

WHITE PAPER

# Expanding the Power of PET with *syngo*<sup>®</sup> MBF

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# Expanding the Power of PET with syngo® MBF

## 1.0 Introduction

PET/CT myocardial perfusion imaging (MPI) using short lived radio-pharmaceuticals like Rubidium-82<sup>1</sup> (<sup>82</sup>Rb) or Nitrogen-13 ammonia (<sup>13</sup>NH<sub>3</sub>) has been shown to have high sensitivity and specificity for diagnosis and characterization of coronary artery disease (CAD). Attenuation correction and stress cardiac-gated MPI for accurate delineation of stress induced LV dysfunction have contributed to the overall high accuracy of PET/CT MPI. The quantitative nature of PET and its dynamic imaging capability enable computation of myocardial blood flow (MBF) during rest and peak stress (in terms of ml/gm/min) and calculation of coronary flow reserve (CFR). This quantitative approach improves the evaluation of myocardial ischemia and functional estimation of coronary stenosis as well as the characterization of diffuse or triple vessel disease. *syngo* MBF, a commercially available, user friendly, software application for computation of MBF and CFR provides the cardiac PET/CT practitioner with the ability to routinely perform such quantitative studies leading to improved diagnostic confidence in a wide range of coronary artery disease states.

### 1.1 Myocardial Perfusion Imaging and Coronary Artery Disease

Conventional evaluation of PET/CT MPI is based on the assumption that the normal myocardium is represented by the region of highest radiopharmaceutical uptake and all other myocardial uptake can be normalized relative to the (best perfused) region of highest uptake. In situations where the best perfused region is actually ischemic, this assumption leads to underestimation of the true extent of disease. Globally reduced perfusion can also be interpreted as normal on relative MPI evaluation. Absolute MBF measures supplement the limited information obtained from standard MPI evaluation, especially in identifying borderline ischemia or diffuse multi-vessel disease.

### 1.2 Myocardial Blood Flow

In subjects with normal coronary vasculature, MBF is controlled via an autoregulation mechanism primarily mediated by the vascular resistance of normal macro- or micro-vasculature. Resting MBF is in the range of 0.8 to 1.2 ml/gm/min and can

increase two- to three-fold at peak exercise. Exercise increases myocardial oxygen demand related to increased cardiac workload secondary to increased heart rate, contractility and blood pressure. In proportion to increasing myocardial oxygen demand, there is a decrease in precapillary arteriolar resistance, which causes arteriolar vasodilatation leading to increased MBF. The presence of significant coronary stenoses, however, reduces the ability of the coronary circulation to increase MBF to match the increased myocardial workload due to exercise or other forms of stress. Maximal vasodilatation achieved with pharmacological stress agent e.g. adenosine, dobutamine or dipyridamole, precipitates a similar reduction in MBF in the territory supplied by the stenosed coronary artery, with shunting of blood to the territories supplied by coronary arteries without flow limitation. Resting myocardial oxygen demand is lower and can be maintained at a normal MBF level by auto-regulatory mechanisms in segments supplied by stenotic arteries unless there is severe stenosis with consequent severe MBF impairment.

### 1.3 Coronary Flow Reserve

CFR is a measure of the vasodilatory reserve of the myocardium, signifying the ability of the vasculature to deliver increased blood flow in response to maximal myocardial workload. CFR is the ratio of the myocardial blood flow at peak stress or maximal vasodilatation to the flow at rest. In adults, CFR is normally 2.5 or higher. CFR can be measured invasively at the time of coronary catheterization; PET, however, has the advantage of making this measurement non-invasively. While there is a progressive decrease in CFR with increasing stenosis levels, it is important to note that mild to moderate reduction in MBF with maximal vasodilatation may be characterized as an abnormal but need not be sufficient to elicit ischemia. Peak MBF and CFR reduction beyond this abnormal level is associated with progressive ischemia with consequent metabolic changes in myocytes. Thus, mild to moderate reduction of peak stress flow and CFR are often the initial signs of early CAD.

