

Study of Coronary Flow Reserve with Intravenous Use of Microbubbles (Contrast Echocardiography) and Adenosine. Protocol for Clinical Application in Patients Suspected of Having Coronary Heart Disease

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Objective - To test the feasibility, safety and accuracy of the adenosine protocol in the study of myocardial perfusion with microbubbles contrast echocardiography.

Methods - 81 pts (64 male, 60±11 years) were submitted to contrast echocardiography with PESDA (sonicated solution of albumin 20%-1ml, dextrose 5%-12ml and decalfluorobutane gas-8ml) to study the myocardial perfusion at rest and after bolus injection of adenosine (6 to 18mg) and to coronary angiography within 1 month each other. For each patient 3 left ventricle perfusion beds were considered (total of 243 territories). 208 territories were analyzed and 35 territories were excluded. PESDA was continuously infused (1-2ml/min), titrated for best myocardial contrast. Triggered (1:1) second harmonic imaging was used.

Results - Coronary angiography showed 70 flow limiting ($\geq 75\%$) lesions and 138 no flow limiting lesions. At rest an obvious myocardium contrast enhancement was seen in at least 1 segment of a territory in all patients. After adenosine injection an unquestionable further increase in myocardial contrast was observed in 136 territories (99%) related to no flow limiting lesions, lasting < 10 s, and a myocardial perfusion defect was detected in 68 territories (97%) related to flow limiting lesions. It was observed only 4 false results. There were no serious complications.

Conclusion - Myocardial perfusion study with PESDA and adenosine protocol is a practical, safe and accurate method to analyze the coronary flow reserve.

Key-words: myocardial perfusion, echocardiographic contrast(microbubbles), coronary disease

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Myocardial echocardiographic identification of contrast injected in peripheral veins is a reality¹⁻⁴. Microbubbles obtained with sonication of fluorocarbon gases (PESDA)⁵⁻⁷ and other echo contrast agents⁸⁻¹² have already been used. In coronary artery disease with significant obstructions, defects in myocardial perfusion (usually demonstrated in the walls with a reduction in perfusion¹³, mainly after pharmacological stress with dipyridamole¹⁴ or dobutamine¹⁵) may be useful in identifying myocardial ischemia¹⁶, myocardial risk area¹⁷, and in determining infarct size¹⁶.

The significant reduction in coronary flow reserve resulting from a significant coronary obstruction ($\geq 75\%$) is the major marker of myocardial ischemia with physiological significance, because in regions perfused by arteries free from obstruction, this flow may increase up to 3 times its resting value¹⁸. Examinations using pharmacological stress with dipyridamole or dobutamine may show the decrease in coronary flow reserve, but with mechanisms of action primarily related to other reasons¹⁹. For both drugs, the appearance of myocardial ischemia is the final effect necessary to show the perfusion defect. These drugs, when used in myocardial perfusion study protocols with intravenous infusion of microbubbles in humans, do not detect the increase in coronary flow in normally perfused walls.

We assessed the hypothesis that intravenous adenosine bolus injection during echocardiography with PESDA microbubbles may not only show the perfusion defect in the hypoperfused coronary bed, but also identify the increase in perfusion in the normal region, due to its promptness in reducing coronary resistance. We also established and tested a protocol for detecting coronary artery disease in humans using echocardiography with PESDA microbubbles at rest and after stress with adenosine.

Methods

We selected 81 patients (mean age = 60.3±11, ranging

from 30 to 83 years, 64 males and 17 females) out of 532 patients undergoing echocardiography with PESDA microbubbles at the Hospital Pró-Cardíaco and at the ECOR (Centro de Diagnóstico Cardiovascular - Rio de Janeiro). This selection aimed to investigate symptoms suggestive of coronary artery disease in patients who underwent coronary angiography within a month after myocardial contrast echocardiography (tab. I). No patient had aortic stenosis or hypertrophic cardiomyopathy. Fourteen patients had a history of systemic arterial hypertension and 4 had diabetes mellitus. Thirty-one (38.3%) patients showed some evidence of previous acute myocardial infarction based on their clinical history, on the presence of pathologic Q waves on electrocardiography at rest, and on the presence of abnormalities in segmentary contraction on left ventriculography and on two-dimensional echocardiography. The left ventricular walls related to the arteries responsible for previous infarcts were excluded from the analysis. In addition to these walls, 4 other walls, in 4 different patients, were also excluded because of the low quality of their echocardiographic images. All patients remained clinically stable in the period between the perfusion study and the coronary angiography. Abnormalities in the segmentary contraction at rest were detected in 55 (67.9%) patients, those with previous acute myocardial infarction inclusive (tab. I).

