Contrast Stress Echocardiography for the Diagnosis of Coronary Artery Disease in Patients With Chest Pain but Without Acute Coronary Syndrome: Incremental Value of Myocardial Perfusion

Nicola Gaibazzi, MD, Claudio Reverberi, MD, Angelo Squeri, MD, Giuseppe De Iaco, MD, Diego Ardissino, MD, and Tiziano Gherli, MD, *Parma, Italy*

Background: The inappropriate admission of patients with noncardiac chest pain is an enormous cost to society. Myocardial perfusion imaging (MPI) could prove effective in the risk stratification of patients in whom acute coronary syndromes are ruled out by electrocardiography and troponin levels, thanks to its incremental sensitivity beyond that of wall motion (WM) criteria for obstructive coronary artery disease, and still maintain the excellent safety profile of dipyridamole-atropine stress echocardiography (DASE). The aim of this study was to test this hypothesis using WM and MPI (WM + MPI) in consecutive patients admitted to a chest pain unit.

Methods: Patients presenting to a chest pain unit between January and June 2008 with chest pain and in whom acute coronary syndromes had been ruled out by normal electrocardiography and cardiac enzyme levels underwent DASE with the addition of contrast MPI. Four hundred consecutive patients were enrolled.

Results: WM + MPI resulted in 71 true-positive findings, compared with 46 by stand-alone WM ($P < .05$).True-positive results accounted for 46 of 50 positive test results for WM and 71 of 82 positive test results for WM + MPI (positive predictive value, 92% vs 87%; P = NS). In the subset of patients who underwent angiography (n = 116), the sensitivity, specificity, and accuracy for WM compared with WM + MPI were 63% versus 97% ($P < .05$), 91% versus 74% ($P < .05$), and 73% versus 89% ($P < .05$).

Conclusions: The addition of MPI to standard DASE increased true-positive test results by >50% compared with WM criteria, with a nonsignificant difference in positive predictive value. Twenty-five patients were diagnosed with obstructive coronary artery disease thanks only to isolated MPI abnormalities; the cardiac origin of their chest pain would have been mistakenly ''ruled out'' on the basis of the absence of WM abnormalities. (J Am Soc Echocardiogr 2009;22:404-410.)

Keywords: Stress echocardiography, Contrast, Chest pain, Myocardial perfusion, Dipyridamole

The inappropriate admission of patients with noncardiac chest pain is an avoidable cost to society. The development of safe and accurate diagnostic tools able to rule out obstructive coronary artery disease (CAD) in patients who complain of chest pain of undetermined origin without electrocardiographic (ECG) or myocardial enzyme changes is a priority. Previous studies showed that predischarge stress echocardiography (SE) had independent predictive value on future cardiac events in patients with chest pain in whom acute coronary syndromes were ruled out by electrocardiography and troponin measurements.[1,2]

The analysis of myocardial perfusion during dipyridamole-atropine SE (DASE) could prove effective in this subset of patients, thanks to its incremental sensitivity beyond standard wall motion (WM) criteria for CAD detection, while maintaining the excellent safety profile of DASE.[3,4] The potential increase in sensitivity obtained with contrast myocardial perfusion imaging (MPI) could be clinically relevant to patients, because MPI analysis has been demonstrated to be capable of predicting mortality and nonfatal myocardial infarctions in patients with suspected CAD after adjustment for clinical data and WM analysis.[5,6]

Perfusion defects during vasodilator stress develop because of a decrease in both components of myocardial blood flow, volume and velocity, in the capillary bed distal to a stenosis.[7,8] Although the quantitative measurement of myocardial blood flow reserve in each myocardial segment has proved accurate in detecting CAD in selected subsets of patients, it is time consuming and technically challenging.

The visual detection of regional discrepancies on MPI during stress is an alternative strategy for CAD detection that may be easier to apply in the clinical setting.[9]

From Dipartimento del Cuore, Azienda Ospedaliero, Universitaria di Parma, Parma, Italy.

Reprint requests: Nicola Gaibazzi, MD, Dipartimento del Cuore, Azienda Ospedaliero, Universitaria di Parma, Via Gramsci 14, 43100 Parma, Italy (E-mail: *nicola.gaibazzi@inwind.it*).

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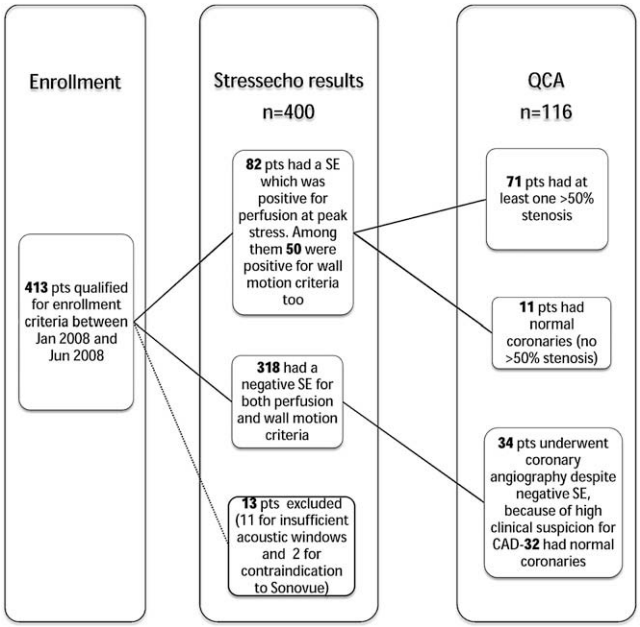

Figure 1 Study design and diagnostic flowchart of patients (pts).

