardiography⁹ was performed with the administration of dobutamine as a graded infusion beginning at 2.5–5 µg/kg/min to a peak dose of 50 µg/kg/min at 3-min intervals. Two-dimensional echocardiographic examination in the parasternal and apical windows, 12-lead ECG, heart rate, and blood pressure were obtained at baseline, at the completion of each stage, and in the recovery phase. The peak tolerated dobutamine dose was identified as the dose at which a study end point occurred, including attainment of target heart rate, intolerable side effects, or maximum dobutamine dose.^{9–11} Only one study was noted as being terminated due solely to the development of a new wall motion abnormality. The administration of atropine to enhance the heart rate response to dobutamine^{11, 12} or metoprolol to facilitate the rapidity of the recovery period¹¹ were at the discretion of the study operator. Atropine was administered in 55 patients.

TABLE I Characteristics of the 115 study patients

	N (%)
Male gender	60 (52)
Age (mean ± SD)	66 ± 11
DSE indications	
Chest pain	
Typical	11 (10)
Atypical	10 (9)
Evaluation of known coronary disease	36 (31)
Preoperative evaluation	26 (23)
Myocardial viability	1 (1)
Other	17 (15)
Medications	
Any antianginal	80 (70)
Beta-adrenergic antagonist	52 (45)
Reason for termination	
Achievement of target heart rate	64 (56)
Angina	24 (21)
Peak dose	16 (14)
Other	7 (6)

Abbreviations: DSE = dobutamine stress echocardiography, SD = standard deviation, N = number of patients.

On-line digital image analysis (Tomtec, Broomfield, Colo.) with videotape backup was performed at study completion by the performing cardiologist. All studies were performed and interpreted by experienced echocardiographers with expertise in stress echocardiography interpretation. The clinical interpretations utilized in this study were those indicated by the final printed study report and were completed with access to the clinical indication for the test, patient medications, and the clinical response to dobutamine including symptoms, hemodynamics, and ECG changes. Blinded image analysis, without knowledge of any patient or clinical data, was performed by the consensus of two experienced echocardiographers, with consultation with a third observer in cases of disagreement. Videotapes were available for review for both clinical and blinded assessments. In the blinded analysis, these were reviewed when necessary due to questions of image quality or gating of digital images. Both sets of interpretations employed a 16-segment model with assignment of regional (anterior and inferoposterior) and global wall motion scores.^{13, 14} For all interpretations, a positive DSE was defined as any new or worsened wall motion abnormality occurring during the stress phase.^{15–17} Regional dyskinesia in a previously akinetic segment was not considered to be indicative of inducible ischemia.

ST-Segment Analysis

The baseline and peak stress ECGs were independently analyzed for ST-segment changes without knowledge of the clinical or DSE results. ST-segment depression or elevation was measured as the maximal change from baseline in the worst precordial or limb lead at 80 ms after the J point.¹⁸ A positive stress ECG was defined as additional ST-segment depression of ≥ 0.5 mm in depth,¹⁰ or any ST-segment elevation.

Cardiac Catheterization

Cardiac catheterization was performed within 6 months of the DSE in 47 patients. Obstructive coronary artery disease was defined as ≥ 70% luminal narrowing in at least one major epicardial coronary artery or its principal branches.

Statistical Analysis

All data are expressed as mean ± 1 standard deviation unless otherwise noted. Univariate analysis of mean data between groups was performed by *t*-test, or either the Mann-Whitney U test or the Kruskal-Wallis H test, as appropriate for nonparametric data. Comparison of proportions between groups was performed by chi-square test. Means among multiple groups were compared by one-way ANOVA. Pearson bivariate correlation coefficients were determined to summarize the relationship between continuous variables. Logistic regression modeling was used to test for clinical variables that were related to the results of either clinical or blinded wall motion analysis (whether the test was considered positive or negative for inducible ischemia) and agreement in the pres-

ence or absence of inducible ischemia between clinical and blinded interpretations. Our models treated clinical variables including patient age, gender, a baseline normal echocardiogram, baseline ST-segment abnormalities, DSE indication, angina during the test, the maximum dobutamine dose obtained, atropine use, the hemodynamic response to stress, achievement of target heart rate, and the results of ST-segment analysis as independent variables. A stepwise selection method was used with an entry criterion of a *p* value of <0.05 for entry of a variable. We considered a two-tailed *p* value of ≤0.05 to be statistically significant. All analyses were performed with the SPSS statistical package (SPSS for Windows, v.6.1, SPSS, Chicago, Ill.).

