Clinical Value of Absolute Quantification of Myocardial Perfusion With $^{15}$O-Water in Coronary Artery Disease

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Background—The standard interpretation of perfusion imaging is based on the assessment of relative perfusion distribution. The limitations of that approach have been recognized in patients with multivessel disease and endothelial dysfunction. To date, however, no large clinical studies have investigated the value of measuring quantitative blood flow and compared that with relative uptake.

Methods and Results—One hundred four patients with moderate (30%–70%) pretest likelihood of coronary artery disease (CAD) underwent PET imaging during adenosine stress using $^{15}$O-water and dynamic imaging. Absolute myocardial blood flow was calculated from which both standard relative myocardial perfusion images and images scaled to a known absolute scale were produced. The patients and the regions then were classified as normal or abnormal and compared against the reference of conventional angiography with fractional flow reserve. In patient-based analysis, the positive predictive value, negative predictive value, and accuracy of absolute perfusion in the detection of any obstructive CAD were 86%, 97%, and 92%, respectively, with absolute quantification. The corresponding values with relative analysis were 61%, 83%, and 73%, respectively. In region-based analysis, the receiver operating characteristic curves confirmed that the absolute quantification was superior to relative assessment. In particular, the specificity and positive predictive value were low using just relative differences in flow. Only 9 of 24 patients with 3-vessel disease were correctly assessed using relative analysis.

Conclusions—The measurement of myocardial blood flow in absolute terms has a significant impact on the interpretation of myocardial perfusion. As expected, multivessel disease is more accurately detected.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00627172.

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Key Words: cardiac-gated imaging techniques ■ positron-emission tomography ■ coronary artery disease ■ perfusion

The detection of functional consequences of epicardial coronary artery disease (CAD) has an established role in the detection of the disease and the guidance of therapy. In addition, the assessment of impairment in microcirculatory reactivity recently has gained more interest. Estimates of myocardial perfusion contain independent prognostic information about future major cardiac events and the effectiveness of risk reduction strategies.

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Although the standard interpretation of myocardial perfusion imaging is based on the assessment of relative myocardial perfusion defects, this approach has obvious limitations. The assessment is based on the assumption that the region with the best perfusion is normal and can be used as a reference. In clinical scenarios, these shortcomings may arise, particularly with patients who have multivessel disease. In addition, global reduction of myocardial perfusion caused by diffuse microvascular disease or balanced multivessel disease may be completely missed when assessment of myocardial perfusion is based on relative uptake of radiotracer.

These limitations may be avoided when using absolute quantification of myocardial blood flow (MBF). At present, the most robust technique to quantify MBF noninvasively in the human heart is PET. PET is a quantitative technique and allows fast and effective imaging protocols.
with relatively low radiation burden in both rest and stress.2–6

Absolute quantification of MBF with PET is performed using the tracer kinetic method, which is based on measuring the in vivo kinetics of a tracer concentration during dynamic acquisition. Normal MBF at rest is from 0.6 to 1 mL/g per minute and increases by 3- to 5-fold in stress as the coronary arteries dilate.7

The tracers most widely used for the quantification of myocardial perfusion with PET are 15O-water and 13N-ammonia. They provide absolute information of MBF over a wide range of blood flows, but their production requires a cyclotron.8 Absolute MBF can, however, be assessed with the more widely used generator-produced perfusion tracer 82Rb.9 Despite this, quantification of MBF with PET mainly has been used in research protocols and studies in which absolute perfusion has been measured on the global level only. These studies have focused on the effect of various risk factors on early coronary dysfunction.10,11 More recently, because of the increased use of PET (and PET/CT) in clinical cardiology and the development of analysis methods, simple and robust perfusion quantification has become available.12–15 However, large patient studies demonstrating the value of absolute quantification in the detection of CAD, as well as in the guidance of the therapy, are still lacking. In a recent study by Hajjiri et al,16 27 patients with known or suspected CAD were studied. In their work, quantification improved the accuracy for the identification of CAD. The aim of the current study was to investigate whether the additional information gained from absolute quantification of myocardial perfusion has a significant clinical impact in a patient population with a moderate pretest probability of CAD.