In 9 patients, coronary angiography was considered normal. Of the 72 patients with coronary artery disease, 12

had disease in 3 vessels, 19 in 2 vessels, 31 in 1 vessel, and 10 patients had no residual coronary lesion after a complete revascularization procedure (implantation of the left internal thoracic artery in 1 patient, percutaneous transluminal angioplasty in 4 patients, and association with stent implantation in 5 patients – tab. I).

In each patient, the left ventricular walls were divided into 3 regions or coronary beds that overlapped. The anterior wall and the anterior part of the interventricular septum were considered part of the region of the anterior descending artery. The anterolateral wall was considered part of the anterior descending artery region or part of the circumflex artery region. The posterolateral wall, the posterior wall, and the posterior part of the interventricular septum were considered part of the circumflex artery region or of the right coronary artery region. Each wall was still divided into 3 segments (basal, middle, and apical)²⁰.

In these 81 patients, 70 regions were related to limiting flow coronary lesions (obstruction $\geq 75\%$), 138 regions were related to normal coronary arteries or to nonlimiting flow lesions, 31 regions were related to previous myocardial infarctions, and 4 regions were not visualized. In cases of sequential arterial obstructions, only the most significant one was considered.

Oral consent was obtained for all patients according to the research protocol approved by the National Committee on Ethics and Research of the Health Ministry and by the Committee on Ethics and Research of the Hospital Pró-Cardíaco.

PESDA was prepared according to the previously reported method²¹ modified to use 20% human albumin instead of the 5% solution. Briefly, 1 mL of 20% human albumin was mixed with 12 mL of 5% glucose solution in a 20-mL syringe connected to a 3-way tap. Another 20-mL syringe containing 8 mL of decafluorobutane gas (Flura Corporation, Rock Hill Laboratories, Newport, TN, USA) was then connected to the first syringe. The contents of the 2 syringes were mixed and agitated for at least 1 minute, and then underwent electromechanical sonication for 80 seconds at a frequency of 20 KHz, with the sonicator (Heat Systems Inc, Farmingdale, NY, USA) at maximum potency. The resulting solution was maintained in the refrigerator and used within 24 hours.

Patients were advised to restrict their ingestion of caffeinated beverages or theophylline during the 12 hours preceding the examination. Drugs containing dipyridamole were suspended 1 day prior to the examination. No other medication was suspended.

The prepared PESDA solution was diluted in 80 mL of 5% glucose solution and continuously infused in a peripheral vein with no infusion pump. Dripping rate depended on the effect obtained with the contrast agent and was performed as follows: we used commercially available equipment (HDI 3000, ATL, Bothell, WA, USA) operating in second harmonic with initial adjustments; intermittent images (trigger mode): 1:1 with the QRS of the electrocardiogram, using T-wave or R-wave peak to obtain the best image; map of the two-dimensional echocardiogram = 8; dynamic range = 60

Table 1 – Clinical, echocardiographic, and coronary angiographic characteristics of the patients (the numbers in parentheses represent regions)

N	81 patients (243)
Age: 30 to 83 years	60.3±11 years
Sex: male/female	64 / 17
Systemic arterial hypertension	14
Diabetes mellitus	4
Abnormal segmentary contraction	55
Previous AMI	31
No coronary obstruction	9 patients (27)
No coronary obstruction after revascularization	10 patients (30)
CABG	1 patient (3)
PTCA	4 patients (12)
PTCA + <i>stent</i>	5 patients (15)
Single-vessel disease	31 patients (93)
Previous AMI	(10)
Nonvisualized	(1)
Nonlimiting flow	(62)
Limiting flow	(20)
Double-vessel disease	19 patients (57)
Previous AMI	(14)
Nonvisualized	(1)
Nonlimiting flow	(19)
Limiting flow	(23)
Triple-vessel disease	12 patients (36)
Previous AMI	(7)
Nonvisualized	(2)
Nonlimiting flow	(0)
Limiting flow	(27)

AMI- acute myocardial infarction; CABG- coronary artery bypass graft;
PTCA- percutaneous transluminal coronary angioplasty.

dB; output adjusted to produce mechanical index (mi) = 0.7 or 0.8; focus adjusted to the level of the mitral valve in an apical 4-chamber view.