## 2.0 Clinical Value of MBF: Multi-vessel disease

Relative assessment with MPI often uncovers only severe coronary stenosis leading to underestimation of the true extent of ischemia. *syngo* MBF is able to reveal myocardial segments with a lesser degree of ischemia by identifying individual coronary vascular territories with abnormal MBF and impaired CFR not readily apparent on standard MPI evaluation. Di Carli et al.<sup>1</sup> studied 18 patients with coronary artery disease and 10 age-matched healthy volunteers with dynamic <sup>13</sup>NH<sub>3</sub> myocardial perfusion imaging (MPI) using short lived PET, at rest and after vasodilatation with dipyridamole. Coronary lesions with 50 percent to 70 percent area stenosis had a higher CFR than those with 70 percent to 90 percent area stenosis (2.4±0.4 versus 1.8±0.5), suggesting a higher vasodilator reserve in segments supplied by coronary arteries with a lower degree of luminal obstruction compared to those with severe stenosis

### 2.1 *Balanced multi-vessel disease*

Of patients with suspected CAD, 5 percent to 10 percent<sup>2</sup> display balanced three-vessel disease. On relative MPI assessment, these patient's images often portray homogenous radiopharmaceutical distribution since the entire LV myocardium is uniformly ischemic. Normalization has little effect and the perfusion image appears normal or equivocal. In such situations, relative assessment will not uncover the global reduction in perfusion. Without the benefit of peak stress MBF and CFR, balanced disease may be completely missed.

Parkash et al.<sup>2</sup>, studied 13 patients with angiographically documented three-vessel disease and 10 patients with single-vessel disease using dynamic <sup>82</sup>Rb PET. Resting flow values were similar for both groups. Standard MPI evaluation, using normalization to region of peak perfusion, identified perfusion abnormalities in all three of the vessel segments in only 46

percent of three-vessel disease patients. In 92 percent of the patients, MBF evaluation identified perfusion decreases in all three vessel segments illustrating the extent of underestimation which may occur with standard MPI and highlighting the advantages of MBF and CFR for patients with three-vessel disease.

### 2.2 *MBF and CFR in remote areas in CAD patients*

In view of the presence of CAD risk factors like diabetes and hyperlipidemia coexisting with coronary stenosis, the question remains if microcirculatory abnormalities related to these risk factors contribute to the impairment of CFR in stenotic segments. Beanlands et al.<sup>3</sup>, studied young and middle-aged volunteers (controls) and CAD patients with dynamic <sup>13</sup>NH<sub>3</sub> PET and quantitative angiography to determine the relation between CFR and stenosis severity and assess CFR impairment in regions supplied by vessels without significant angiographic disease. A progressive decrease in CFR with increasing stenosis, was reported. However, myocardial segments not supplied by the stenotic artery also showed lower CFR values than those of similar segments in non-CAD controls demonstrating that the functional severity of coronary disease measured by quantitative PET varied for a given stenosis but was related to angiographic severity. The finding of reduced CFR among CAD patients in myocardial regions without significant angiographic stenoses compared to regions in control subjects, indicated that vascular reactivity was more diffusely impaired in CAD patients than suggested by angiography.

### 2.3 *Microvascular disease*

There is controversy about the role of decreased resting MBF as the pathophysiologic mechanism of hibernating myocardium. Studies have shown that higher resting MBF was clearly associated with higher contractile reserve in chronic