**Methods**

**General Study Protocol**

Initially, 107 consecutive patients with chest discomfort and 30% to 70% pretest likelihood of CAD were enrolled. Before invasive coronary angiography, coronary CT angiography followed by PET perfusion imaging during adenosine stress were performed in 104 of these patients using 15O-water and dynamic nongated imaging (GE Discovery VCT PET/CT; GE Healthcare; Waukesha, WI). In 3 subjects, a PET study was not possible because of technical reasons. The main results of hybrid PET/CT imaging in this population have been published recently.17 As the reference method, all patients underwent invasive coronary angiography (ICA) with fractional flow reserve (FFR) within 2 weeks, during which time no cardiac events took place. During ICA, FFR measurements were performed for stenoses >30%. However, there were some stenoses not subject to FFR because of logistics, the operator’s clinical and visual assessment of complicated lesions, or technical reasons in some extremely tight stenoses.

**PET Imaging**

Rest-stress perfusion cardiac PET was performed with 900 to 1100 MBq of 15O-labeled water (Radiowater Generator; Hidex Oy; Turku, Finland) at rest as an intravenous bolus over 15 s at an infusion rate of 10 mL/min. A dynamic, nongated acquisition of the heart over 4 minutes 40 s was performed (14×5 s, 3×10 s, 3×20 s, and 4×30 s). After 10-minute decay of the radioactivity, an adenosine-induced stress scan was performed. Adenosine was started 2 minutes before the scan start and infused at 140 μg/kg body weight per minute.17

**ICA and FFR**

All coronary angiographies were performed on a Siemens Axiom Artis coronary angiography system (Siemens; Erlangen, Germany). Quantitative analysis of coronary angiograms was performed using software with an automated edge-detection system (Quantra; Siemens) by an experienced reader (M.P.) blinded to the results of the PET, CT angiography, and FFR. Seventeen standard segments were analyzed.

In the presence of 30% to 70% stenosis, FFR measurement was performed using the ComboMap pressure/flow instrument and 0.014-inch BrightWire pressure guidewires (Volcano Corporation; San Diego, CA). The pressure was measured distally to the lesion during maximal hyperemia induced by 18 μg intracoronary boluses of adenosine with simultaneous measurement of aortic pressure through the catheter. FFR was calculated as the ratio of mean distal pressure to mean aortic pressure.14–20

**Analysis and Interpretation of the Studies**

The perfusion studies were analyzed using validated software. First, absolute blood flow for the standard 17 myocardial segments were calculated using a standard anatomic template and Carimas software14,17 (www.turkupetcentre.net/carimasturku). The PET images were fused with corresponding CT angiographic images to a GE ADW workstation (CardIQ Fusion; GE Healthcare) to determine the individual regions supplied by each artery. Absolute myocardial flow in any region of <2.5 mL/g per minute during stress was considered abnormal.17 In patient-based analysis, the result was interpreted as pathological if any region showed abnormal perfusion.

Although it is customary in clinical practice to evaluate relative perfusion abnormalities visually, we chose to use calculated MBF values as the basis of the relative uptake analysis as well. The region of the highest perfusion (regardless of the absolute flow) was assigned a value of 1, after which all the other areas were graded relative to that. For example, if the MBF were 2.0 mL/g per minute in the left anterior descending coronary artery territory, 1.5 mL/g per minute in the left circumflex coronary artery territory, and 1.0 mL/g per minute in the right coronary artery-supplied area, the corresponding relative values would be 1, 0.75, and 0.5. The optimal cutoff for the relative uptake would be 0.8

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| **Table 1. Analysis of Quantitative Blood Flow, Results per Patient** |
|-----------------------------|-----------------------------|
| **ICA + FFR**               | **ICA + FFR**               |
| PET with quantitative blood flow (n=104) | PET with quantitative blood flow (n=104) |
| +                         | +                         |
| 36                        | 6                         |
| –                         | –                         |
| 2                         | 60                        |