Initial dripping was 30 to 40 drops/minute. After approximately 1 minute, the velocity of infusion was readjusted to provide maximum contrast (close to white in the gray scale) in the left ventricular cavity without production of shadows by the microbubbles. However, if these microbubbles produced a shadow inside the left ventricle, dripping was reduced so that the shadow would remain inside the left atrium, behind the mitral valve, in an apical 4-chamber view.

Obtaining images at rest - After the infusion velocity was established, the controls were adjusted to provide an optimal identification of the contrast agent in the walls (fig. 1) as follows: with a mechanical index of 0.7 or 0.8 (as initially established), the gain was increased until the contrast in the walls was considered satisfactory; time-gain compensation (TGC) was then adjusted to homogenize, from the left ventricular apex to its base, the identification of the contrast in the walls with no difference in the gray scale, mainly in the adjacent regions. Output-power was then diminished step-by-step, reducing the mechanical index, until all segments of the wall became black, allowing, or not, visualization of the maintenance of homogeneity of the contrast agent in the segments of the wall, always comparing segments located within the same distance from the transducer. For example, in the apical 4-chamber view, the basal segment of the lateral wall can only be compared with the basal segment of the interventricular septum; output-power was then increased until the mechanical index of 0.6 or 0.7 was reached. With this adjustment, the contrast in the walls may be perfectly identified, and conditions for its intensification or reduction after adenosine use exist.

After image optimization, all controls of equipment and of PESDA dripping were maintained constant, and the images were recorded on videotape. One ampoule (6mg) of adenosine (Adenocard®, LIBBS Farmacêutica Ltda, São Paulo, Brazil) was then injected in bolus in the same venous route producing a rapid intensification of the contrast agent in at least 1 segment of the left ventricular wall. If no respon-

se was observed, 2 (12mg) or 3 (18mg) ampoules were injected. Adenosine begins to act approximately 20 to 60 seconds after its injection and continues for an additional 20 to 30 seconds. Simultaneously, tachypnea appears and may impede examination. Patients were alerted to the phenomenon and advised to maintain respiratory excursion for at least 5 seconds from the moment they felt the need to inhale deeper.

Echocardiographic imaging was obtained with a specific transducer, which operated at 2 MHz when in the nominal frequency, and at 1.67 MHz for emission and 3.34 MHz for reception, when in second harmonic.

All patients were studied with apical 4-chamber and 2-chamber views. Whenever possible, we also used the transverse view of the short left ventricular axis at the level of the papillary muscles, and a modified apical (shortened) view with the ultrasound beam entering in the left ventricular apex and leaving in the inferobasal region.

Image acquisition started right after optimization of the equipment and PESDA dripping controls, and immediately before adenosine injection, continuing until its effect on the myocardium disappeared. Visual gradation of the contrast in the myocardium at rest and of its intensification after adenosine bolus injection was performed by 2 independent reviewers, based on videotape images in loop format using the computerized system ImageVue DCR (Nova MicroSonics, Allendale, NJ, USA). Each reviewer assessed the distribution and homogeneity of the contrast, at rest, in each left ventricular wall and in all echocardiographic views used. After adenosine injection, we assessed intensification, reduction, or maintenance of the intensity of the contrast agent in the walls, which could be observed during the maximum effect of the drug.

The normal myocardial perfusion image at rest was present when the contrast, in a certain echocardiographic view, had a homogeneous distribution in all segments of the left ventricular walls; comparison was always performed between segments situated at the same depth in a given echocardiographic view (fig. 1). Persistence of this homogeneity with a decrease in the mechanical index was normal until the contrast agent could no longer be observed in the myocardium (fig. 2) in all images obtained. After adenosine bolus injection, the normal perfusion image had a marked intensification of the contrast agent in all left ventricular wall segments (fig. 3).

The myocardial perfusion image at rest was considered abnormal when the contrast agent was heterogeneously distributed in the left ventricular wall segments (fig. 4), or when this heterogeneity could be induced or better demonstrated with a decrease in the mechanical index, a condition in which the abnormal segment would appear darker than its contralateral segment (fig. 5). After adenosine injection, the abnormal perfusion image showed lack of intensification of the contrast agent in defective segments at rest (fig. 6) or, as more frequently observed, a reduction in the contrast agent in normally or poorly contrasted segments at rest (fig. 7).

