

Simultaneous assessment of function and perfusion during dipyridamole-handgrip Tc-99m sestamibi imaging in chronic coronary artery disease

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The main goal of this work was to know the value of ventricular function in addition to perfusion Tc-99m sestamibi images in the assessment of coronary artery disease (CAD) when using dipyridamole (DIP) associated to isometric exercise. We analyzed 52 patients with suspected CAD; 40 of them had coronary lesions $\geq 50\%$ and 12 patients without CAD, conforming study and control groups, respectively. Twenty-eight patients had prior myocardial infarction. A two-day sestamibi protocol was employed with i.v. DIP-handgrip and rest injections, acquiring ECG-gated first pass and planar perfusion images.

Sensitivity for perfusion images was 85% and specificity was 91.7%. There was no change between rest and DIP ejection fraction (EF) in controls. CAD patients presented a significant EF decrease with DIP ($p: 0.0015$). Patients with ischemia in perfusion images had larger EF decrease ($p: 0.0001$). For the analysis, an EF drop $\geq 5\%$ and any wall motion abnormality (WMA) were considered as having an abnormal response to DIP. CAD sensitivity improved significantly to 92.5% when adding EF drop and to 90% when adding WMA parameters, but specificity decreased to 75% with EF drop, and to 58.3% with WMA. In conclusion, first pass parameters from DIP-isometric exercise in addition to perfusion images are not a significant help in the assessment of CAD.

Key words: dipyridamole, Tc-99m sestamibi, ventricular function, isometric exercise

INTRODUCTION

RADIONUCLIDE PERFUSION STUDIES are used widely for assessing coronary artery disease (CAD) and vasodilators such as dipyridamole (DIP) or adenosine may replace exercise with sensitivity and specificity around 70-95% for both Thallium-201 and Technetium-99m sestamibi. This latter also offers the alternative of measuring ventricular function simultaneously by the first pass technique and more recently by gated SPECT. Its value with

exercise stress has been well demonstrated¹ but combined with DIP or adenosine is controversial.²⁻⁵ The goal of this report was to evaluate the additive value of sestamibi functional parameters (EF and regional wall motion) over perfusion images when using DIP in association with handgrip in CAD patients. The use of pharmacological stress, especially vasodilators is very common in clinical practice and some groups, including echocardiographic ones, have combined it with isometric exercise in order to improve ischemia detection.⁶ We wanted to include isometric exercise in our protocol because it could increase its sensitivity, and also diminish collateral effects due to the increase in sympathetic tone; even though it has been demonstrated that left ventricular function changes with isometric handgrip do not allow sufficient clear discrimination between normal and CAD subjects.⁷ The value of DIP first pass angiography appears also as a good predictor of future events in CAD patients.⁸

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MATERIALS AND METHODS

We prospectively studied 52 patients with suspected CAD (37 males and 15 females, age 58 ± 9 years old, ranging from 39 to 76) who submitted to contrast coronary angiography as a screening procedure, or for CAD evaluation (12 with stable angina, one with coronary bypass grafting and 28 with prior myocardial infarction); 40 of them had significant coronary stenosis of $\geq 50\%$, 14 with single, 16 with double, and 10 patients with triple-vessel disease. Twelve other patients (8/12 females) without significant angiographic lesions ($< 35\%$) were the control group; 5 were hypertensive, one had right ventricle arrhythmogenic dysplasia, one had mild aortic stenosis, but the other 5 did not have any demonstrable disease detected with other methods. Their age was 55 ± 8 y.o. (p : ns from the CAD group). Beta-blockers and xantines were withdrawn 24 hours prior to the radionuclide study, performed within 3 months of contrast angiography (16 ± 18 days).

Sestamibi Protocol: First day: DIP was administered and immediately a first pass angiography was acquired. One hour later a perfusion image set was done. Second day: the same study was performed at rest. Quality control of Tc-99m sestamibi demonstrated labeling efficiency of $97.8 \pm 1.3\%$.

Dipyridamole Test: A standard 4 minute DIP continuous infusion was used (0.56 mg/kg). At minute eight, 925 MBq of Tc-99m MIBI was injected as a bolus in an external jugular or right antecubital vein.

Isometric Exercise with a handgrip was performed during minutes 6–10 of DIP infusion (approximately at 25%–50% of maximum). The model was a Harpenden British Indicators Ltd. AM006-003. Aminophylline was administered in some cases, after the radionuclide injection.

First pass angiography: ECG-gated list mode acquisition in RAO 30 degrees, were acquired with a Digital PDP 11-34 computer, and a 32×32 matrix. The first 20 studies were acquired with a high resolution collimator; and for the other 32 we had available a high sensitivity one. For processing we included in the analysis only those studies with good quality bolus, at least 5 similar beats and enough statistical information (2,000 counts at end diastole), and the computer generated a representative cycle. The studies were read by one observer blinded to the patient's condition information. Segmental wall motion was analyzed visually. Manual end diastolic and end systolic after lung background correction regions of interest were applied for EF measurement. Linear correlation between rest sestamibi EF and contrast EF was 0.52, but the slopes were significantly different ($p < 0.0001$).

