Diabetes supersedes dobutamine stress echocardiography in predicting cardiac events in female patients

H. Isma'eel, W. Shamseddeen, M. El Khoury, A. Dimassi, A. Nasrallah, M.S. Arnaout

Division of Cardiology, Department of Internal Medicine, American University of Beirut, Beirut (Lebanon)

Summary

Background: The many available choices for testing for coronary artery disease (CAD) brought about several questions regarding suitability of certain tests for different groups of patients and the prognostic value of obtained results in predicting events and mortality. The aim of this study is to describe the prognostic value of dobutamine stress echocardiography (DSE) results in predicting cardiac events and mortality in ≥ 60-year-old females. *Methods:* 49 women (≥ 60 years old) who were referred for DSE were included in the study. Data including CAD risk factors, and results of tests and a follow-up of events (MI, unstable angina, progression of CHF) and death. *Results:* Eleven patients were considered to have a positive DSE result. There was no difference between DSE (+) and DSE (-) patients in cardiac events and cardiac death. However when interventions were included to events, analysis showed DSE (+) to have more overall events. Non-cardiac deaths and "all deaths" were 11 and 8 times more common among DSE (+) patients compared with DSE (–) patients $p < 0.01$. Multivariable logistic regression showed that diabetics and DSE (+) patients were 32 ($p = 0.01$) and 23 ($p = 0.02$) times more likely to have an event compared with non-diabetics and DSE (–) patients, respectively. *Conclusion:* DSE is a safe procedure to be used in ≥ 60-year-old female patients and can provide informative prognostic information regarding all-cause deaths and cardiac events (including interventions) over a 4-year period. In addition we find that diabetes is a strong predictor of events regardless of DSE result.

Key words: Dobutamine stress echocardiography; Coronary artery disease; Diabetes.

Introduction

The proliferation of cardiology technology assisting in early detection of coronary artery disease (CAD) has provided the physician with a bouquet of choices [1]. Concomitantly, because of worldwide-improved health care more patients of advanced ages are presenting with angina [2] and subsequently for non-invasive CAD detection. This fact has posed several questions regarding suitability of tests offered to older patients and the prognostic value of information received from each test. Physicians well appreciate this once they consider the physical limitations of treadmill exercising among the elderly for example, where dobutamine stress echocardiography (DSE) is presented as an acceptable alternative [3]. Moreover, for years CAD remained to be perceived as a male disease until a change in this perception was founded [4]. This change was driven by the discovery of differences in the prognostic value of certain noninvasive tests in females as in the case of elevated false-positive rate of treadmill exercise ECG in premenopausal women [3]. Therefore the aim of this study is to describe the suitability and prognostic value of DSE results in predicting cardiac events and mortality in a specific group of elderly (≥ 60 years old) females in a Middle East tertiary care center.

Revised manuscript accepted for publication December 10, 2009

Materials and Methods

Patient population

The study group consisted initially of 50 females who are greater than or equal to 60 years old. One patient had a non-diagnostic DSE so she was excluded from the analysis. DSE and wall motion scoring was performed in accordance with standard protocol [6-8].

The Institutional Review Board approved the study, and the participants signed an informed consent.

Baseline and follow-up characteristics

Follow-up data were obtained for almost all patients. At the time of DSE, baseline information regarding medical history and coronary risk factors were recorded for each patient and included age, tobacco usage, diabetes, hypertension (HTN), angina, family history of coronary artery disease (FHx), hypercholesterolemia, congestive heart failure (CHF), previous myocardial infarction, cerebrovascular accident (CVA), percutaneous transluminal coronary angioplasty (PTCA) intervention and baseline left ventricular ejection fraction.

A follow-up questionnaire was used to record the data on each subject. Follow-up data were collected after a review of the patient's hospital chart, private clinics or Out Patient Department records; the referring physicians were identified and contacted, and telephone interview with the patient or patient's relatives was done. The clinical events recorded during the follow-up were cardiac and non-cardiac deaths, acute coronary syndrome (STEMI, NSTEMI), pulmonary edema, malignant arrhythmias and coronary revascularization (surgery or angioplasty). The diagnosis of acute myocardial infarction was made on the basis of symptoms, electrocardiographic changes, and cardiac enzyme level increases. Revascularization was considered as a clinical end point reflecting new or progressive symptoms.

