Effect of Pharmacologic Stress Test Results on Outcomes in Obese versus Nonobese Subjects Referred for Stress Perfusion Echocardiography

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Background: Real-time contrast stress echocardiography (RTCSE) permits the simultaneous analysis of myocardial perfusion and wall motion during stress echocardiography, which has resulted in improved coronary artery disease detection. Although several studies have confirmed a protective effect of obesity in coronary artery disease, it is unclear whether this benefit is dependent on the functional significance of the disease. The objective of this study was to compare outcomes in obese versus nonobese subjects referred for pharmacologic RTCSE.

Methods: A retrospective comparison of wall motion and myocardial perfusion with RTCSE was assessed in 481 obese and 961 nonobese patients matched for age and gender without known coronary artery disease referred for either dobutamine (n = 1,056) or dipyridamole (n = 386) stress echocardiography at two separate institutions. Outcomes (death or nonfatal infarction) were determined over a median follow-up period of 1,195 days.

Results: Abnormal myocardial perfusion and/or wall motion was seen in 207 (20%) dobutamine and 61 (16%) dipyridamole studies. Abnormal rates were similar in obese (17%) and nonobese (19%) subjects. Event-free survival was significantly worse only for nonobese subjects referred for dobutamine RTCSE, with obesity (not test result) being an independent predictor of event-free survival on multivariate analysis (P = .001). No protective effect of obesity was observed following dipyridamole RTCSE.

Conclusions: Obese subjects in the United States referred for demand stress testing have better outcomes when directly compared with age- and gender-matched nonobese subjects with similar degrees of inducible ischemia. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Obese, Outcome, Perfusion, Wall motion, Stress echocardiography

Real-time contrast stress echocardiography (RTCSE) has been used to assess myocardial perfusion (MP) during stress testing and has the advantage of allowing the simultaneous analysis of wall motion (WM).[1] MP assessment during RTCSE has increased the sensitivity of the test for both detecting coronary artery disease (CAD)[2-4] and predicting cardiac events.[5-8] This added sensitivity of RTCSE may be useful in several clinical subgroups, among which obese subjects (OS) are of particular interest, because of the highly debated "obesity paradox."[9]

Current data suggest that overweight subjects with established cardiovascular (CV) disease typically have a better prognosis compared with subjects with normal body mass index values between 20 and 25 kg/m^2,[9-20] a counterintuitive association between obesity as an established risk factor for incident cardiac disease[21] and better event-free survival in OS that is referred to as the obesity paradox. The paradox is generally considered specific to OS with cardiac disease, but a recent systematic review in unselected populations suggested that it might extend to overweight subjects or those with mild obesity without established CV disease.[22]

Only a few studies[23,24] have investigated the obesity paradox in patients undergoing provocative testing for suspected CAD, and these have suggested that a better prognosis exists for OS in this setting. What is unclear is how protective obesity is compared with other pertinent clinical variables, as well as the outcomes from different stress imaging responses. This is especially important with pharmacologic stress testing, which is often required in OS because of comorbidities that prevent diagnostic treadmill electrocardiographic testing.[25] In this study, we aimed to determine what independent role the obesity paradox plays in a population of patients undergoing different forms of pharmacologic RTCSE for suspected

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Abbreviations

CAD = Coronary heart disease
CV = Cardiovascular
DIP = Dipyridamole
DOB = Dobutamine
HR = Heart rate
MI = Mechanical index
MP = Myocardial perfusion
nOS = Nonobese subjects
OS = Obese subjects
RTCSE = Real-time contrast stress echocardiography
WM = Wall motion
WMA = Wall motion abnormality

CAD. Furthermore, we also sought to determine whether the paradox relates to the result of the test (ischemic or normal). Specifically, we analyzed whether obesity has a favorable prognostic impact in patients on the basis of the type of pharmacologic RTCSE (dobutamine [DOB] or dipyridamole [DIP]) and on the basis of whether the results were normal or abnormal, using both MP and WM responses during stress imaging.

METHODS

Data Sources

A retrospective analysis of OS and nonobese subjects (nOS) was performed from consenting patients, recorded in the data banks of the University of Nebraska Medical Center (Omaha, NE) (from 2005 to 2009) and the University of Parma Medical Center (Parma, Italy) (from 2008 to 2010). OS and nOS were age and gender matched (one OS for every two nOS) from the same source of data.