left ventricular dysfunction. Panza et al.<sup>4</sup>, performed trans-esophageal echocardiography during dobutamine infusion and resting dynamic PET with Oxygen-15 water ( $H_2^{15}O$ ) and  $^{13}NH_3$ , in 23 patients. Systolic wall thickening, at progressive levels of dobutamine infusion, and resting MBF were analyzed at mid-ventricular level. Myocardial segments with normal wall motion at rest showed well preserved resting MBF and adequate contractile reserve. Among myocardial regions with poor resting contractility, there was a clear linear correlation between resting MBF and degree of contractile reserve. There was a clear association between lower resting MBF in these hypokinetic segments and a subnormal increase in contractility and systolic wall thickening with dobutamine. This study emphasized the value of resting MBF measurement by dynamic PET in identifying segments with preserved contractile response. Patients with micro-vascular disease, and associated conditions like diabetes, hyperlipidemia and hypertension, usually demonstrate diffuse reduction in myocardial perfusion and impaired vasodilatory response. MBF and CFR estimation in at-risk (for CAD) patients may identify early CAD, evaluate CAD progression, and assess the effect of therapy and lifestyle modification. PET MBF, at rest and in response to sympathetic stimulation by cold pressor testing (CPT), provides information on endothelium-related coronary vasomotor function. Schindler et al.<sup>5</sup>, evaluated a group of 72 patients with CAD risk factors, but with normal coronary angiograms, using  $^{13}NH_3$  PET MBF measurement at rest and with CPT, to ascertain if patients with impaired MBF response to CPT are at increased risk for cardiovascular events. Cardiovascular events, including cardiovascular death, acute coronary syndrome, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, etc., were assessed as clinical outcome parameters over a mean follow-up period of 66 +/- 8 months. Patients with decreased

MBF response to CPT were particularly at-risk in spite of normal coronary angiograms, due to endothelial dysfunction related to coronary risk factors. These results demonstrate that a finding of decreased MBF response to sympathetic stimulation is important in independently defining cardiovascular risk.

#### **2.4 Coronary Calcium Score**

The relationship of stress MBF to the level of coronary calcium, a marker for coronary atherosclerotic burden, has also been investigated. Schindler et al.<sup>6</sup>, compared 34 patients with type 2 diabetes mellitus (DM) without history of CAD and 32 normal subjects. CT calcium score and dynamic  $^{13}NH_3$  PET MBF at rest, adenosine stress and cold pressor testing were performed. The results suggest that progressively increasing vessel stiffness due to atherosclerosis causes raised resistance to coronary flow, leading to impaired vasodilatory capacity in diabetic patients with higher coronary calcification.

A large study, correlating Framingham risk scores with MBF and CFR in patients with multiple risk factors but without documented CAD, has been published as the RAMPART study<sup>7</sup>. Two hundred eighty-nine asymptomatic, nondiabetic subjects, with hypercholesterolemia and low (<10%) to intermediate (10-20%) 10-year CAD risk, underwent dynamic  $^{13}NH_3$  PET. A linear inverse relationship between CFR and 10-year CAD risk based on Framingham score was found, clearly demonstrating that preclinical abnormalities in vasodilator reserve, as measured by PET, relate to higher estimated CAD risk. This result suggests that aggressive risk factor modification should be considered in those subjects who may otherwise not be considered suitable for intensive pharmacological therapy based on the Framingham risk score alone.

**Figure 1.** Siemens Biograph™ TruePoint™ and mCT, respectively, are leading-edge 3-dimensional (3D) lutetium oxyorthosilicate (LSO) high resolution and time-of-flight PET/CT devices, capable of simultaneous static, dynamic, and gated cardiovascular imaging through list mode (LM) acquisition.<sup>9</sup>



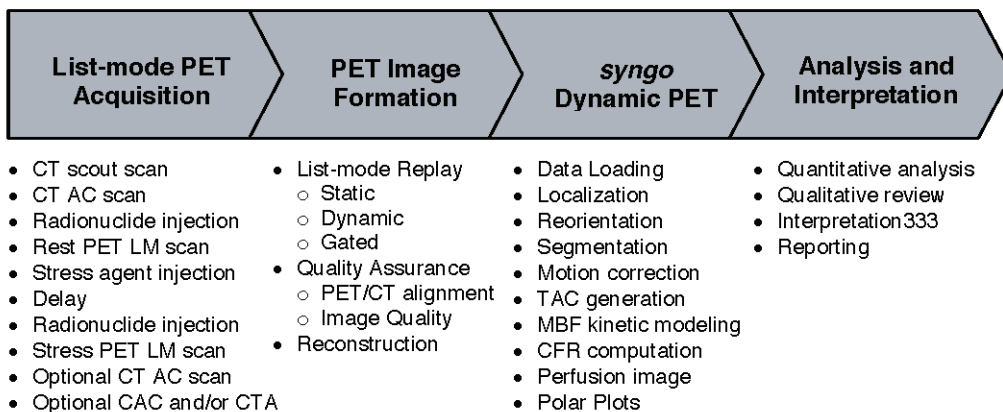
### 3.0 Operational Transition to Dynamic Flow Quantification