Interobserver and intraobserver variability in the analysis of the perfusion images reported was determined by

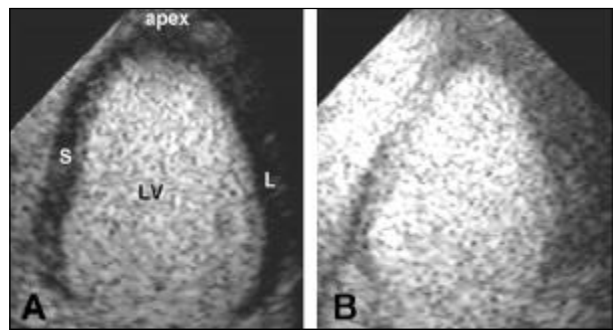


Fig.1 - A) - Prior to final preparation, a great quantity of microbubbles can be seen inside the left ventricle (LV), but not in the walls. Absence of a shadow inside the LV indicates that the dripping velocity of the microbubble solution is satisfactory. B) After final adjustments, the contrast distribution is homogeneous and intense in the walls. L- lateral wall; S- interventricular septum.

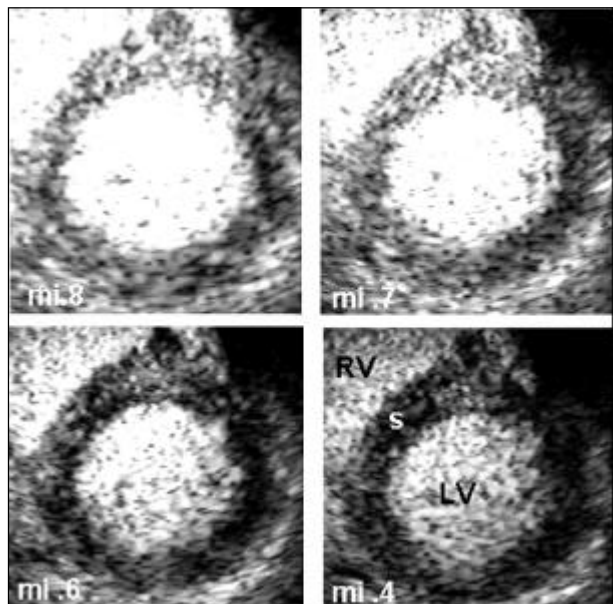


Fig. 2 - Persistence of homogeneity in all images obtained during the gradual reduction in the mechanical index (mi) until no more contrast agent can be seen in the walls. LV- left ventricle; RV- right ventricle; S- interventricular septum.

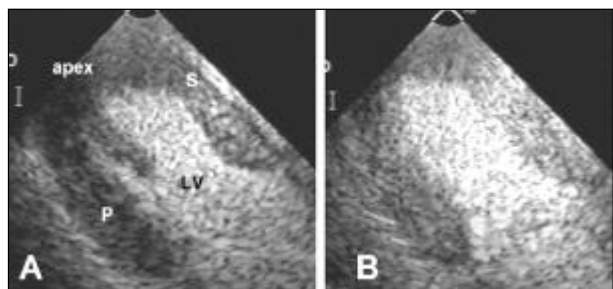


Fig. 3 - Normal pattern of myocardial perfusion: before (A) and after (B) adenosine bolus injection. The normal pattern of perfusion is the marked intensification of the contrast agent observed at rest in all segments of the LV walls. P- posterior wall; S- interventricular septum; LV- left ventricle.

comparison of the percentage of concordance between the 2 independent observers in all patients.

Statistical analysis - To determine inter- and intraobserver variability, we used the kappa (κ) statistic with values greater than 0.4, 0.6, and 0.8 indicating low, good, and excellent concordances, respectively²². The chi-square test was used to determine the significance or nonsignificance of the distribution of concordance between coronary obstruction and the perfusion defect, and also between the absence of coronary obstruction and normal perfusion. Sensitivity, specificity, global accuracy, and positive and negative values of the examination were also calculated²³. The Student *t* test for paired samples was used to compare the means of heart rate before and after adenosine bolus injection. For all statistical tests, a value lower than 0.05 was considered significant.