**ICAS + FFR indicates invasive coronary angiography with fractional flow reserve.**

**Abbreviations as in Table 1.**

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| **Table 2. Analysis of Relative Uptake, Results per Patient** |
|-----------------------------|-----------------------------|
| **ICA + FFR**               | **ICA + FFR**               |
| PET with relative uptake (n=104) | PET with relative uptake (n=104) |
| +                         | +                         |
| 28                        | 18                        |
| –                         | –                         |
| 10                        | 48                        |

**Abbreviations as in Table 1.**
(ie, 80% of the maximal uptake in any region) on the basis of the receiver operating characteristic curve.

Parametric images of the blood flow were produced from the data. The scaling of the images was either automatic (with the relative scale, the best perfused region always has the brightest color regardless of the actual blood flow, and the other regions have colors reflecting the flows relative to the best region) or manual (with the absolute scale, the flow in mL/g per minute relates to a predefined color).

When FFR was performed during ICA, stenoses with FFR >0.8 were classified as nonsignificant, regardless of the degree of narrowing. In cases without FFR, luminal diameter narrowing ≥50% in quantitative analysis of coronary angiograms was considered significant.

Statistical Analyses

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for both quantitative blood flow and quantitative relative uptake. Receiver operating characteristic analyses were performed with the Youden index, and the areas under the curves were calculated. McNemar test was performed to compare accuracy of quantitative blood flow and quantitative relative uptake against the reference method (ICA with FFR). A P<0.05 was considered statistically significant. The statistical tests were performed with SAS version 9.1 (SAS Institute Inc; Cary, NC) software.

Results

According to the reference method (ICA with FFR), 38 of 104 patients who underwent PET had significant CAD. Two of the 3 patients without PET data had significant CAD, but they were not included in the analysis. Of the 38 patients, 24 had multivessel disease, and 14 had single-vessel disease. Eighteen patients had either a totally occluded vessel or >90% stenosis in which FFR was not technically possible. In 4 other patients, FFR could not be performed because of scheduling or technical reasons. A total of 238 of 312 arteries were normal or had nonsignificant disease, and 74 were significantly diseased.

Patient-Based Analysis

Quantitative blood flow analysis correctly identified 36 of the 38 patients with positive findings. There were 2 false negatives in which the flow was ≥2.5 mL/g per minute in all regions and 6 false positives. Of these, 5 patients had

![Figure 1. Patient-based assessment. Quantitative blood flow versus relative uptake is shown in adenosine-induced stress with invasive coronary angiography and fractional flow reserve as the reference method (n=104). Normal flow is ≥2.5 mL/g per minute in quantitative blood flow (blue bar) and ≥80% of the maximal uptake in relative uptake (burgundy bar). NPV indicates negative predictive value; PPV, positive predictive value.](image1)

![Figure 2. A, Regional (per-vessel) assessment (n=312). B, Regional (per-vessel) assessment in patients with multivessel disease (n=312). Quantitative blood flow versus relative uptake is shown in adenosine-induced stress with invasive coronary angiography with fractional flow reserve as the reference method. Normal flow is ≥2.5 mL/g per minute in quantitative blood flow (blue bar) and ≥80% of the maximal uptake in relative uptake (burgundy bar). Abbreviations as in Figure 1.](image2)
diffusely reduced flow, whereas 1 patient had <2.5 mL/g per minute flow in just 1 vascular region. Quantitative analysis resulted in a sensitivity of 95%, a specificity of 91%, a PPV of 86%, and an NPV of 97%.

With relative myocardial uptake analysis, PET was able to correctly identify only 28 of 38 patients with significant CAD. There were 10 false negatives and 18 false positives. This resulted in a sensitivity of 74% and a specificity of 73%, PPV and NPV were 61% and 83%, respectively. The results of the patient-based analysis are shown in Tables 1 and 2 and in Figure 1.