#### 3.1 List-mode Imaging and syngo MBF Implementation

The following section describes a new dynamic imaging workflow that utilizes list-mode (LM) acquisition and replay along with syngo MBF. As described below, this technique provides additional objective, functionally significant, physiological measures of coronary artery stenosis, e.g., MBF and CFR, without any complexity, additional radiopharmaceutical administration, or imaging time added to the standard PET/CT MPI examination.

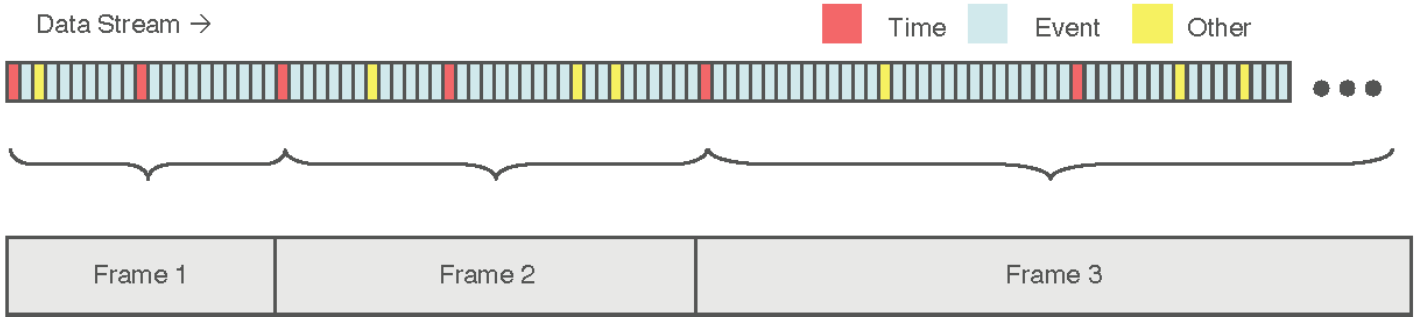
The dynamic workflow begins as patients are placed head first and supine on the PET/CT patient handling system. An initial low-dose CT scout scan is obtained for proper patient placement in subsequent low-dose CT attenuation correction (CT AC) and

PET scans. Unlike standard <sup>82</sup>Rb and <sup>13</sup>NH<sub>3</sub> MPI acquisition start delays of ~90 s and 3 min post-radionuclide administration for blood pool clearance, respectively, LM acquisition starts with radionuclide administration to obtain data upon radionuclide arrival in the right and left ventricle (LV) and continues for 6 to 8 min and 10 to 20 min for <sup>82</sup>Rb and <sup>13</sup>NH<sub>3</sub>, respectively. LM replay is an ideal approach, in that multiple image reconstructions (i.e., cardiac and/or respiratory gated, static, dynamic, and summed gated frames) can be obtained from a single radiopharmaceutical (tracer) administration and LM acquisition. Gated image formation requires additional physiological information typically obtained using ancillary equipment (e.g., ECG, pressure