We prospectively tested whether the addition of real-time MPI after dipyridamole can increase the sensitivity of DASE for the detection of CAD in a population of patients admitted to our chest pain unit, clinically at low to intermediate risk for CAD, in whom acute coronary syndromes were ruled out by normal ECG results and troponin levels. The relative values of WM and MPI criteria were compared for accuracy in a subgroup of patients who underwent coronary angiography.

METHODS

Patient Population

All consecutive patients presenting to our chest pain unit between January and June 2008 in whom acute coronary syndromes were ruled out by serial electrocardiography and cardiac enzyme levels and who met the inclusion criteria were enrolled and underwent DASE within 5 days after their index chest pain episode. The inclusion criteria were (1) a stress test requested by the cardiology consultant for an episode of chest pain of suspected cardiac origin, unexplained by extracardiac conditions; (2) the absence of new ischemic changes on electrocardiography or raised cardiac enzyme levels on $\geq$2 serial measurements; and (3) low to intermediate pretest risk for CAD, as estimated using a table of risk based on age, gender, chest pain type, and number of risk factors (Diamond and Forrester's[10] criteria integrated with Duke database data[11]). The exclusion criteria were (1) left ventricular ejection fraction (LVEF) $<$ 35%, (2) severe valvular disease, and (3) frequent or sustained ventricular arrhythmias or hemodynamic instability of any cause.

Study Protocol

All patients with positive results on DASE, on the basis of abnormal WM or MPI results or both, underwent quantitative coronary angiography (QCA) per protocol; patients with negative results on DASE underwent QCA only when felt appropriate by the referring physician, on the basis of clinical judgment (Figure 1).

The study complied with the Declaration of Helsinki. Patients gave specific informed consent when the administration of SonoVue (Bracco Imaging Italia srl, Milan, Italy) occurred $<$ 48 hours after the chest pain episode; in fact, this situation is still interpreted as a relative contraindication in the 2008 European Medicines Agency's[12] recommendations for SonoVue administration, even if the presence of a stable condition at the time of administration seems to be the real reason for this warning. All patients gave written informed consent to the study protocol, which was approved by the institutional review board of our hospital.

Clinical Evaluation

All patients were assessed clinically, including history, evaluation of cardiac risk factor profile, medication use, height, and weight.

Echocardiography

Stress Protocol. Patients underwent standard DASE with adjunctive MPI between the end of dipyridamole infusion (0.84 mg/kg over 10 minutes) and the beginning of atropine infusion 4 minutes later (atropine up to 1.5 mg in 2 minutes). Aminophylline was used to reverse the effect of dipyridamole. Consolidated endpoints and contraindications to DASE were used. Known allergy to sulfonamides, pregnancy, and lactation were considered contraindications to the administration of echocardiographic contrast media (SonoVue). In cases of contraindications to dipyridamole, dobutamine was used as a substitute, and in cases of contraindications to atropine, dobutamine 20 μg/kg/min was infused after the dipyridamole stage. All patients entered a follow-up program.

Standard and Myocardial Contrast Echocardiography. Patients underwent both WM and MPI studies using an iE33 echocardiograph with an S5 scan head (Philips Ultrasound, Bothell, WA). MPI was performed activating low–mechanical index (MI) power modulation imaging after the end of dipyridamole infusion, while WM acquisition was performed after atropine infusion, at peak heart rate. Flash-replenishment cine loops in the apical 4-chamber, 3-chamber, and 2-chamber views were digitally acquired, starting 1 minute after the initiation of SonoVue infusion (0.8-1.0 cm^3/min) and continuing through the end (4 minutes later, using one vial of SonoVue). A rotating infusion pump was used (BR-INF 100; Bracco Imaging Italia). After the 4 minutes dedicated to MPI, atropine was administered and SonoVue infusion stopped. Left ventricular opacification generally persisted long enough to allow for peak WM imaging with the left ventricle still opacified; if not, the residual contrast in the pump tubing (0.8 cm^3) was infused at this time by means of a saline bolus. MPI was performed acquiring both triggered and real-time flash-replenishment sequences at low MI (0.08-0.12) for each view; triggered images were acquired at 1 image per cardiac cycle using ECG gating at 250 ms after the R wave, while real-time mode acquired images at 39 frames/s. High-MI "flash" frames (8 frames; MI = 1.13) were delivered to destroy the microbubbles; on completion of the flash sequence, low-MI imaging automatically resumed. Myocardial contrast replenishment was visualized, and images were acquired from 1 cycle before flash frames through 10 cycles afterward.

Interpretation of WM. Regional WM analysis was evaluated at baseline and at peak stress by a semiquantitative assessment of the WM score index with the 16-segment model of the left ventricle, according to the recommendations of the American Society of Echocardiography.[13] Positive test results were defined as the occurrence in $\geq$1