Results

Patient Characteristics

A total of 115 patients (60 men, 55 women) with a mean age of 66 ± 11 years were studied. The indications for DSE are outlined in Table I. Approximately 60% of the studies were performed for either the evaluation of known coronary artery disease, preoperative cardiovascular risk assessment, or evaluation of a chest pain syndrome. Attainment of target heart rate was the most common reason for stopping the test (55.7%). The provocation of angina occurred in 20.9% of patients. A minority of studies (13.9%) were discontinued at peak tolerated dobutamine dose without achieving target heart rate. The mean peak dobutamine dose was 36 ± 10 $\mu\text{g/kg/min}$.

Overall, 53 patients (46%) had a positive ST-segment response to dobutamine, with ST depression noted in 41 patients (36%). The mean ST depression observed was 1.1 ± 0.6 mm. Among patients with ST depression, 13 had between 0.5 to <1 mm and the remaining 28 had ≥1 mm of ST depression. ST elevation was observed in 10% (*n* = 12) of the study group; pathologic Q waves were present in the baseline ECGs in 4 of these patients. There were no significant differences between patients with and without ST-segment changes in the peak tolerated dobutamine dose, atropine administration, and peak rate–pressure product. Patients with ischemia on blinded wall motion analysis demonstrated significantly greater mean ST-

segment depression than patients without inducible ischemia (0.73 ± 0.65 vs. 0.42 ± 0.67 mm; *p* = 0.008). Among those studies with ischemia on blinded wall motion analysis, there was no correlation between the magnitude of ST-segment depression and the extent of ischemia (*r* = 0.19; *p* = 0.24).

Agreement between Clinical and Blinded Wall Motion Analysis

Overall, agreement between clinical and blinded wall motion analysis was observed in 102 studies, with results considered normal in 62 studies and abnormal in 40 (Table II). In the 13 studies in which there was disagreement in wall motion analysis, the results of blinded analysis were normal in 6 and abnormal in 7. Comparisons of demographic and DSE variables between these four groups of patients (agree—normal or abnormal study, and disagree—normal or abnormal on blinded analysis) showed no significant differences in patient age, peak dobutamine dose, or double product attained. ST-segment depression was more severe in studies considered to be positive for ischemia on both clinical and blinded analysis compared with those in which the clinical and blinded analysis disagreed (0.73 ± 0.65 vs. 0.19 ± 0.56 mm; *p* = 0.012, Fig. 1). In studies in which there was disagreement, angina occurred in six patients, and was absent in the other seven. Significant ST-segment changes were absent in 11 of these 13 studies. Agreement between interpretations was unrelated to the location of ischemic response that was seen in 27 of 31 cases of anterior ischemia and 32 of 35 cases of inferior ischemia. Logistic regression found that the presence of an ECG, which was positive for ischemic changes (odds ratio 10.6, 95% confidence interval 1.7–65.4; *p* = 0.01), and the absence of angina (odds ratio 0.18, 95% confidence interval 0.04–0.78; *p* = 0.02) were associated with agreement between clinical and blinded analysis.

Factors Related to Results of Clinical and Blinded Wall Motion Analysis

Logistic regression was performed to determine which factors were individually related to the results of clinical and

TABLE II Comparison of clinical and blinded wall motion analysis

	Agreement		Disagreement		<i>p</i> Value
	Normal	Abnormal	Normal blind	Abnormal blind	
Number of patients	62	40	6	7	
Age	66 ± 12	66 ± 10	63 ± 17	67 ± 13	0.89
Gender (males) (%)	27 (44)	28 (70)	4 (67)	2 (29)	0.03
Baseline normal echocardiogram (%)	53 (85)	11 (28)	5 (83)	1 (14)	0.0001
Peak dobutamine dose ($\mu\text{g/kg/min}$)	37 ± 11	35 ± 12	32 ± 10	43 ± 8	0.22
Achieved target heart rate (%)	49 (79)	27 (68)	4 (67)	5 (71)	0.61
Peak heart rate	135 ± 19	128 ± 16	122 ± 29	136 ± 18	0.17
Atropine use (%)	39 (63)	16 (40)	6 (100)	4 (57)	0.09
Angina	1 (2)	14 (35)	4 (67)	2 (29)	0.0001
Maximum ST depression (mm)	0.42 ± 0.67	0.73 ± 0.65	0.33 ± 0.82	0.07 ± 0.19	0.008