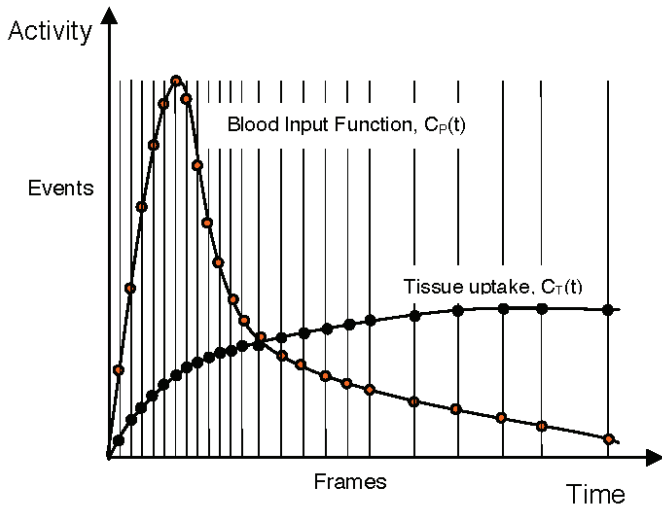


**Figure 2.** Siemens syngo MBF PET/CT cardiac workflow

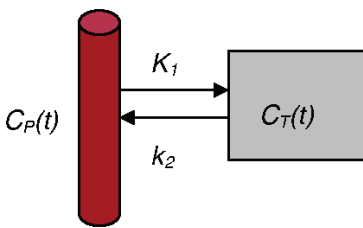
# Dynamic LM Replay



**Figure 3.** During list-mode (LM) acquisition, the PET system records incoming timing, event location and other (phase) information in order of their occurrence.

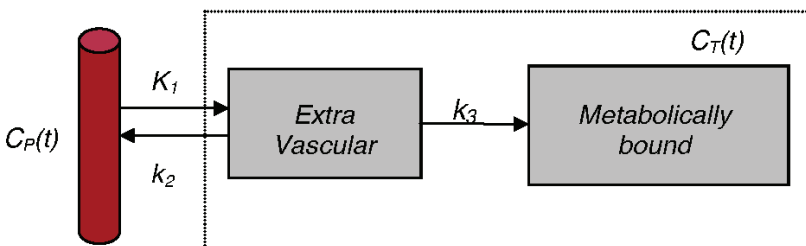


**Figure 4.** Time-activity curves. Accumulated events per unit volume over time at an image ROI location are proportional to the radionuclide concentration at the corresponding anatomical location.



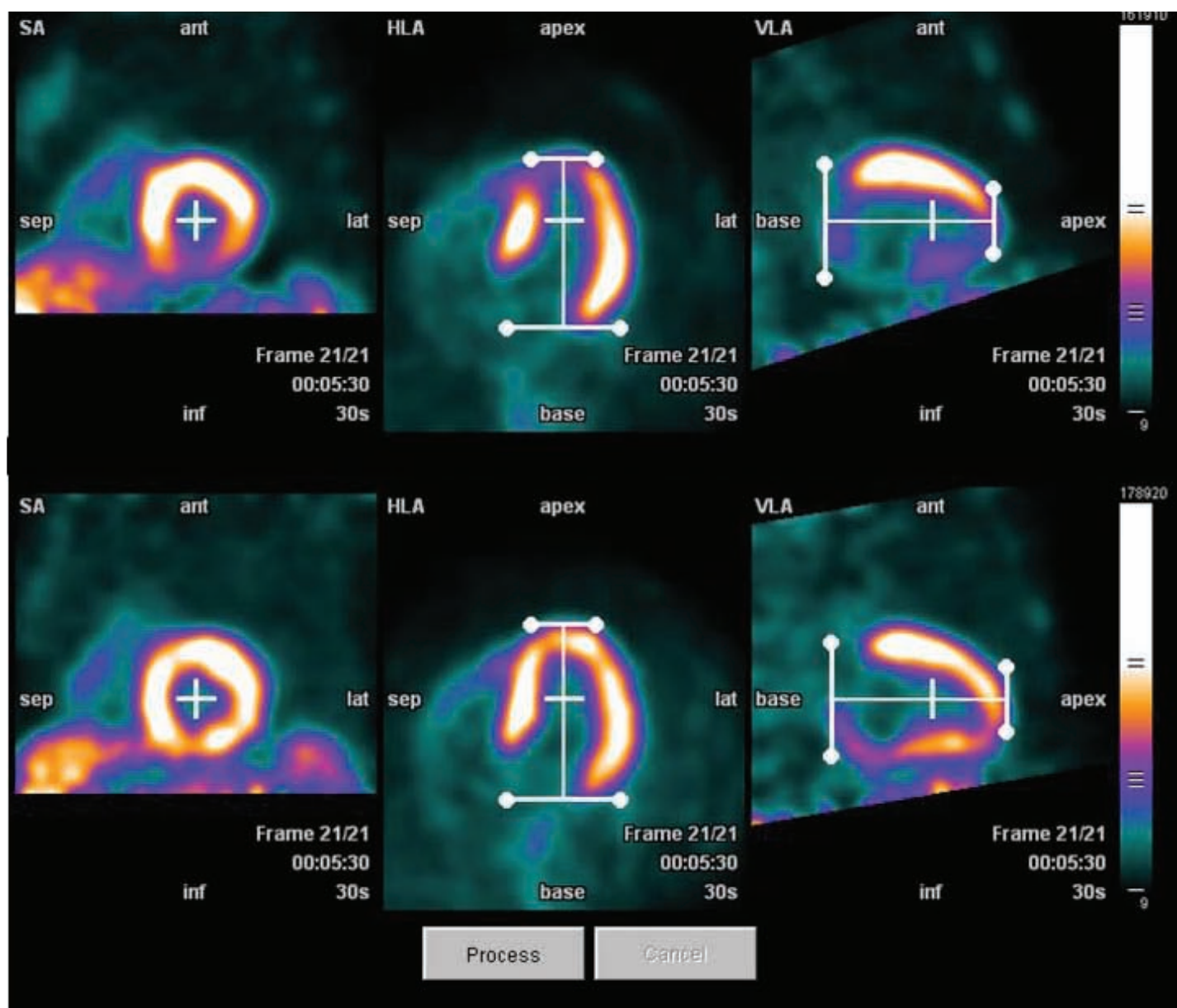
(a)