Statistical Analysis

Categorical data were reported as percentages, and continuous data were reported as mean ± standard deviation (SD). Continuous variables were compared with the Student independent *t-test* whereas differences of categorical variables were assessed by the chi-square test. DSE was considered positive if the cardiac tissue was found to be ischemic, viable or non-viable, and negative in case of non-ischemic tissue. Statistical significance was considered if $p < 0.05$.

Results

The final patient population consisted of 49 female patients. The average age was 67.8 ± 6.5 years (range 60 to 90 years). The DSE was done to test for the presence of viable myocardium (4 patients) and for the presence of ischemia (45 patients). These patients were not considered as two different populations and were used in the same analysis. DSE revealed the presence of ischemia in seven patients, viable tissue in two patients, and non-viable tissue in two patients. Thus, the test was considered to be positive in 11 patients (22.4%). During the test four patients (8.2%) complained of nausea, three (6.1%) of dyspnea, and one (2.0%) of dizziness.

Comparing DSE (+) to DSE (-) patients, there was no significant difference between the two groups with respect to age and except for history of a myocardial infarction (MI), there was no significant difference with respect to past medical history. Patients with positive DSE were respectively eight and ten times more likely to have a history of MI and coronary artery bypass grafting (CABG) as compared to patients with negative DSE. Among the medications, only statins were significantly associated with DSE result (Table 1). With respect to electrocardiographic and echocardiographic parameters, patients with positive DSE were more likely to have resting or peak ST segment/T-wave changes (Table 2).

Forty-five patients {10 DSE (+) and 35 DSE (-)} had a two-year follow-up and one of them died in these two years. There was no significant difference between the two groups with respect to having a cardiac event or the type of event if they had any. Cardiac event was defined as having a MI, unstable angina (UA), and deterioration of congestive heart failure (CHF). Of the ten DSE (+) patients four underwent PTCA with stent deployment and six underwent (CABG) subsequent to the DSE result, which was significantly higher than DSE (–) patients (Table 3). Thirty-one patients [9 DSE (+) and 22 DSE (–)] were followed-up for an additional two years. Again, there was no significant difference between the two groups with respect to having a cardiac event and the type of the event.

To investigate the difference in overall mortality, the 31 patients (followed-up for four years) and the one patient who died in the first two years were combined in one sample. There was no difference between the DSE (+) and DSE (-) patients with respect to cardiac death within four years. Events of non-cardiac deaths and "all deaths" were 11- and 8-times more common among DSE (+) patients compared with DSE (-) patients (Table 3). The same was done to investigate overall occurrence of events. Patients with an event in the first two years and no further follow-up were added to the 31 patients with four years follow-up. There was no significant association between the DSE result and having at least one cardiac event during the four years despite higher occurrence in the DSE (+) group. However, if performed interventions are considered among cardiac events, then the DSE (+) patients will be significantly more likely have a cardiac event (Table 3).

Table 1. — *Clinical characteristics for the DSE (+) and DSE (–) groups*.

	DSE+ n = 11	DSE- n = 38	*p* value
Mean age (years)	67.3 ± 8.3	67.9 ± 6.0	0.78
Diabetes	4 (36.4)	15 (39.5)	0.85
Hypertension	4 (36.4)	25 (65.8)	0.08
Hypercholesterolemia	7 (63.6)	14 (36.8)	0.11
Smoking	4 (36.4)	11 (28.9)	0.64
COPD	1 (9.1)	6 (15.8)	0.58
Carotid stenosis	0 (0.0)	1 (2.6)	0.44
PVD	2 (18.2)	5 (13.2)	0.68
CHF	1 (9.1)	2 (5.3)	0.64
Stroke	1 (9.1)	3 (7.9)	0.90
CRF	2 (18.2)	5 (13.2)	0.68
Old MI	6 (54.5)	5 (13.2)	**< 0.01**
Use of antiplatelets	8 (72.7)	16 (42.1)	0.07
Use of beta blockers	4 (36.4)	10 (26.3)	0.52
Use of ACEI/ARB	4 (36.4)	12 (31.6)	0.77
Use of statins	4(36.4)	2 (5.3)	**0.01**
Prior PTCA	0 (0.0)	3 (7.9)	0.33
Prior CABG	4(36.4)	2 (5.3)	**0.01**