FIG. 1 Bar graph depicting the degree of ST-segment depression in categories of studies based on agreement between clinical and blinded study interpretation. Categories include (1) agreement, normal study; (2) agreement, abnormal study; (3) disagreement, normal study on blinded analysis; (4) disagreement, abnormal study on blinded analysis. Data displayed as mean $\pm$ standard error of the mean. Patients with ST-segment elevation are excluded. ANOVA $p = 0.008$. NI = normal; Abnl = abnormal. $\square$ = Agree NI, |||| = agree Abnl, ■ = disagree NI, ▨ = disagree Abnl.

blinded wall motion analysis. Patient gender, a baseline normal echocardiogram, angina during the test, and dobutamine-induced ST-segment changes were all related to the results of clinical interpretations (Table III). In contrast, only angina during the test and a baseline normal echocardiogram were related to the results of blinded analysis.

Significant coronary artery disease was present in 36 of the 47 patients who underwent coronary arteriography. Single-vessel coronary artery disease was identified in 14 of these 36 patients (39%). In this select subgroup of 47 patients who underwent cardiac catheterization, the clinical and blinded DSE results were comparable. Clinical DSE interpretations correctly identified 22 of 36 patients with and 9 of 11 without coronary artery disease. Blinded DSE interpretations correctly identified 19 of 36 patients with and 10 of 11 without coronary artery disease.

TABLE III Selected logistic regression coefficients

Variable	Standard coefficient	Standard error	p Value
Positive clinical wall motion analysis			
Male gender	-1.89	0.64	0.003
Baseline normal echo	-1.76	0.59	0.003
ST-segment changes	1.13	0.59	0.05
Angina during the test	3.86	0.94	<0.0001
Positive blinded wall motion analysis			
Male gender	-0.99	0.62	0.11
Baseline normal echo	-3.15	0.66	<0.0001
ST-segment changes	0.84	0.61	0.17
Angina during the test	3.09	0.82	0.0001

Logistic regression coefficients obtained using stepwise logistic regression including the variables described under "Methods."

Discussion

Dobutamine stress echocardiography is an accurate test for the detection of ischemic heart disease, demonstrating improvement over the results of standard ECG stress testing.¹⁻⁴ As reports on the accuracy of this test are typically obtained utilizing detailed wall motion analysis performed in a blinded manner, one could reasonably conclude that blinded image analysis should also be utilized in clinical settings if the promised results of published studies are to be reproduced in the "real world." Yet, in clinical practice, the physician performing the test may also be responsible for image interpretation and thus, for practical reasons, would have access to a variety of patient and DSE parameters. Access to such ancillary information could affect the wall motion analysis through the introduction of observer bias. Recognizing this potential problem, this study sought to examine the relationship between wall motion analysis under these different conditions and to investigate which factors may influence the results of unblinded wall motion analysis.

We have found that, in general, the agreement between clinical and blinded DSE interpretations is excellent, achieving a level observed between independent blinded reviewers.^{3, 19} Both clinical and blinded interpretations were related to angina and ST-segment changes, consistent with known correlates of myocardial ischemia induced during DSE.^{3, 10} However, on multiple regression analysis, we identified different associations between ancillary test data and the results of clinical and blinded wall motion analysis. Specifically, clinical wall motion analysis was associated with both an ischemic ECG response and male gender, whereas blinded wall motion analysis was not. Furthermore, when the clinical and blinded analysis disagreed and an ischemic wall motion response was considered to be present on the blinded analysis, the stress ECG was normal. These results suggest a discernible effect of ancillary test data on the subjective interpretation of wall motion changes.

Bias is defined as "any process at any stage of inference which tends to produce results or conclusions that differ systematically from the truth."⁵ Sackett identified 35 possible types of bias, indicating that they can arise in any phase of a study or test.⁵ Some that are relevant to unblinded interpretations of DSE could include "diagnostic suspicion bias" (knowledge of a patient's risk factors for coronary artery disease that could influence the intensity and outcome of the diagnostic test), and "previous opinion bias" (the results of a previous diagnostic test, e.g., cardiac catheterization or the results of DSE electrocardiography, may affect the results of a subsequent diagnostic test).⁵ Other biases identified within physician assessments include referral- and value-induced bias,⁷ and selection bias²⁰ which has been identified within noninvasive testing. An observer influenced by one of these or other biases has the potential to make inaccurate judgments during the subjective interpretation of test data.

