Myocardial Perfusion and Ventricular Function Measurements During Total Coronary Artery Occlusion in Humans
A Comparison With Rest and Exercise Radionuclide Studies

Salvador Borges-Neto, MD; Joseph Puma, DO; Robert H. Jones, MD; Michael H. Sketch, Jr, MD; Richard Stack, MD; Michael W. Hanson, MD; R. Edward Coleman, MD

Background The purpose of this investigation was to compare the magnitude of change in myocardial perfusion and function during exercise with that obtained during total coronary artery occlusion. Radionuclide studies are widely used for the diagnosis and determination of prognosis in patients with suspected or known coronary artery disease. These studies are based on the premise that the relative deficit of coronary blood flow, which is induced by exercise and recognized as increased demand, relates to the jeopardy experienced by the decrease or sudden absolute interruption of coronary blood flow that is recognized as decreased supply and is associated with coronary stenosis or total coronary artery occlusion. The magnitude of exercise-induced perfusion and function abnormalities compared with those induced by total coronary artery occlusion in humans has not been previously reported.

Methods and Results We prospectively studied 20 patients with ≥50% diameter stenosis documented by quantitative coronary angiography in at least one vessel. A same-day rest/exercise sestamibi myocardial function and perfusion study was performed within 24 hours before percutaneous transluminal coronary angioplasty. At 1 minute after balloon inflation, while the vessel was occluded, sestamibi was injected, and a myocardial perfusion and function study was performed. Perfusion defect size was greater during occlusion (28±3%) than during exercise (13±2%) (P<.01). Ejection fraction was greater during exercise (53±3%) compared with values measured during occlusion (41±2%) (P<.01).

Conclusions Physiological abnormalities induced by coronary occlusion are greater than those that occur during exercise, thereby indicating that stress-induced ischemia may not reflect the total potential myocardium in jeopardy from a stenotic lesion, if sudden occlusion occurs. (Circulation. 1994;89:278-284.)

Key Words • sestamibi • ischemia • angioplasty • coronary disease

The diagnostic and prognostic power of radionuclide studies is closely related to the consequences of a significant coronary artery stenosis or total coronary artery occlusion. Results of these studies are based on the premise that a relative deficit of coronary blood flow, induced by exercise and recognized as increased demand, relates to the jeopardy experienced by the decrease of coronary blood flow that is associated with total coronary artery occlusion and recognized as decreased supply.

Controlled coronary occlusion during percutaneous transluminal coronary angioplasty (PTCA) permits assessment of the effects of ischemia on cardiac function and myocardial perfusion that occurs when a stenotic vessel becomes totally occluded. The 99mTc-labeled radiopharmaceutical, 99mTc-sestamibi, permits the simultaneous assessment of myocardial perfusion and ventricular function during a single tracer injection.1,2

Unlike thallium-201, this tracer does not show significant redistribution, and its 6-hour half-life allows the assessment of the effect of interventions several hours after the procedure is performed.3,4 The injection of 99mTc-sestamibi during angioplasty allows the assessment of the effect of acute coronary occlusion on myocardial perfusion and ventricular function. Therefore, the purpose of this investigation was to compare the magnitude of change in myocardial perfusion and ventricular function during exercise with those obtained during controlled coronary occlusion with PTCA.

Methods

Study Population

The study population consisted of 20 patients who were referred for PTCA and were offered a rest and treadmill exercise 99mTc-sestamibi perfusion and function study. The decision to perform angioplasty was made before the radionuclide study, and intervention was performed regardless of the physiological study results. Participation in the study required permission from the attending physician and patient consent. The research protocol was approved by the Institutional Review Board of Duke University Medical Center.

Study Plan

A same-day rest/exercise 99mTc-sestamibi study was performed 1 day before PTCA. The radionuclide study protocol has been described in detail previously.5 Briefly, a rest first-pass RNA was recorded using a bolus injection of 7 mCi (259

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mBq) of $^{99}$Tc-sestamibi. Single photon emission computed tomographic (SPECT) images were obtained 1 hour later, with the patient in the supine position. Subsequently, patients performed treadmill exercise using the Bruce protocol. When patients attained an exercise end point (85% for age-predicted maximal heart rate, severe fatigue, angina, arrhythmias, or severe ventricular dysfunction), first-pass study was obtained using a rapid bolus injection of 21 mCi (777 mBq) of $^{99}$Tc-sestamibi. Exercise was terminated 1 minute after injection, and SPECT imaging began 30 minutes after the second injection. A computer motion-corrected algorithm was applied to the first-pass study to correct for motion that occurred during treadmill exercise.6

During PTCA studies, after correct balloon positioning and 1 minute of balloon inflation, 15 mCi (555 mBq) of $^{99}$Tc-sestamibi was injected, and the first-pass study was acquired. When the interventional procedure was terminated, and at least 1 hour after tracer injection, patients were taken to the nuclear medicine laboratory for tomographic perfusion imaging (Fig 1). The first-pass study and SPECT images were evaluated using a previously described method to estimate the extent of perfusion and function abnormalities.1 Quantitative coronary angiography was performed in all patients by a method generated from the visual interpretation of the cinefilms by an experienced staff cardiologist and used as a reference guide to localize and quantitate the lesions.7 All stenoses described as ≥25% diameter were quantitated by previously described techniques.7

**Statistics and Data Analysis**

Baseline characteristics of the population were described as absolute values for categorical variables and by the average, minimal, and maximum values for continuous variables. A Student's paired t test was used to assess the differences between rest, exercise, and PTCA measurements. A P value of <.05 was considered significant for differences between all variables measured.