**Figure 5.** The one- and two-compartment tracer kinetic models for  $^{82}\text{Rb}$  (a) and  $^{13}\text{NH}_3$  (b), respectively.  $C_P(t)$  is the blood input function and  $C_T(t)$  the myocardial tissue compartment. The  $^{13}\text{NH}_3$  model contains extra-vascular or interstitial "free" and intracellular or "trapped" spaces.  $k_1$  represents myocardial extraction,  $k_2$  the rate of transport back to the blood, and  $k_3$  the rate of  $^{13}\text{NH}_3$  metabolic conversion into  $^{13}\text{N}$ -glutamine.



(b)

**Figure 6.** Automatically, the weighted sum of the later frames in each dynamic sequence is used to locate, delineate, and re-orient the LV myocardium along its long-axis for all frames in the dynamic sequence.



sensors). Dynamic image sequences are formed at prescribed time intervals throughout LM acquisition and are dependent upon the physical and pharmacokinetic properties of the tracer. The individual images (or frames) of a dynamic PET sequence do not necessarily yield clinically relevant information as they are often noisy due to their short duration and image pixels of the myocardium obtained early in the dynamic sequence contain

blood pool radioactivity (spill-over). However, pixel wise time-activity-curves (TACs) derived from the entire ensemble of early to late dynamic frames, can produce a quantitatively accurate estimate of the desired physiological parameter (e.g., regional or global MBF or CFR) by an image processing procedure called mathematical "tracer kinetic" modeling (i.e., *syngo* MBF).