Data is presented as mean value ± SD or number (%) of patients.
DSE +/–,Positive/negative echocardiographic result of dobutamine stress testing; *COPD,* Chronic obstructive Pulmonary Disease; *PVD*, Peripheral Vascular disease; *CHF,* Congestive heart failure; *CRF*, Chronic renal failure; *ACEI/ARB*, Angiotansin Converting enzyme Inhibitor/Angiotensin Receptor Blocker. PTCA, percutaneous transluminal coronary angioplasty; *CABG,* coronary artery bypass grafting.

Table 2. — *Electrocardiographic, baseline, and stress echocardiography characteristics for the DSE (+) and DSE (-) groups*.

	DSE+ n = 11	DSE- n = 38	*p* value
Previous myocardial infarction	2 (18.2)	4 (10.5)	0.50
Resting ST segment/ Twave changes	2 (18.2)	0 (0.0)	**0.01**
Peak exercice ST segment/ T wave changes	2 (18.2)	1 (2.6)	**0.058**
VT or AF during the test	0 (0.0)	1 (2.6)	0.59
Hypotension	0 (0.0)	0 (0.0)	–
Bradycardia	0 (0.0)	0 (0.0)	–
RWMSI > 1.15	7 (70.0)	5 (13.9)	< 0.001
PEWMSI > 1.15	6 (100.0)	4 (11.4)	< 0.001

Data is presented as mean value ± SD or number (%) of patients.
DSE+/DSE-, Positive/negative echocardiographic result of dobutamine stress testing; VT, Ventrivular Tachycardia; AF Atrial Fibrillation; RWMA, Resting Wall Motion Abnormalities; NWMA, New Wall Motion Abnormalities; RWMSI, Resting Wall Motion Score Index, PEWMSI, Peak Exercise Wall Motion Score Index.

Table 3. — *Events according to the result of stress echocardiography in the DSE (+) and DSE (-) groups.*

	DSE+	DSE-	*p* value
Two years FU			
PTCA	4/10 (40.0)	3/35 (8.6)	**0.02**
CABG	6/10 (60.0)	3/35 (8.6)	**< 0.01**
Any cardiac event	3/10 (30.0)	4/35 (11.4)	0.15
Type of cardiac event			
UA	1/10 (10)	2/35 (5.7)	0.24
MI	1/10 (10)	2/35 (5.7)	
CHF	1/10 (10)	0/35 (0)	
Four years FU			
Any cardiac event	3/9 (33.3)	3/22 (13.6)	0.21
Type of cardiac event			
UA	1/9 (11.1)	2/22 (9.1)	0.36
MI	1/9 (11.1)	1/22 (4.5)	
CHF	1/9 (11.1)	0/22 (0)	
All events[1]			
At least one cardiac event	3/9 (33.3)	6/25 (24.0)	0.59
At least one cardiac event (including intervention)	8/10 (80.0)	8/26 (30.8)	**0.01**
Cardiac deaths	2/9(22.2)	2/23 (8.7)	0.30
Non cardiac deaths	3/9 (33.3)	1/23 (4.3)	**0.03**
All deaths	5/9 (55.5)	3/23 (13.0)	**0.01**

DSE+/DSE–, Positive/negative echocardiographic result of dobutamine stress testing; 1) Grouping patients with 4 years follow-up and those who had an event in the first two years with no additional follow-up.