**Results**

**Baseline Characteristics**

Clinical and catheterization characteristics of the 20 patients at the time of scintigraphy are described in Table 1. Cardiac medications received by patients at the time of study included calcium antagonists in 12 patients, nitrates in 13 patients, and β-blockers in 7 patients. Patients were advised to withhold β-blockers at least 48 hours before the exercise radionuclide study.

**Rest, Exercise, and Coronary Occlusion RNA Measurements**

Mean values for left ventricular ejection fraction (LVEF) and for volumes measured at rest, exercise, and during controlled coronary occlusion are summarized in Table 2. LVEF changes were greater during coronary occlusion than during exercise (Fig 2). Although some individual variation was present, a marked decrease in LVEF during occlusion was the predominant change. The end-diastolic volume and end-systolic volume increased during exercise as well as during occlusion, and no significant differences were observed between exercise and occlusion. However, most patients revealed a higher end-diastolic volume and a lower end-systolic volume at exercise compared with coronary occlusion measurements (Fig 3).

**Rest, Exercise, and Coronary Occlusion Perfusion Measurements**

The mean values for quantitative perfusion measurements obtained at rest, exercise, and during balloon occlusion are also summarized in Table 2. Total exercise perfusion defect size was slightly larger than resting measurements and significantly increased during total coronary artery occlusion (Fig 2). Despite some individual variation, most patients demonstrated an absolute increase in perfusion defect size when coronary blood flow was interrupted.

**Correlation Between Clinical, Angiographic, and Functional Measurements**

Despite significant differences between rest, exercise, and occlusion measurements, overall exercise perfusion...
and functional measurements were not a good predictor of magnitude and direction of those measurements obtained during sudden coronary artery occlusion. When we addressed the question of whether certain clinical characteristics such as age, history of myocardial infarction, stenosis severity, use of β-blockers, heart rate, and exercise time would relate to the prediction of the change in perfusion and function during occlusion by exercise measurements, no apparent relation was found (Table 1). The lack of correlation between stenosis severity and functional abnormality in our study can be explained by the fact that a significant number of patients (50%) had multivessel disease and/or previous myocardial infarction (45%). For instance, a patient with a 70% stenosis of the right coronary artery, previous myocardial infarction, and three-vessel disease is expected to have greater perfusion and function abnormalities than a patient with a single 90% mid left anterior descending coronary artery (LAD) lesion but no previous myocardial infarction.

Four patients had total or subtotal occlusion of the angioplastied vessel. All these vessels had some degree of antegrade and/or retrograde distal flow noted on angiograms, and laser angioplasty was performed. The presence of collaterals as visualized by angiography was seen in one patient only and did preclude the assessment of that variable. However, the potential impact of collaterals may be even more difficult to assess, because functional collaterals may be present but not fully identified by angiography.

Some patients demonstrated resting perfusion defects with no documentation of prior myocardial infarction. This finding has been reported with the clinical use of 99mTc-sestamibi, and most recently investigators have demonstrated myocardial perfusion defects and impaired coronary flow at rest in patients with significant coronary artery stenosis using 99mTc-human albumin microspheres.

### Discussion

This report compares measurements of myocardial perfusion and ventricular function at rest, during exercise, and during total coronary artery occlusion in humans.

### Table 1. Clinical and Catheterization Characteristics of Patients at Scintigraphy

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MI indicates myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; %DS, percent diameter stenosis; NDV, number of diseased vessels; EF, ejection fraction; PDS, perfusion defect size; Ex, exercise; HR, heart rate; SBP, systolic blood pressure; Occ EF, ejection fraction during occlusion; Occ PDS, occlusion perfusion defect size; RCA, right coronary artery; Lox, left circumflex artery; and LAD, left anterior descending coronary artery.

### Table 2. Perfusion/Function Measurements

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<td>Perfusion defect size, %</td>
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LVEF indicates left ventricular ejection fraction; EDV, end-diastolic volume; and ESV, end-systolic volume. Results are expressed as mean±SEM.
Prior animal studies have extensively evaluated the effects of coronary arterial constriction on coronary flow. The classic work of Gould et al demonstrated the progressive decrease in the hyperemic response of the myocardium in relation to various degrees of coronary artery stenosis. This work was followed by a series of studies documenting the ratio of maximal flow in a normal to stenotic coronary artery of at least 2:1 before defects appear in the myocardial perfusion study.

Perfusion defects seen on myocardial scintigraphy are induced by regional abnormalities in blood flow and/or metabolic abnormalities caused by ischemia. The latter mechanism plays a key role in the development of functional abnormalities as assessed by radionuclide angiogram. The relative importance of each of these mechanisms in producing abnormalities on radionuclide studies will certainly depend on the stenosis severity and on myocardial oxygen requirements. Experimental studies have correlated the degree of global and regional functional impairment and coronary occlusion.