Patients With Multivessel Disease
There were 24 patients with significant multivessel disease. All but 1 (who had a false-negative result) were identified by abnormal quantitative blood flow. In addition, there were 5 false positives with diffusely reduced MBF but no CAD according to ICA and FFR.

Using relative uptake, we were able to detect in 22 of the 24 patients significant CAD, whereas 2 patients were erroneously interpreted as being without CAD (both had very low, but diffusely reduced flow). In addition, 26 patients were classified as having multivessel disease, although they did not. The results of the analysis of patients with multivessel disease are presented in Figure 2A and 2B.

Regional Analysis
In regional (vessel-based) analysis, quantitative blood flow had a sensitivity and specificity of 95% and 92%, respectively, for the detection of significant CAD. PPV, NPV, and accuracy were 78%, 98%, and 92%, respectively. When relative flow analysis was used, PPV, NPV, and accuracy were 64%, 85%, and 82%, respectively. The results of the 2 analysis methods also were compared by means of receiver operating characteristic analysis. The area under the curve was 0.94 (quantitative blood flow) and 0.73 (relative uptake).

The relative perfusion method failed to assess the underlying extent of the disease in 13 of 24 patients with multivessel CAD because the patients were believed to have single-vessel disease only. In addition, 7 other patients given a diagnosis of multivessel disease really had single-vessel disease. The region-based results are presented in Tables 3 and 4 and in Figures 2 and 3.

Discussion
Myocardial perfusion yields independent and important information about risk stratification in patients with CAD.

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<th>PET with quantitative blood flow (n=312)</th>
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Abbreviations as in Table 1.

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Abbreviations as in Table 1.

In the present study, we compared the conventional approach of assessing relative radiotracer uptake with quantitative measurement of MBF and found that the latter method was more sensitive and accurate. In particular, in the presence of the multivessel disease, relative differences in regional myocardial radiotracer uptake may underestimate the severity of CAD.

There are 3 main patient groups that account for the differences between relative uptake and quantitative blood flow. The first group is the patients with 3-vessel disease and balanced, uniform reduction of perfusion. The second group of discrepant findings comprised 13 other patients with multivessel disease. In these patients, presence of CAD was detected using relative uptake analysis, but only 1 region was considered pathological. This too is easy to understand because the region with the best perfusion is considered to represent normal flow in relative analysis, which is, however, not usually the case in patients with multivessel disease.

The third group of discrepancies comprised patients with high MBF but inhomogeneous radiotracer uptake erroneously
interpreted as perfusion defects. According to ICA and FFR, these patients had no significant CAD. Such misinterpretation is most likely to occur with tracers with a linear relationship between the measured and the actual flow, even at a high range, such as $^{15}$O-water, but also may be important with other tracers with high extraction. This potential pitfall is avoided when using quantitative blood flow analysis. Two case examples of false findings in relative uptake and their counterpart images based on the quantitative blood flow are shown in Figures 4 and 5.

An interesting subgroup is the patients with normal (or nearly normal) epicardial vessels but with diffusely reduced MBF. With quantitative PET, these patients with possible microcirculatory disease often cannot be separated from those with epicardial multivessel disease. This finding may have important implications for decisions about referral to ICA, but it should be noted that hybrid PET/CT imaging can lead to a correct diagnosis in such patients. On the other hand, the relative perfusion method frequently classifies these patients as normal. Of course, the relative number of patients with multivessel and single-vessel disease as well as impaired microcirculation reflects a particular patient population and the pretest probability of CAD in that group.

We used hybrid PET/CT images to visualize the location of the actual coronary arteries and their territories. The normal variation in anatomy is considerable, and possible nonanatomical pseudolesions in perfusion images are more easily distinguished from real abnormalities. In our opinion, it is advisable to use hybrid images for anatomy and flow values for function if both are available.

A limitation of the current study is that the poor performance of relative uptake analysis at a high perfusion range should not be directly extrapolated to other perfusion tracers used in PET imaging or conventional nuclear medicine. Most tracers (eg, sestamibi, tetrofosmin, ammonia, rubidium) exhibit nonlinear flow characteristics between detected signal and actual perfusion, thus naturally omitting heterogeneity in perfusion at the high end of the normal perfusion range. These relationships are demonstrated in Figure 6.