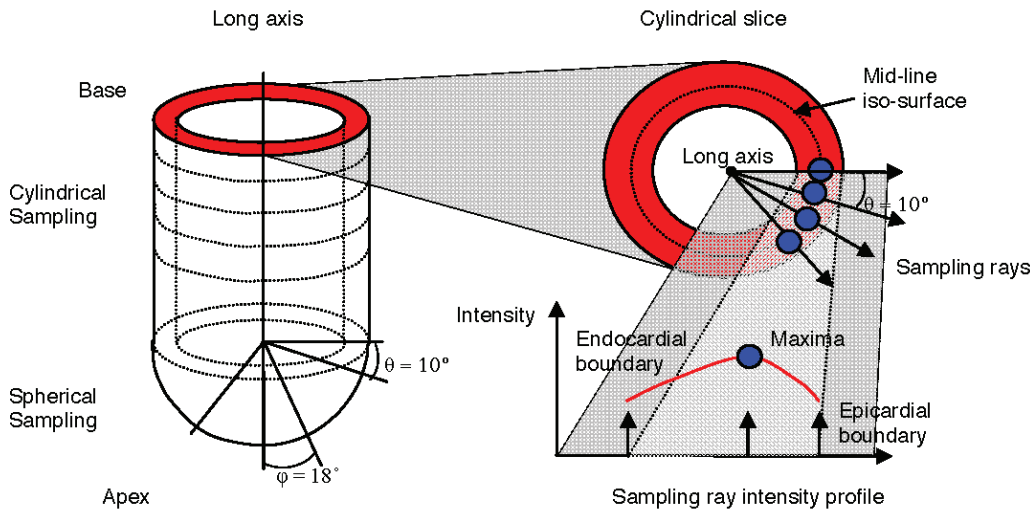


Figure 7. The syngo MBF application uses the conventional cylindrical-spherical model<sup>17</sup> for dynamic myocardial sampling.

After rest imaging and allowing for radionuclide decay, stress imaging is performed pharmacologically using adenosine, dipyridamole, or dobutamine. Heart rate, blood pressure, and ECG are typically recorded at baseline rest and throughout pharmacological stress imaging. Detailed recommendations for cardiac PET imaging procedures, including pharmacologic stress agent and radionuclide administration, are available in the referenced literature.<sup>8-12</sup>

### 3.2 Processing of PET data with syngo MBF

A number of automated image processing steps are required to obtain the blood input function and tissue uptake time-activities curves for the compartmental tracer kinetic analysis in the determination of MBF and CFR. These steps, shown and described below in the context of their syngo MBF implementation, start with the selection of stress and rest dynamic PET (transaxial) image sequences from the syngo MBF patient browser followed by loading the data into the MI Circulation application and then launching syngo MBF.

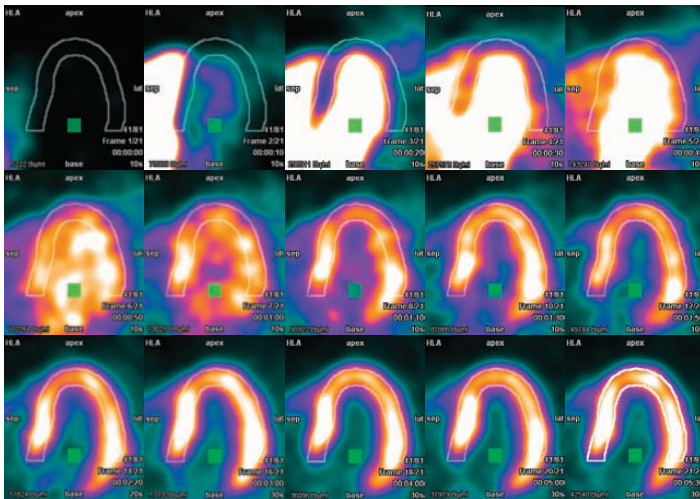


Figure 8. The blood input function used for all kinetic analyses is obtained from the dynamic sequence by averaging the activity in a cylindrical region-of-interest placed in the middle of the left ventricle in the most basal slice for each time frame. This blood pool ROI is displayed as a green cylindrical overlaid on the three orthogonal views.