Study Selection

Eligible patients were those who required pharmacologic RTCSE to evaluate suspected CAD or risk stratification and who provided written informed consent to participate in the pharmacologic stress database. Patients at the University of Nebraska Medical Center underwent DOB stress, while those at Parma underwent DIP stress. Exclusion criteria were history of known CAD (defined as a history of myocardial infarction, coronary revascularization, or the presence of an angiographically documented coronary stenosis >50% before RTCSE), severe valvular or congenital heart disease, pregnancy, known hypersensitivity to ultrasound contrast media, inability to obtain follow-up data, and inadequate acoustic window. Hypertension was defined as a history of blood pressure elevations >140/90 mm Hg or use of antihypertensive medications at the time of the stress study. Hyperlipidemia was defined as total cholesterol >200 mg/dL or use of lipid-lowering medications at the time of the study.[5,6] This resulted in a total of 1,442 patients who underwent either DOB (n = 1,056) or DIP (n = 386) contrast RTCSE. Patients in the DIP database had their short-term prognostic results published previously.[6] Beta-blockers were withheld for 24 hours before all stress echocardiographic examinations, as recommended in current guidelines.

Of these 1,442 patients, 481 (33%) met criteria for obesity (body mass index ≥ 30 kg/m^2). Table 1 describes the demographics of the OS and nOS. Within the entire study population, the mean age was 59 ± 12 years, 811 subjects (56%) were women, 429 (30%) had diabetes, 999 (69%) had hypertension, and 687 (48%) had hyperlipidemia.

Study Protocols

The lipid-encapsulated microbubble contrast agent Definity (Lantheus Medical Imaging, North Billerica, MA), as a 3% continuous infusion, and the lipid-encapsulated microbubble contrast agent SonoVue (Bracco Imaging, Milan, Italy), as a continuous 1 mL/min diluted infusion or repeated 0.5-mL slow boluses, were used as ultrasound contrast media for DOB and DIP studies, respectively. RTCSE was performed using commercially available ultrasound scanners (Sonos 5500 or iE33 [Philips Medical Systems, Andover, MA] or Acuson Sequoia 512 [Siemens Medical Solutions USA, Mountain View, CA]) equipped with low–mechanical index (MI) real-time pulse sequence schemes. The low-MI setting was set between 0.09 and 0.20 and the frame rate between 20 and 40 Hz. The high-MI impulses, or flash impulses, were a brief number of frames at an MI > 1.0 applied in each view during the infusion, and myocardial contrast replenishment was analyzed at the low-MI setting in real time for analysis of changes in MP.[26]

For DOB studies, DOB was infused at a starting dose of 5 μg/kg/min, followed by increasing doses of 10, 20, 30, and 40 μg/kg/min to a maximal dose of 50 μg/kg/min in 3- to 5-min stages. Atropine (up to 2 mg) was added in patients without symptoms or signs of myocardial ischemia to achieve 85% of the age-predicted maximal heart rate (HR). Blood pressure and cardiac rhythm were monitored before and during the DOB infusion. Twelve-lead electrocardiograms were obtained at 3-min intervals. End points of the stress test were achievement of target HR, maximal DOB and atropine doses, development of severe or extensive WM abnormalities (WMAs), ST-segment elevation > 0.1 mV in non-Q-wave leads, sustained arrhythmias, severe chest pain, and intolerable side effects.

For DIP studies, DIP was infused at a total dose of 0.84 mg/kg in all patients using either a 10-min 0.84 mg/kg DIP infusion plus atropine administration (up to 1 mg) or a 6-min protocol, consisting of the 0.84 mg/kg DIP infusion and no additional atropine administration. Two-dimensional echocardiography, 12-lead electrocardiography, and blood pressure monitoring were performed in accordance with established standard protocols. Aminophylline was routinely used to reverse the effect of DIP.

Data Analysis

The left ventricle was divided into 17 segments according to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography.[27] MP was visually assessed by experienced reviewers (N.G. read 386 studies, T.R.P. read or directly supervised 1,056 studies). The criteria for analysis were as follows: normal MP during stress imaging was assigned if myocardium was fully replenished with contrast within 2 sec after the end of the flash impulse, and an MP defect was defined as any two contiguous myocardial segments that did not fully replenish with contrast in this time period. Normal MP at rest was defined as complete replenishment within 4 sec after the flash impulse. An MP defect was scored as reversible on the basis of its absence at rest. Basal segments were excluded from MP analysis if there was attenuation (defined as failure to delineate endocardial and epicardial borders). Reversible WMAs were defined as stress-induced new WMAs or worsening of rest hypokinesis in at least one contiguous segment. In all cases, the results of both MP and WM analysis were made available to the referring physicians. Interobserver agreement data for WMAs and MP within each center have been previously published,[5,6] but a repeat analysis of 40 study cases (20 DIP, 20 DOB) was performed at each site to assess interinstitutional agreement.

Data collection was performed through June 2012. Outcomes were determined from patient interviews at outpatient clinics, hospital chart reviews, and telephone interviews with patients or referring