Table 4. — *Predictors of having at least one cardiac event (including intervention) within 4 years.*

	Cardiac event (including intervention)			
	No n = 20 (%)	Yes n = 16 (%)	OR (95% CI)	*p* value
Demographics				
Age ≥ 70 years	10 (50.0)	13 (81.3)	0.3 (0.94-20.0)	**0.08**
Medical History				
Diabetes	4 (20.0)	11 (68.8)	8.8 (1.9-40.3)	**0.01**
Hypertension	11(5.0)	10 (62.5)	1.4 (0.4-5.2)	0.65
Dyslipidemia	9 (45.0)	9 (56.3)	1.6 (0.4-5.9)	0.50
Smoking	6 (30.0)	5 (31.3)	1.1 (0.2-4.4)	0.93
COPD	4 (20.0)	1 (6.3)	0.3 (0.03-2.7)	0.24
PVD	1 (5.0)	5 (31.3)	8.6 (0.9-83.7)	**0.07**
CHF	0 (0.0)	2 (12.5)	–	0.10
Stroke	0 (0.0)	2 (12.5)	–	0.10
CRF	3 (15.0)	1 (6.3)	0.4 (0.04-4.0)	0.94
Old MI	4 (20.0)	6 (37.5)	2.5 (0.6-11.1)	0.24
Medications				
Use of antiplatelets	6 (30.0)	11 (68.8)	5.1 (1.2-21.4)	**0.04**
Use of beta blockers	6 (30.0)	6 (37.5)	1.4 (0.3-5.6)	0.63
Use of ACEI/ARB	6 (30.0)	7 (43.8)	1.8 (0.5-7.2)	0.40
Use of Statins	1 (5.0)	5 (31.3)	8.6 (0.9-83.7)	**0.07**
Prior PTCA	3 (15.0)	0 (0.0)	–	0.11
Prior CABG	1 (5.0)	5 (31.3)	8.6 (0.9-83.7)	**0.07**

Data is presented as mean value ± SD or number (%) of patients.
COPD, Chronic obstructive Pulmonary Disease; PVD, Peripheral Vascular disease; CHF, Congestive heart failure; CRF, Chronic renal failure; ACEI/ARB, Angiotansin Converting enzyme Inhibitor/Angiotensin Receptor Blocker. PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.

The 34 patients (31 patients with 4-year follow-up and three patients with an event in the first two years) were categorized based on whether they had an event or not and compared with respect to their past medical history. Compared to those with no cardiac event, patients with at least one event were 32 times more likely to be diabetics, and 10.2 times more likely to have history of hypertension. The same analysis was repeated but after considering those with an intervention as having an event. In addition to DSE (Table 3), diabetes and antiplatelet use were significantly associated with having an event (Table 4). The three variables were used in a multivariable logistic regression. Diabetics and DSE+ patients were 32 (p = 0.01) and 23 (p = 0.02) times more likely to have an event compared with non-diabetics and DSE- patients, respectively. Antiplatelets were not found to be statistically significant in the final analysis.

Discussion

It is required for exercise stress testing that the patient is capable of performing the test with no risk of harm infliction. With aging the risk of harm or limitations precluding from exercise testing (osteoarthritis, joint problems, muscular deconditioning) increase and alternatives such as DSE are offered [3]. Clearly the results above indicate that DSE can be performed safely with no fear of serious complications (nausea, dyspnea, and shortness of breath 2-8%) in ≥ 60-year-old females. This is in line with the reported literature for other age groups and both males and females, thus eliminating potential restrictions for performing the test in this group specifically [3, 5].

Furthermore, the above-listed results show that a DSE (+) result indicates unfavorable all-death and non-cardiac death prognosis over four years, and though not statistically significant but also an increased incidence of cardiac death. This could be explained by the fact that as DSE (+) patients undergo subsequently coronary angiography and intervention, cardiac death rate decreases because of intervention [9]. On the other hand as a DSE (+) result indicates coronary atherosclerosis, which by itself is a marker of generalized ill-health; it is not surprising that all-death is elevated in this group in comparison to DSE (-) patients [5].