Results

Intravenous infusion of PESDA produced myocardial

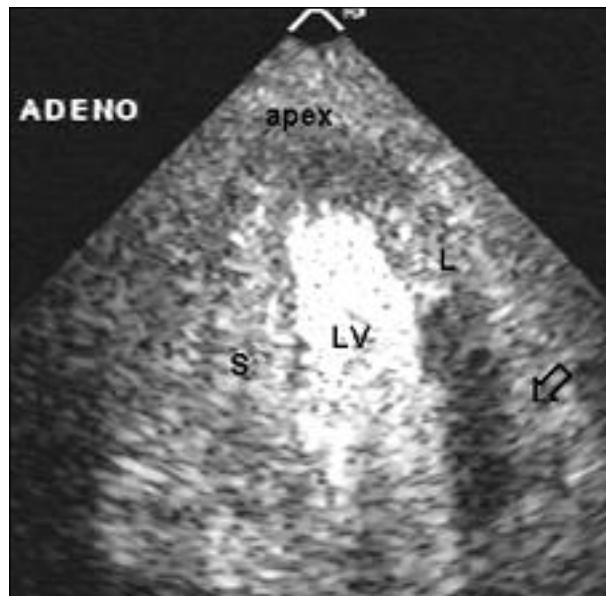


Fig. 4 - Evident perfusion abnormality at rest, prior to adenosine administration, in the basal part of the lateral wall (arrow). L- lateral wall; S- interventricular septum; LV- left ventricle.

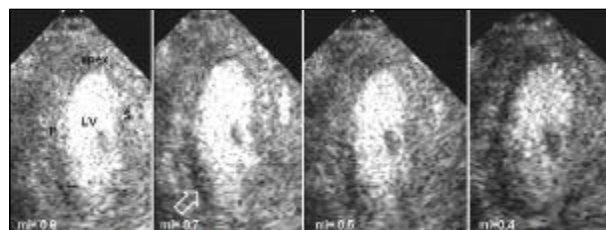


Fig. 5 - Heterogeneous pattern of myocardial perfusion at rest induced by gradual reduction in the mechanical index (mi). The mechanical index reduction from 0.8 to 0.7 documents the perfusion abnormality in the basal part of the posterior wall, and the progression in mechanical index reduction down to 0.4 documents the perfusion abnormality in all the wall extension. P- posterior wall; S- interventricular septum; LV- left ventricle.

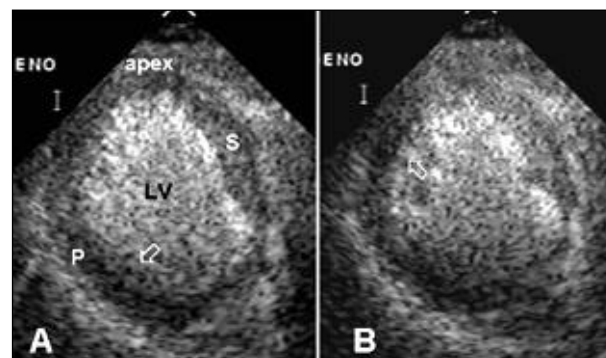


Fig. 6 - At rest (A), perfusion abnormality is seen in the basal part of the posterior wall (arrow). After adenosine administration (B), the abnormal region becomes darker and can be seen spreading to the apical part of the posterior wall (arrow). P - posterior wall; S - interventricular septum; LV - left ventricle.

contrast, which was intensified by the adenosine bolus injection in at least 1 segment of the left ventricular walls, in all patients when visually estimated by 2 reviewers.

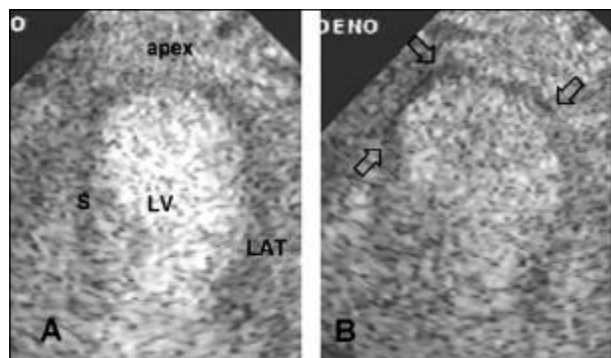


Fig. 7 – Homogeneous perfusion (normal) at rest (A). After adenosine administration (B), the perfusion abnormality (dark area) can be seen in the apex and apical region of the interventricular septum. S - interventricular septum; Lat - lateral wall; LV – left ventricle.

To obtain contrast intensification in the left ventricular walls, 62 (76.5%) patients required 1 single ampoule (6mg) of adenosine, 14 (17.3%) patients required 12mg, and 5 (6.2%) patients required 18mg to obtain the same result.