Perfusion images: All patients received a caloric snack 20 minutes after radionuclide injection, intending to diminish gallbladder activity. Three view gated images with 10 frames were recorded in a 64×64 matrix selecting the best lateral anterior oblique, anterior or right anterior oblique and left lateral views. Summed original, background subtracted diastolic and systolic from gated images were analyzed by 2 blinded observers (including

Table 1 Hemodynamic data in control and CAD groups at baseline and under dipyridamole-handgrip (mean \pm SD)

	Coronary artery disease		Controls	
	baseline*. \S	dipyridamole#. \S	baseline*. \dagger	dipyridamole#. \dagger
Heart rate (bpm)	67 \pm 11	93 \pm 13	69 \pm 9	101 \pm 10
Blood pressure (mmHg)				
Systolic	134 \pm 19	145 \pm 23	138 \pm 21	151 \pm 29
Diastolic	82 \pm 11	87 \pm 15	80 \pm 11	88 \pm 12
Double product	8.899 \pm 1.857	13.483 \pm 3.065	9.472 \pm 2.160	5.343 \pm 3.893

*. $\#$: $p = ns$ \dagger . \S : $p < 0.04$

Table 2 Baseline and dipyridamole-handgrip ejection fraction (%) in controls and coronary artery disease group and also according to presence of ischemia perfusion scan

	Controls	Coronary artery disease patients		
		All	Ischemia on perfusion scan	
			absent	present
Rest EF \pm SD	46.9 \pm 9.3	40.0 \pm 14.3*	51.3 \pm 10.2 \S	36.7 \pm 13.7#. \S
DIP EF \pm SD	45.5 \pm 8.6	35.9 \pm 16.0*	53.4 \pm 13.0 \dagger	30.8 \pm 12.0#. \dagger

*: $p = 0.0015$, \S : $p = 0.034$, #. \dagger : $p < 0.0001$

DIP: dipyridamole

summed radial profiles comparing rest with DIP). Five myocardial segments were compared with contrast angiography: antero-lateral, septal, inferior, postero-lateral and infero-apical. All perfusion studies were technically adequate and only one had bowel activity very close to left ventricle.

Statistics: Diagnostic accuracy and predictive values were calculated for radionuclide perfusion and function studies, considering both the decrease in EF and wall motion abnormality at rest or detection of new defects. The additive value of function over perfusion was also calculated. EF variation was analyzed by t test ($p < 0.05$). The DIP EF normal limit was considered to be at 5% under the rest value. This figure was obtained after analysis of our control group behavior.

RESULTS

Baseline and DIP changes in hemodynamic parameters in both control and CAD groups are shown in Table 1; there was no difference between controls and CAD patients in heart rate or blood pressure values, but there was a difference ($p < 0.04$) after DIP in both groups; 57% of CAD patients had an abnormal electrocardiogram with DIP but none of controls. New perfusion defects appeared with DIP in 23 CAD patients and in one control.

The sensitivity for perfusion images was 85% and the specificity 92%; CAD prevalence was 77%. Excluding infarcted patients, sensitivity was 83%; accuracy 88%; positive and negative predictive values were 91% and 85%, respectively.

No change was observed between rest and DIP EF in controls mean values were 46.9 ± 9.3 and $45.5 \pm 8.6\%$, respectively; CAD patients presented a significant EF decrease with DIP ($p: 0.015$). The analysis of CAD patients according to the presence of ischemia on perfusion images is shown in Table 2; those with ischemia had a significant EF decrease with DIP ($p < 0.0001$) and also a lower rest EF than non ischemic patients ($p: 0.034$). CAD patients without ischemia did not have a significant EF change. On the other hand, basal EF was similar in the control group compared to patients with a different number of diseased vessel. However, DIP EF was significantly lower in patients with single or double vessel disease ($p < 0.05$); triple-vessel patients had the same trend.

New wall motion abnormalities with DIP were observed in 11 CAD patients and also in 4 controls. Sensitivity and specificity with EF drop $\geq 5\%$ or the occurrence of new wall motion abnormalities were lower than perfusion values (Table 3). Combined function and perfusion CAD sensitivity improved from 85% to 92.5% if adding EF drop and to 90% if adding new wall motion abnormalities. Specificity decreased from 91.7% to 75% with EF drop and to 58.3% when using new motion abnormalities, but none of the differences were significant (Table 4). The agreement between perfusion and functional abnormali-

Table 3 Diagnostic value of perfusion and functional abnormalities in coronary artery disease patients

	Sensitivity	Specificity
Perfusion	85.0%	91.7%
EF drop $\geq 5\%$	47.5%	83.3%
New WMA	27.5%	66.6%

EF: Left Ventricular Ejection Fraction, WMA: Wall Motion Abnormality

Table 4 Additive diagnostic value of function over perfusion sestamibi studies for coronary artery disease

	Sensitivity	Specificity
Perfusion	85.0%	91.7%*
Perfusion plus:		
EF drop $\geq 5\%$	92.5%	75.0%
New WMA	90.0%	58.3%*
New WMA + EF drop	90.0%	83.3%

* $p = 0.06$

$p > 0.3$ for all others

EF: Left Ventricular Ejection Fraction, WMA: Wall Motion Abnormality

ties was only 54% ($\kappa = 0.13$).