Another limitation is the lack of ECG gating in our approach. Gated images provide information about wall motion, and this information could improve the accuracy of relative analysis. A third limitation of the study is the relatively small number of patients with significant CAD (n=38). This reflects the patient population but warrants further study with more patients. On the other hand, this population with intermediate likelihood of disease should be ideal for assessing diagnostic methods, especially because we avoided referral bias by performing ICA in all patients.

Conclusions
Quantification of MBF is superior to the assessment of relative uptake only. In particular, assessment of the absolute Figure 4. False-positive finding in relative uptake analysis. A, Relative uptake in hybrid PET/CT angiography images (automatic color scale). The heterogeneity in perfusion was erroneously interpreted as reduced perfusion in the left anterior descending and left circumflex coronary artery territories. Normal perfusion is indicated by yellow or red and reduced perfusion by green or blue. B, Quantitative blood flow with a preset color scale of 0 to 3.5 mL/g per minute. Normal perfusion is ≥2.5 mL/g per minute (yellow or red), and reduced perfusion is <2.5 mL/g per minute (green or blue). Invasive coronary angiography and fractional flow reserve were found to be normal.

Figure 5. False-negative finding in relative uptake analysis. A, Relative uptake in hybrid PET/CT angiography images (automatic color scale). This appeared normal in all regions and was false-negative finding. Normal perfusion is indicated by yellow or red and reduced perfusion by green or blue. B, Quantitative blood flow images with a preset color scale of 0 to 3.5 mL/g per minute. Normal perfusion is ≥2.5 mL/g per minute (yellow or red color), and reduced perfusion is <2.5 mL/g and minute (green or blue). Blue reflects severely impaired perfusion in all 3 major vascular territories. Invasive coronary angiography and fractional flow reserve were found to be abnormal in all 3 vessels.
flow improves the correct detection of multivessel disease. In addition, patients with diffusely reduced flow but with no significant epicardial stenoses are easily identified using quantification methods. Furthermore, local variances within normal high flow can be separated from regionally compromised perfusion. This is particularly important when tracers with high extraction are used.

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Disclosures

None.

References


2. Hara T, Michihata T, Yokoi F, Sakamoto S, Masuoka T, Iio M. Significant epicardial stenoses are easily identified using absolute myocardial perfusion and tracer uptake. The lines of fusion is increased. MIBI indicates sestamibi. Reproduced with permission from the American Society of Nuclear Cardiology.


CLINICAL PERSPECTIVE

The standard interpretation of perfusion imaging is based on the assessment of relative perfusion defects. This approach has limitations, particularly in the detection of multivessel disease and microvascular dysfunction. Using PET, it is possible to overcome these handicaps by measuring myocardial blood flow in absolute terms. We investigated 104 patients with a moderate (30%–70%) pretest likelihood of coronary artery disease. The patients underwent PET during adenosine stress using $^{15}$O-water and dynamic imaging. Absolute myocardial blood flow was calculated from which both standard relative uptake images and images exhibiting quantitative myocardial blood flow were produced. The patients and the main vessel regions then were classified as normal or abnormal and compared against the reference of conventional angiography with fractional flow reserve. In patient-based analysis, the positive predictive value, negative predictive value, and accuracy of quantitative blood flow in the detection of obstructive coronary artery disease were 86%, 97%, and 92%, respectively. The corresponding values with relative uptake analysis were 61%, 83%, and 73%, respectively. In region-based analysis, the receiver operating characteristic curves confirmed that the absolute quantification was superior to relative assessment. In particular, the specificity and positive predictive value were low using just relative differences in flow. Only 9 of 24 patients with 3-vessel disease were correctly assessed using relative analysis. The measurement of myocardial blood flow in absolute terms has a significant clinical impact on the interpretation of myocardial perfusion. As expected, particularly multivessel disease is more accurately detected.
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