In these 81 patients, a total of 208 regions not associated with infarcts related to obstructed coronary arteries were analyzed (tab. II and fig. 8). We observed that 138 coronary arteries (or regions) were normal or had an obstruction <75%, and that 70 coronary arteries (or regions) had a severe obstruction (lesion ≥75%). Of these 70 obstructions, impairment of the area of the anterior descending coronary artery was observed in 18 patients, of the area of the circumflex artery or of the obtuse marginal artery in 33 patients, and of the area of the right coronary artery in 19 patients.

The visual pattern of normal perfusion at rest and after adenosine bolus injection was observed in 136 of the 138 regions (98.6%) perfused by a normal coronary artery or an artery with obstruction <75%. In the 2 other regions, the perfusion pattern was considered abnormal (false-positive).

In the 70 regions perfused by arteries with total obstruction or obstruction ≥75%, as compared with the normally perfused segments, a reduction in the intensification of the contrast agent at rest was observed (consensus between the 2 reviewers) in at least 1 segment in 52 (74.3%) regions. In regard to these regions, adenosine bolus injection increased the abnormal area in 20 (38.5%) regions, but did not change the abnormal area in the remaining 32 (61.5%) regions. In 16 (22.9%) normally perfused regions at rest, an

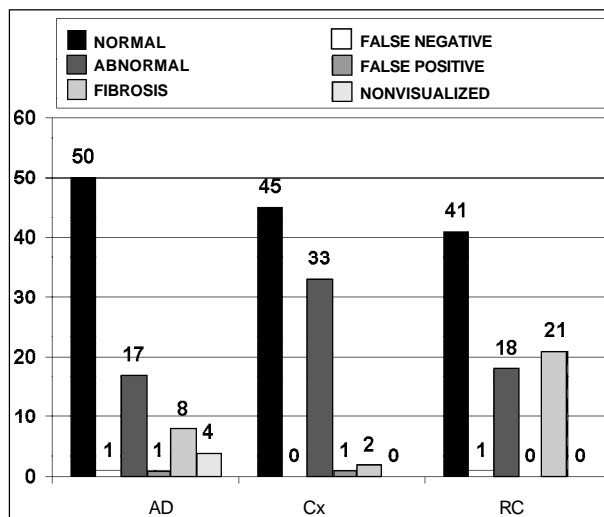


Fig. 8 - Distribution of the myocardial perfusion patterns in the region-by-region analysis. AD - anterior descending artery; Cx- circumflex artery; RC- right coronary artery.

abnormality was only demonstrated after adenosine bolus injection. Only 2 regions showed the normal perfusion pattern at rest and after adenosine injection (false-negative).

Sensitivity was 97.1% (68 of the 70 regions related to arteries with limiting flow obstructions); specificity was 98.6% (136 of the 138 regions related to normal arteries or arteries with nonlimiting flow obstruction); and global accuracy was 98.1% (204 of the 208 regions analyzed). Positive and negative predictive values were 97.1% and 98.6%, respectively. The odds ratio for an abnormal test was 0.694, and 0.34 for a normal test (p<0.001).

Concordance between absence or presence of coronary obstruction and normal or abnormal perfusion using the chi-square test was statistically significant ($\chi^2=186.21$, p<0.001), with only 4 discordant cases (2 in normal regions and 2 in abnormal regions). Intra- and interobserver concordances were excellent, with k=0.94 and k=0.91, respectively.

Adenosine, at the dosages used, did not cause abnormalities in segmentary contraction in any patient. On the other hand, it induced a mild, but significant, increase in heart rate (from 71±8 to 84±14 bpm, p<0.001). Two patients who received 12mg and 1 who received 18 mg of adenosine had asymptomatic and transient (8 to 10 seconds) third-degree atrioventricular block. The sensation of facial heat, chest discomfort, and cephalgia were reported in 10 (12%), 3 (3.7%), and 4 (4.9%) patients, respectively. All patients developed tachypnea, which lasted less than 30 seconds, did not require treatment, and did not impede new adenosine injections when necessary.

Discussion

This study shows that myocardial contrast echocardiography with continuous PESDA infusion and adenosine bolus injection may assess coronary flow reserve, and, therefore, may be used to identify coronary artery disease, be-

Analyzed = 208						Excluded = 35					
AD = 67	Cx = 78	RC = 59	AD = 12	Cx = 2	RC = 21						
NL AN	NL AN	NL AN	nv fib	nv fib	nv fib						
50 17	45 33	41 18	4 8	0 2	0 21						
IFN@IFP&	- IFP& IFN@	-	-	-	-						

AD- anterior descending artery; Cx- circumflex artery; RC- right coronary artery; NL- normal perfusion; AN- abnormal perfusion; nv- nonvisualized; fib- fibrosis; FN- false-negative; FP- false-positive; @ - related to the same patient; & - 2 different patients.

cause the abnormal perfusion sites correlate with the regions related to obstructed arteries.