Previous studies have established the presence of bias occurring within subjective interpretations. Physician estimates of the probability of coronary artery disease have been found

to be more accurate when based upon objective data and when the identities of the patients are unknown.⁸ Patient histories have also been identified as a possible source of observer bias, tending to occur more commonly in mild disease states and in the subjective assessments of less experienced clinicians.²¹ The use of computer-assisted data or consultation with a blinded observer have both been cited as methods to improve upon entirely subjective data analysis.⁷

Serial 12-lead ECG monitoring is routinely performed during DSE and, after wall motion changes, is the primary objective data available for review. However, the appropriate degree of significance ascribed to ST-segment changes during DSE is unknown and its diagnostic usefulness has been recently questioned. Daoud *et al.*, in a study of electrocardiography in DSE, found the sensitivity of a positive stress ECG, when defined as ST depression ≥ 1 mm, to be 38% for the detection of an angiographic coronary artery stenosis of $\geq 50\%$.²² When considered after the results of stress echocardiography, there was little additive benefit to the ST-segment analysis. Stress-induced ST depression during DSE as a correlate of the echocardiographic ischemic burden has recently been described by Elhendy *et al.*.¹³ This study, designed to examine stress-induced left ventricular dysfunction in patients with symptomatic and asymptomatic ischemia, found inducible ST depression to be associated with a greater number of ischemic segments that had normal baseline function. However, the total number of ischemic segments and the observed change in global wall motion score were similar in patients with and without ST depression. Thus, dobutamine stress electrocardiography has a limited role in the diagnosis of ischemic heart disease.

Study Limitations

The purpose of this study was to compare wall motion analysis performed under two different conditions. Notably, there is no objective standard of reference for the presence of inducible ischemia, and cardiac catheterization was obtained in only a clinically selected subset of patients. Thus, blinded wall motion analysis may either overestimate or underestimate the true prevalence of inducible ischemia relative to clinical interpretations. The sensitivity which we report within the subgroup of patients who underwent cardiac catheterization (53%) is somewhat lower than that reported by other investigators.^{1-4, 10} A number of factors known to reduce the sensitivity of DSE may have contributed to a reduced test sensitivity, including the frequent presence of single-vessel coronary artery disease^{1, 19} and the failure to achieve target heart rate in a significant minority of cases.¹⁰ Finally, future studies should define the optimal interaction between clinical and blinded wall motion analysis that achieves the greatest degree of test accuracy.

Conclusions

Despite the subjective nature of wall motion analysis, clinical DSE interpretations correlate well with the results of

blinded wall motion analysis. However, the potential exists for the introduction of observer bias, as we have found that an association with the availability of ancillary testing data, including patient gender and the ECG response to stress, is discernible. To avoid potential observer bias and to ensure comparability in the accuracy of clinically performed dobutamine stress echocardiography to published results, wall motion analysis should optimally include an interpretation by an observer unfamiliar with the patient and the clinical response to dobutamine. In the future, objective aids to wall motion analysis may limit the potential for observer bias in stress echocardiography interpretations.

Acknowledgments

The authors wish to thank Teri Manolio, M.D., M.H.S., Director, Epidemiology and Biometry Program in the Division of Epidemiology and Clinical Applications, National Heart, Lung and Blood Institute, Bethesda, Maryland, for thoughtful commentary and review of this manuscript.