Concerning the prognostic value of DSE in predicting cardiac events, only after including PTCA or CABG to the cardiac events (MI, UA or progression of CHF) was this endpoint shown to occur more in a statistically significant manner in DSE (+) patients in comparison to DSE (-). This could very well be attributed to the small sample size, and also to the inclusive indication of DSE (+) i.e., presence of coronary atherosclerosis and thus need for intervention. On the other hand these results indirectly suggest that identifying CAD using DSE and intervening is decreasing the number of events – excluding interventions – over a 4-year period, though not eliminating event occurrence. The latter is explained when the CAD risk factor profile of our cohort is analyzed and not surprisingly patients who suffered from cardiac events were 30- and 10-times more likely to be diabetic and hypertensive, respectively [5, 10]. It is worth noting here that diabetes among the female gender appears to be a very risky factor reflected in the multivariable logistic analysis showing that diabetic patients regardless of DSE

result were 32 times more likely to have an event. This is in line with the literature that shows that cardiac mortality and morbidity of diabetic females is an area of minor – if any – success. Thus whereas cardiovascular mortality among male diabetics has decreased it has remained stable or some suggested that it has even increased by 23% in female diabetics [10, 11]. Moreover in a recently published article, a similar result showed that a normal DSE predicted a less favorable outcome in diabetic in comparison to non-diabetic patients overall [10].

In conclusion, we find that dobutamine stress echocardiography is a safe procedure to be used in females ≥ 60 year old and can provide informative prognostic information regarding all-cause deaths and cardiac events (MI, UA, progression of CHF, PTCA and CABG) over a 4-year period. In addition we find that diabetes is a strong predictor of events regardless of DSE result in our cohort and needs to be addressed aggressively in this group of patients.

References

[1] Alter D.A., Stukel T.A., Newman A.: "Proliferation of cardiac technology in Canada: a challenge to the sustainability of Medicare". *Circulation,* 2006, *113*, 380.

[2] Zaher C., Goldberg G.A., Kadlubek P.: "Estimating angina prevalence in a managed care population". *Am. J. Manag. Care,* 2004, *10* (11 suppl.), S339.

[3] Mieres J.H., Shaw L.J., Arai A., Budoff M.J., Flamm S.D., Hundley W.G *et al*.. "Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association". *Circulation,* 2005, *111*, 682.

[4] Miller T.D., Roger V.L., Hodge D.O., Hopfenspirger M.R., Bailey K.R., Gibbons R.J.: "Gender differences and temporal trends in clinical characteristics, stress test results and use of invasive procedures in patients undergoing evaluation for coronary artery disease". *J. Am. Coll. Cardiol*., 2001, *38*, 690.

[5] Biagini E., Elhendy A., Schinkel A.F., Rizzello V., van Domburg R.T., Krenning B.J. *et al*.: "Comparison of all-cause mortality in women with known or suspected coronary artery disease referred for dobutamine stress echocardiography with normal versus abnormal test results". *Am. J. Cardiol.,* 2005, *95,* 1072.

[6] Picano E., Lattanzi F., Masini M., Distante A., L'bbate A.: "High-dose dipyridamole echocardiography test in effort angina pectoris". *J. Am. Coll. Cardiol*., 1986, *8,* 846.

[7] McNeill A.J., Fioretti P.M., El-Said E.S.M., Salustri A., Forster T., Roelandt J.R.T.C.: "Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography". *Am. J. Cardiol*., 1992, *70,* 41.

[8] Picano E., Pingitore A., Conti U., Kozáková M., Boem A., Cabani E. *et al*.: "Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dipyridamole echocardiography". *Eur. Heart. J*., 1993, *14*, 1216.

[9] Marwick T.H., Case C., Sawada S., Rimmerman C.., Brenneman P.., Kovacs R. *et al*.: "Prediction of mortality using dobutamine echocardiography". *J. Am. Coll. Cardiol*., 2001, *37*, 754.

[10] Cortigiani L., Bigi R., Sicari R., Landi P., Bovenzi F., Picano E.: "Prognostic value of pharmacological stress echocardiography in diabetic and nondiabetic patients with known or suspected coronary artery disease". *J. Am. Coll. Cardiol*., 2006, *47,* 605.

[11] Gu K., Cowie C.C., Harris M.I.: "Diabetes and decline in heart disease mortality in US adults". *JAMA,* 1999, *281*, 1291.

Address reprint requests to:
M.S. ARNAOUT, M.D., FESC
Division of Cardiology
Department of Internal Medicine
American University of Beirut
P.O. Box 11-0236
Beirut (Lebanon)
e-mail: sarnaout@aub.edu.lb