The severity of coronary obstruction assessed on coronary angiography is usually expressed as a percentage of stenosis in relation to the diameter of the vessel. This method has limitations, because it does not take into consideration other characteristics of the lesion, such as length, shape, and eccentricity, which are known to affect coronary flow resistance. The weak correlation existing between the coronary angiographic assessment of the degree of obstruction and the postmortem examination findings is also known²⁴⁻²⁶. A great intra- and interobserver variation exists²⁷⁻²⁹, as well as a limited capacity of the observers to predict the hemodynamic significance of a certain coronary stenosis^{30,31}. Quantitative coronary angiography improved the evaluation of the degree of coronary stenosis³², but limitations still persist^{33,34}. In addition, the demonstration of the stenosis and its degree does not describe the level of the perfusion defect, or the myocardial area involved.

Analysis of coronary flow reserve should be used to assess the hemodynamic consequences of coronary artery stenosis³⁵⁻³⁷. The measurement of coronary flow reserve during quantitative coronary angiography has been proposed to assess all anatomical factors that influence the severity of arterial stenosis^{38,39}. A good correlation between coronary flow reserve analyzed on intracoronary Doppler and the arterial stenosis detected on quantitative coronary angiography has also been reported⁴⁰. Myocardial contrast echocardiography has also been proposed to assess the physiological significance of coronary lesions during pharmacological vasodilation induction⁴¹⁻⁴⁵.

Adenosine is a potent coronary vasodilator. Peripheral venous adenosine injection increases coronary flow 3 to 4 times due to a drop in coronary resistance⁴⁶, which results in an increase in myocardial vascularization and in myocardial blood flow. In coronary artery disease with single-vessel obstruction, adenosine injection increases blood flow in normally perfused regions, where resistance will decrease. In the areas perfused by an artery with limiting flow obstruction, the resistance vessels are maximally dilated and no changes will occur, or a reduction in flow may happen due to the coronary steal phenomenon⁴⁷⁻⁴⁹.

Variation in the intensity of the contrast reflects changes in myocardial blood flow⁵⁰. Therefore, an increase in the intensity of the contrast is expected to occur in the absence of coronary artery stenosis. In our patients, this fact was observed in 136 of the 138 regions perfused by normal coronary arteries or by coronary arteries with nonsignificant obstructions. However, in cases of significant coronary stenosis, coronary flow reserve is reduced and the response to adenosine injection (vasodilation and capillary recruitment) is not observed, and, therefore, the normal increase in myocardial blood volume does not occur⁵⁰. Therefore, the same increase in contrast intensity observed in normal regions did not occur in 68 of the 70 regions perfused by coronary arteries with significant obstructions. In our study, the use of these perfusion patterns had a global accuracy of 98.1%,

with high positive and negative predictive values (97.1% and 98.6%, respectively).

Despite the alterations in the distribution of coronary flow, adenosine injection does not necessarily induce myocardial ischemia, even when it causes abnormalities in myocardial blood volume and makes the intensification of myocardial contrast in the abnormal segments heterogeneous⁵¹.

Adenosine bolus injection caused a marked difference (easily identified from the point of view of visual assessment) between the lowest myocardial contrast observed in the region perfused by a critically stenotic vessel and the intensification of the contrast seen in the region supplied by a normal vessel or a noncritically stenotic vessel. These data are in accordance with the fact that coronary flow reserve is reduced in the coronary bed related to a critical obstruction when compared with that related to the normally perfused coronary bed.

If in a certain territory the intensity of contrast demonstrated at rest does not increase after adenosine or diminishes, as frequently noted, one may infer that that region is supplied by a critically stenotic artery. This observation is supported by a study by Lang et al⁵², who showed that the increase in the intensity of contrast is greater in the regions related to obstructed arteries that undergo angioplasty than in regions related to normal arteries due to subsequent hyperemia.

Techniques with pharmacological stress are widely used to diagnose coronary artery disease⁵³⁻⁵⁸. Dipyridamole is one of the most used drugs to cause myocardial ischemia with segmentary contraction abnormalities on two-dimensional echocardiography⁵⁸, with sensitivity similar to that of thallium-201 myocardial perfusion scintigraphy. With this drug, which has a relatively long persistence, episodes of severe ischemia, myocardial infarction, and even death, though rare, have been reported⁵⁸⁻⁶⁰.

