Positive Myocardial Perfusion Scans in Patients with Chest Pain and Non-Obstructive Coronary Artery Disease

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During a 24 month period, 78 patients were prospectively studied who had chest discomfort suggestive of myocardial ischemia and positive stress thallium-201 myocardial SPECT perfusion scans yet coronary angiography indicated absent or < 50% sub-obstructive coronary artery disease. Of these 78 patients, 11 had a positive scan with no coronary atherosclerosis on angiography and 3 subjects had a positive scan which did not correlate with coronary lesion location. Sixty-four patients had a sub-obstructive coronary lesion which was correlated anatomically with a perfusion abnormality (correlated vs. non-correlated, $p < 0.001$). Of the 64, 51 patients had a correlated defect which was single whereas 10 patients had double defects and 1, 3 defects. Correlated defect distribution was as follows: Left anterior descending = 40, right coronary artery = 10 and left circumflex = 3. Two patients had left main coronary artery disease. A majority of subjects with correlated defects had multi-vessel sub-obstructive coronary lesions. Thirteen of 64 subjects (20.3%) had single vessel disease with good correlation. It is concluded that: 1) sub-obstructive coronary artery disease noted on angiography can result in perfusion defects, 2) the perfusion defects usually correlate with at least one diseased coronary artery, 3) this phenomenon is noted most frequently with left anterior descending coronary artery disease and 4) given current concepts regarding acute myocardial infarction and sub-obstructive coronary artery disease, such scanning offers a possible technique for detection. **(CardRes.org, July 2006)**

Key Words: myocardial perfusion scan, coronary artery disease

During the mid 1990's we noted that patients with chest discomfort suggestive of angina pectoris had positive thallium SPECT stress perfusion scans with coronary arteriograms that demonstrated < 50% obstructive disease. These findings were initially attributed to "false positivity" since the prevalence of false positive and false negative rates has been reported to be between 10 and 20 percent. Indeed, the sensitivity and specificity of myocardial perfusion imaging based on the 2003 ACC/AHA/ASNC Radionuclide Imaging Guidelines range from 71 to 97 percent and 36 to 100 percent respectively.[1] Of concern was the fact that there seemed to be correlation between the sub-obstructive lesions and the perfusion defects.

With the advent of intravascular ultrasound (IVUS) discrepancies between angiographically defined disease, myocardial stress perfusion scans and sub-obstructive disease on coronary arteriography became apparent, usually in an anecdotal fashion. In

1999 Galli et al, reported on a 57-year-old postmenopausal woman who was admitted to the hospital because of worsening angina pectoris and the diagnosis of "syndrome X". At treadmill testing chest pain and ST-segment depression developed with a positive reversible tracer uptake defect in the anterior region of her myocardium. Coronary angiography did not show any "significant" stenosis yet intracoronary Doppler flow measurements at rest and after adenosine showed a reduced maximal hyperemic flow velocity in the left anterior descending coronary artery (LAD). Intracoronary ultrasound imaging revealed an occult atherosclerotic plaque of the proximal LAD occupying 45% of the vessel area with vascular remodeling.[2] This finding in addition to our prior observations provided the impetus for the current study.

OBJECTIVE

The purpose of this investigation was to describe the association of thallium-201 redistribution abnormalities with sub-obstructive lesions. To our knowledge this phenomenon had not been studied prospectively at the time of its initiation (1999).

STUDY GROUP

The study group comprised 78 patients whose ages ranged from 47 to 84 years. All subjects had angina pectoris or chest discomfort thought to represent myocardial ischemia. These were all consecutive patients who were studied prospectively and had sub-critical coronary artery disease (< 50%) and abnormal stress thallium-201 myocardial SPECT perfusion scans. Subjects were excluded if they had echocardiographically moderate to severe left ventricular hypertrophy, severe aortic stenosis, and/or coronary artery bypass grafts.

METHODS

Patients were studied at an on-campus clinical facility. Multi-plane thallium augmented images were obtained post-dobutamine or treadmill exercise stress test. A single highly-experienced reader interpreted the myocardial perfusion scans. A second observer reviewed any borderline studies (4/78, 5%). Quantitative assessment of myocardium at risk was performed. Statistical analysis was undertaken utilizing SPSS® software and a binomial test was employed for data analysis. "Correlation" was defined as a region of myocardial ischemia subtended by a coronary artery with less than 50% stenosis by visual estimation.

RESULTS

Sixty-four of 78 subjects (82.0%) were found to have a correlating myocardial stress perfusion scan defect ($p < 0.001$). Three of 78 subjects (3.8%) showed no correlation and

11 patients (14.1%) had no identifiable coronary artery disease on angiography. Fifty-one of 64 subjects (79.7%) had single correlating defects, 10/64 (15.6%) patients had two correlating defects and 1/64 (1.6%) patient had three correlating defects. The distribution of correlated defects was as follows: LAD = 40, right coronary artery = 10 and left circumflex coronary artery = 3. Two subjects had sub-critical left main disease and a majority of patients had sub-obstructive lesions noted in all three coronary arteries. Thirteen of 64 subjects (20.3%) had single vessel disease.