DISCUSSION

In the results the value of DIP-handgrip perfusion images for CAD assessment was good and comparable with that reported in the current literature for exercise and pharmacological stress,^{1,9} and our specificity was somehow higher considering we did not include true normal subjects. When left ventricular functional parameters are added, rest images may help to detect CAD only if they are abnormal. A decrease in left ventricular EF or WMA with stress indicates ischemia in CAD patients.

In exercise and DIP, the normal response of hemodynamic parameters differs: isotonic exercise induces a clear increase in EF, blood pressure and heart rate. Isometric exercise has a different behavior with only a weak EF effect in normals (it could even decrease and some patients develop motion abnormalities); compared to bicycle exercise, heart rate and blood pressure have a greater increase.^{7,10,11}

The response to DIP infusion in normals is a mild decrease in systolic, diastolic and mean blood pressure and an increase in heart rate and EF. It has been reported that DIP induced coronary hyperemia produces mild hemodynamical changes in patients with and without CAD.¹² Moreover, aging does not affect EF DIP response when healthy young are compared to an elderly population.¹³ In CAD, EF behavior was similar for DIP and exercise for Indolfi¹⁴; DIP EF changes sensitivity and specificity were 75% and 76%, respectively. Cates² re-

ported that DIP was very specific but a moderately sensitive test in severe CAD. Konishi studied a group of CAD patients finding a low correlation between exercise and DIP in EF and WMA, only 8% of the group DIP EF decrease versus 77% in exercise. The discrepancy was lower for WMA and also less abnormalities were observed with DIP.¹⁵

The lack of EF improvement in our controls may be explained by the combined effects of DIP and handgrip. These could be supported by the observations made with isometric exercise when compared with isotonic exercise, with opposite effects in left ventricular EF.¹⁶

Another study in young healthy volunteers compared 4 different stresses: dobutamine exercise, adenosine triphosphate (ATP) and DIP¹⁷; dobutamine obtained the greater left ventricular EF increase and DIP the minor (4 ± 3%; with a doses of 0.84 µg/kg/min), they used equilibrium ventriculography; furthermore, another group using standard doses had reported an EF decrease of more than 3% with DIP as a normal limit¹⁸ for CAD detection (with first pass ventriculography); 77% of their patients with reversible thallium-201 defects were under their normal EF limit.

Sciagra⁴ evaluated the value of DIP first pass added to perfusion sestamibi images and his results demonstrated no helpful clinical information over perfusion images alone, his EF sensitivity was 63% and 70% for WMA, and 77% for any parameters. These exercise values are higher than our results. On the other hand, Bodenheimer,¹⁹ considered handgrip EF to be more sensitive than WMA for detecting CAD.

Ischemic patients had a significantly diminished EF with DIP-handgrip in the protocol, as expected. Nevertheless, there are some reports that indicates little value in adding DIP or even exercise functional data to perfusion in CAD evaluation^{5,20} and our experience with DIP-handgrip also support this. On the other hand, triple vessel patients did not reach a significant decrease in DIP-handgrip EF versus basal EF, whereas single and double vessel patients did, probably due to the smaller size of that subgroup. Takeishi²¹ compared DIP EF in different patients also, and significant changes were observed only in multi-vessel disease.

Limitations of the study

Our control group had a rest EF value lower than usual considering the exercise and DIP values; this may be explained by problems with the measurement, but the analysis of EF changes was performed by comparing the same group under 2 sets of conditions, and they have statistical value. Another point is that the low correlation between DIP-handgrip perfusion and function (54%) may also be related to difficulties in acquiring first pass data with a single crystal camera. We only included studies with good technical characteristics in counts and bolus for the analysis, in which adequate processing was done.^{22,23}

Other reports with DIP gave similar results,^{15,24} i.e. Zafrir et al. reported a 65% agreement between perfusion and function.

We are aware that normal catheterized patients are not *true normals* but, after all, they represent clinical practice. It is well known that patients with low probability of CAD have better specificity for perfusion studies than patients with normal angiograms submitted to the test to evaluate a possible CAD. As reported by Rozansky²⁵ this is true also for radionuclide ventriculography exercise. In that work angiographically normal patients included about a third of patients with abnormal EF and abnormal wall motion response, but in this paper we did not analyze exercise stress. DIP has a different mechanism of action; even reflex vasoconstriction stenoses in isometric exercise plays a role,²⁶ and is able to modify the response.

In conclusion, in these patients, simultaneous assessment of perfusion and function during DIP and handgrip stress has a limited incremental diagnostic value for the detection of CAD. Considering the importance of cost versus benefit concepts, this protocol does not appear a good choice, but for risk stratification assessment it needs to be established.

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