Coronary vasodilation produced by dipyridamole is due to its blocking effect on cellular uptake of adenosine, which results in an increase in endogenous adenosine, therefore potentiating its vasodilating effect^{61,62}. Intravenous adenosine, which has a very short half-life (<20 seconds), has been used as an alternative to dipyridamole as a potent coronary vasodilator. The protocols for pharmacological stress tests with adenosine recommend the continuous infusion of the drug at the dosage of 0.14 mg/kg/min⁶³⁻⁶⁵. The side effects observed with adenosine are of short duration, but much more frequent and less well tolerated than those occurring with dipyridamole⁶⁴. These side effects impede obtainment of a maximum test in approximately 25% of patients⁶⁵. This high proportion of submaximum studies diminishes the sensitivity of adenosine echocardiography, when the objective is to cause ischemia with the appearance of segmentary contraction alteration. However, as in this protocol, adenosine is administered in intravenous bolus, and, consequently, with a very short persistence, stress does not cause imbalance in myocardial oxygen delivery and consumption for a time long enough to induce segmentary

contraction abnormalities. A regional mismatch occurs in myocardial perfusion, which becomes heterogeneous when a region depends on a coronary artery with critical stenosis.

Several clinical trials have determined the sensitivity and specificity of myocardial perfusion during adenosine infusion using thallium-201 scintigraphy⁶⁶⁻⁶⁹ or the alteration in segmentary contraction of the left ventricular walls with echocardiography^{63,70}. Three studies have compared sensitivity and specificity in myocardial perfusion imaging using adenosine infusion and dipyridamole^{38,70,71}. In all these studies, adenosine was administered as an intravenous infusion, and no increase in the intensity of myocardial contrast was observed in the regions related to normal arteries. As far as we know, this is the first report on the effect of adenosine, when administered in intravenous bolus, on coronary flow reserves during myocardial contrast echocardiography.

Adenosine injection in bolus caused total and asymptomatic transient (less than 10 seconds of duration) atrioventricular block in 3 of the 81 patients of this study. However, atrioventricular blocks with no sequelae^{72,73} and a high incidence of other side effects^{74,75} have also been reported during adenosine infusion. Chest pain, headache, facial rubor, and dyspnea may more often occur with adenosine than with dipyridamole⁷⁶. After adenosine bolus injection, these effects were very discrete and transitory, completely disappearing in 20 to 30 seconds, unlike those resulting from dipyridamole administration, which last longer and may require the intravenous antidote (aminophylline).

The results of this study may have been influenced by some methodological limitations.

We compared the results of myocardial perfusion obtained through microbubble echocardiography with those obtained through coronary angiography in regard to the presence or absence of intensification of the myocardial contrast and critical ($\geq 75\%$) or noncritical ($< 75\%$) coronary

artery obstruction, not considering the continuous spectrum of the severity of obstruction.

The reduction in the capacity of arterial vasodilation and in coronary flow reserve has been shown to increase as the severity of coronary stenosis increases^{77,78}. A previous study⁷⁹ inferred that the relative, more than the absolute, estimation of myocardial perfusion reserve would be a more sensitive physiological indicator than the severity of arterial stenosis on coronary angiography.

Anatomical factors of coronary lesions, such as the shape and eccentricity of the obstructions, and the presence of serial stenoses, which may affect coronary flow resistance, were not considered.

Another limitation of this study was the use of qualitative and not quantitative estimations of coronary flow resistance. However, quantitative assessments also have significant restrictions⁸⁰.

Finally, the high global accuracy with very high positive and negative values is, at least in part, due to the high incidence of coronary artery disease in our patients. The values calculated for the odds ratio (normal test = 0.34 and abnormal test = 0.694) confirm this observation.

In summary, in patients with coronary artery disease, qualitative noninvasive assessment of coronary flow reserve using myocardial perfusion echocardiography with microbubbles, before and after adenosine bolus injection, is a safe method that is closely related to the presence of critical coronary obstructions detected on coronary angiography. This information may provide a better definition of the functional relevance of an already known coronary lesion. In addition, this method may be clinically useful for detecting silent ischemia, for monitoring progression or regression of coronary obstructions, and for assessing revascularization procedures. The short persistence and clearance of adenosine may reduce the time necessary for examination, and also reduce the duration of any side effects that may appear.

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