DISCUSSION

In 2002 this data was accepted for oral presentation at the Cardiovascular Section of the American Federation for Medical Research.[3] Despite the fact that there was no clear cut explanation for such findings one of the current investigators (GW) as early as 1999 had set forth a hypothesis. Based on hydraulic and rheologic equations from the biophysics literature it was postulated that those coronary arteries with sub-obstructive coronary artery disease might not dilate appropriately during conditions of stress, thereby resulting in a myocardial perfusion scan which was positive for ischemia. Since then, a body of literature has appeared which seems to substantiate the latter hypothesis.

In 2001, De Bruyne et al demonstrated that diffuse coronary atherosclerosis without focal stenosis at angiography causes a graded, continuous pressure fall along arterial length. This resistance to flow contributes to myocardial ischemia and has consequences for decision-making during percutaneous coronary interventions. Fractional flow reserve was significantly lower in those subjects with nonstenotic coronary artery disease.[4] This is not surprising since both intravascular ultrasound and pathologic study have demonstrated that when a stenosis is visible at arteriography the balance of the coronary arterial circulation is diffusely involved by atherosclerosis although the latter is frequently not identified by coronary arteriography.[5,6,7,8] On the other hand, maximal myocardial blood flow has been show to be reduced only when the coronary artery diameter is reduced by 50%.[9,10] It would seem that diffuse atherosclerosis without segmental obstruction should have no influence on myocardial blood flow but the current findings indicate otherwise.

It has been proposed that the observed resistance of diffusely atherosclerotic coronary arteries without focal stenosis is most likely due to mild diffuse structural narrowing and to vasoconstriction since the benchmark study on this subject was performed after the intracoronary infusion of isosorbide dinitrate.[4]
These findings indicate that the abnormal resistance of the coronary arterial vasculature due to diffuse disease without focal stenosis may in part contribute to stress-induced myocardial ischemia and flow maldistribution on perfusion scintigrams, even after vasodilatation of the epicardial arteries by nitrates.[4]

Rodés-Cabau et al. recently concluded that plaque burden as determined by IVUS may partly explain the presence of myocardial perfusion defects in cases with angiographically non-obstructive coronary lesions. The high fractional flow reserve

values associated with these lesions suggested that other mechanisms such as endothelial/microvascular dysfunction may also account for perfusion abnormalities in these patients.[11] It is unfortunate that the term "non-significant" or "insignificant" is used in studies of this nature, since a large body of evidence suggests that the qualitative biologic features of atherosclerosis may be as significant or even more so than quantitative stenosis in a given vessel.[12] Indeed, most myocardial infarctions occur as a result of the disruption of arterial lesions that are not hemodynamically significant.[13]

The above considerations beg the question: Is coronary arteriography the "gold standard" for determining the presence or absence of disease which results in a positive myocardial perfusion scan? The 2005 ACC/AHA/SCAI guideline update for percutaneous coronary intervention has a class IIb indication which is stated as follows: IVUS may be considered for determination of the extent of atherosclerosis in patients with characteristic anginal symptoms and a positive functional study with no focal stenosis or mild coronary artery disease on angiography.[14] The classification indicates that a majority of the committee did not feel that it was appropriate to perform such study at this time whereas others did. The point is emphasized further by Merz who points out in a discussion of the assessment of patients at intermediate cardiac risk that coronary angiograms may demonstrate no evidence of obstructive coronary artery disease yet IVUS may reveal coronary atherosclerosis.[15] In such subjects, Doppler coronary flow testing may reveal reduced coronary flow reserve in response to adenosine, indicating that the patient's myocardial ischemia was caused by an inability of the coronary arteries to dilate adequately in response to stress rather than as a result of flow-limiting plaque obstruction.

There are major implications in regards to the current study. Stress thallium-201 studies may be able to detect impaired myocardial perfusion before hemodynamically significant stenoses appear on angiography. Such early detection would allow aggressive secondary prevention to be instituted. Limitations of the current study are as follows: 1) The patient population was small, 2) there was no control group, 3) no coronary or fractional flow reserve measurements were made, 4) no IVUS was performed in the study group, 5) quantitative coronary arteriographic measurements were not performed and 6) this study did not account for possible microvascular disease. Despite these limitations, our findings accord with recent data which indicates that so called "insignificant" or "non-obstructive" coronary arterial disease can result in positive myocardial stress perfusion scans with a high degree of correlation between the anatomic location of these lesions and the redistribution findings on scanning.

It is concluded that:

- In this patient population stress thallium perfusion scanning appears able to identify myocardial ischemia in patients with non-obstructive coronary lesions.
- This information may permit an earlier institution of aggressive secondary medical management.

- In many cases it appears that the designation "false positive" may not be correct and our findings may account for the wide variance in specificity noted in the extant literature.
- A prospective study utilizing IVUS, 64 slice CT and SPECT myocardial perfusion scanning in a large population with quantitatively defined sub-critical lesions appears to be warranted.

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