References

- Previtali M, Lanzarini L, Fetiveau R, Poli A, Ferrario M, Falcone C, Mussini A: Comparison of dobutamine stress echocardiography, dipyridamole stress echocardiography and exercise stress testing for diagnosis of coronary artery disease. *Am J Cardiol* 1993;72: 865-870
- Hoffmann R, Lethen H, Kleinhans E, Weiss M, Flachskampf FA, Hanrath P: Comparative evaluation of bicycle and dobutamine stress echocardiography with perfusion scintigraphy and bicycle electrocardiogram for identification of coronary artery disease. *Am J Cardiol* 1993;72:555-559
- Mazeika PK, Nadazdin A, Oakley CM: Dobutamine stress echocardiography for detection and assessment of coronary artery disease. *J Am Coll Cardiol* 1992;19:1203-1211
- Marwick TH, Anderson T, Williams MJ, Haluska B, Melin JA, Pashkow F, Thomas JD: Exercise echocardiography is an accurate and cost-efficient technique for detection of coronary artery disease in women. *J Am Coll Cardiol* 1995;26:335-341
- Sackett DL: Bias in analytic research. *J Chronic Dis* 1979;32: 51-63
- Wynder EL: Investigator bias and interviewer bias: The problem of reporting systematic error in epidemiology. *J Clin Epidemiol* 1994;47:825-827
- Detrano R, Bobbio M, Olson H, Shandling A, Ellestad MH, Alegria E, Martinez-Caro D, Righetti A, Janosi A, Steinbrunn W: Computer probability estimates of angiographic coronary artery disease: Transportability and comparison with cardiologists' estimates. *Comput Biomed Res* 1992;25:468-485
- Bobbio M, Detrano R, Shandling AH, Ellestad MH, Clark J, Brezden O, Abecia A, Martinez-Caro D: Clinical assessment of the probability of coronary artery disease: Judgmental bias from personal knowledge. *Med Decis Making* 1992;12:197-203
- Pelikka PA, Roger VL, Oh JK, Miller FA, Seward JB, Tajik AJ: Stress echocardiography. Part II. Dobutamine stress echocardiography: Techniques, implementation, clinical applications, and correlations. *Mayo Clin Proc* 1995;70:16-27
- Mairesse GH, Marwick TH, Vanoverschelde JL, Baudhuin T, Wijns W, Melin JA, Detry JM: How accurate is dobutamine stress electrocardiography for detection of coronary artery disease? Comparison with two-dimensional echocardiography and technetium-

- 99m methoxyl isobutyl isonitrile (mibi) perfusion scintigraphy. *J Am Coll Cardiol* 1994;24:920-927
11. Mertes H, Sawada SG, Ryan T, Segar DS, Kovacs R, Foltz J, Feigenbaum H: Symptoms, adverse effects, and complications associated with dobutamine stress echocardiography. Experience in 1118 patients. *Circulation* 1993;88:15-19
 12. Fioretti PM, Poldermans D, Salustri A, Forster T, Bellotti P, Boersma E, McNeill AJ, el-Said ES, Roelandt JR: Atropine increases the accuracy of dobutamine stress echocardiography in patients taking beta-blockers. *Eur Heart J* 1994;15:355-360
 13. Elhendy A, Geleijnse ML, Roelandt JR, Cornel JH, van Domburg RT, Fioretti PM: Stress-induced left ventricular dysfunction in silent and symptomatic myocardial ischemia during dobutamine stress test. *Am J Cardiol* 1995;75:1112-1115
 14. Marwick T, D'Hondt AM, Baudhuin T, Willemart B, Wijns W, Detry JM, Melin J: Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: Combination with echocardiography or scintigraphy, or both? *J Am Coll Cardiol* 1993;22:159-167
 15. Bach DS, Muller DW, Gros BJ, Armstrong WF: False positive dobutamine stress echocardiograms: Characterization of clinical, echocardiographic and angiographic findings. *J Am Coll Cardiol* 1994;24:928-933
 16. Beleslin BD, Ostojic M, Stepanovic J, Djordjevic-Dikic A, Stojkovic S, Nedeljkovic M, Stankovic G, Petrasinovic Z, Gojkovic L, Vasiljevic-Pokrajacic Z: Stress echocardiography in the detection of myocardial ischemia. Head-to-head comparison of exercise, dobutamine, and dipyridamole tests. *Circulation* 1994;90:1168-1176
 17. Carstensen S, Ali SM, Stensgaard-Hansen FV, Toft J, Haunso S, Kelbaek H, Saunamaki K: Dobutamine-atropine stress echocardiography in asymptomatic healthy individuals. The relativity of stress-induced hyperkinesia. *Circulation* 1995;92:3453-3463
 18. Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML: Exercise standards: A statement for health care professionals from the American Heart Association. *Circulation* 1995;91:580-615
 19. Hoffmann R, Lethen H, Marwick T, Arnesen M, Fioretti P, Pingitore A, Picano E, Buck T, Erbel R, Flachskampf FA, Hanrath P: Analysis of interinstitutional observer agreement in interpretation of dobutamine stress echocardiograms. *J Am Coll Cardiol* 1996;27:330-336
 20. Salerno DM, Wang K, Goldenberg IF, Van Tassel RA: The impact of selection bias on measurement of noninvasive test accuracy. *Am J Cardiol* 1993;72:223-225
 21. Teitler N: Examiner bias: Influence of patient history on perceptual ratings of videostroboscopy. *J Voice* 1995;9:95-105
 22. Daoud EG, Pitt A, Armstrong WF: Electrocardiographic response during dobutamine stress echocardiography. *Am Heart J* 1995;129:672-677