Based on prior animal studies, physiological abnormalities induced by coronary artery occlusion are more prominent than those caused by stress. Therefore, it would seem appropriate to compare measurements obtained during noninvasive testing with those obtained during coronary artery occlusion in humans to assess and confirm the discrepancies between myocardial demand and decreased blood supply.

Since the introduction of PTCA, several investigators have used this therapeutic procedure as a model to study and address questions related to the impact of a total coronary artery occlusion on human cardiac physiology. Pfisterer et al studied 25 patients during...
selective PTCA of a single LAD lesion and found perfusion defects on "occlusion" images obtained using sestamibi but not on "open vessel" images obtained 20 to 24 hours later in 21 patients. They also found a significant difference between proximal and distal LAD occlusions, and, most importantly, the only factor that related to the presence or absence of ischemic defect was the presence of collateral vessels. Several limitations are present in this particular study: First, planar imaging was performed with no quantitation; second, rest images were obtained after the occlusion images and may have disclosed perfusion abnormalities induced by PTCA; third, comparison with exercise was made only in 12 patients (50%) using thallium-201, which certainly may have caused the discrepancies of stress perfusion defects on 201T1-compared with 99mTc-sestamibi occlusion studies; and, fourth, ventricular function was not assessed. Recently, Verani et al.\(^1\) assessed global and regional function during balloon occlusion using the first-pass technique. They found that ventricular dysfunction induced during angioplasty was observed when proximal occlusion was performed, mostly in the LAD. However, in that study, the patients did not undergo exercise for comparison between coronary occlusion and exercise studies, and perfusion measurements were not performed. In a most recent preliminary report by the same laboratory, they found that perfusion and functional measurements during PTCA demonstrated greater changes when occlusion was performed in the LAD compared with the right and left circumflex arteries.

With the continuous growth of interventional procedures, assessment of jeopardized myocardium may play a key role in patient management. Haronian et al.\(^2\) have recently used 99mTc-sestamibi during PTCA to evaluate the myocardium at risk during coronary occlusion. They found a discrepancy between perfusion measurement of area at risk and angiographic estimation of area at risk. They suggested that myocardial perfusion measurements using 99mTc-sestamibi may be of value in identifying vessels that would have a significant impact on myocardial perfusion, if occluded.

**Clinical Implications**

Our study demonstrates that the physiological abnormalities induced by coronary occlusion (decreased supply) are greater than the ones observed during exercise (increased demand) in humans (Fig 4). An explanation for this finding is that the stenosis may not be severe enough to induce perfusion and functional abnormalities at the level of the stress performed by these patients when compared with total occlusion measurements (Fig 4).

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**Fig 4.** Maps show quantitative measurements of myocardial perfusion and left ventricular function at rest, exercise, and coronary artery occlusion in a patient with >50% diameter stenosis in the right coronary artery. PTCA indicates percutaneous transluminal coronary angioplasty; SPECT, single photon emission computed tomography; and EF, ejection fraction.
5). Moreover, variables such as presence of functioning collaterals (not visualized on angiography) and stenosis severity may have a different impact on the development of perfusion and functional abnormalities during exercise compared with abrupt coronary occlusion. On the other hand, and probably most important, some patients experience sudden vessel occlusion and severe myocardial ischemia caused by a superimposed thrombus on a less-than 50% unstable plaque. Therefore, a physiological study evaluating increased myocardial demand in the clinical setting may in some circumstances underestimate the potential jeopardy of a 50% stenotic lesion, which may result in decreased blood supply.

Another clinical implication is the potential use of this methodology in assessing ventricular function impairment, perfusion area at risk, and anatomic area at risk during angiography.19-21 This implication could play an important role in clinical decision making and further patient management.

Study Limitations

Our small patient population did not allow the performance of a multivariate regression analysis to define the relation between several physiological variables with the prediction of the magnitude and direction of perfusion and functional abnormalities induced by coronary occlusion.

In our study, 50% of the patients had multivessel disease, and 45% had documented myocardial infarction. These factors would certainly represent a major limitation in the assessment of the impact of a single-vessel occlusion on regional myocardial perfusion and function. However, the study of single-vessel disease was not the objective of this work. The purpose of this study was to assess global perfusion and function in the same patient under exercise and during vessel occlusion, and this study did allow us to compare the magnitude of change in functional parameters during noninvasive testing (increased demand) with that obtained during occlusion (decreased supply), which is most likely seen in patients during acute myocardial infarction.

The use of the results of the present study for prognostic purposes must be viewed with caution because the patient population is small, and 50% have single-vessel disease. Our results also should not be extrapolated to a patient population with multivessel disease and more severely impaired left ventricular function.

The results of this study raise several questions, but they certainly could serve as a basis for further studies on a much larger and heterogeneous population to compare and define the relation between exercise-induced ischemia and interruption of coronary blood flow in humans.
Acknowledgments
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References
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