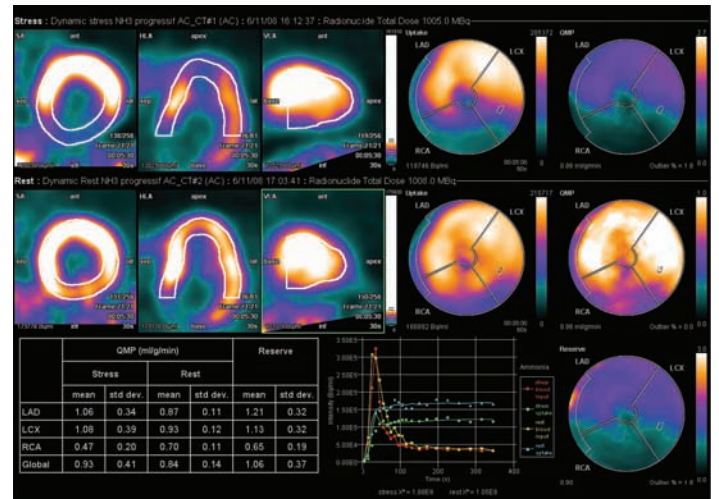
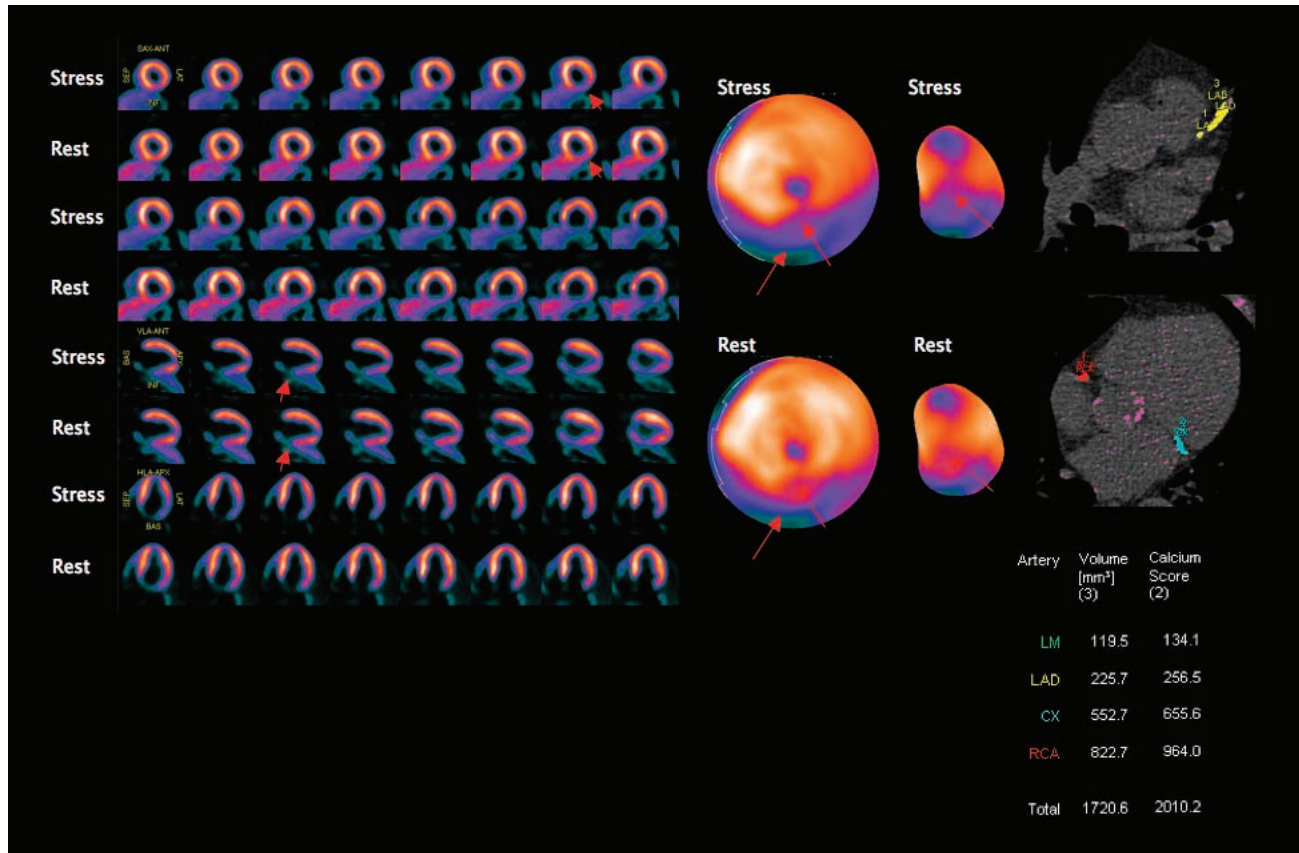


Figure 9. The results of tracer kinetic analysis include polar plots for stress MBF, rest MBF and CFR. For each of the polar plots, an overlay demarking the three main vascular territories from which a parametric chart of the vascular territory statistics (mean and standard deviation) is derived, along with a marked out section close to the basal septum

Figure 10 Data courtesy of the University of Geneva, Geneva, Switzerland

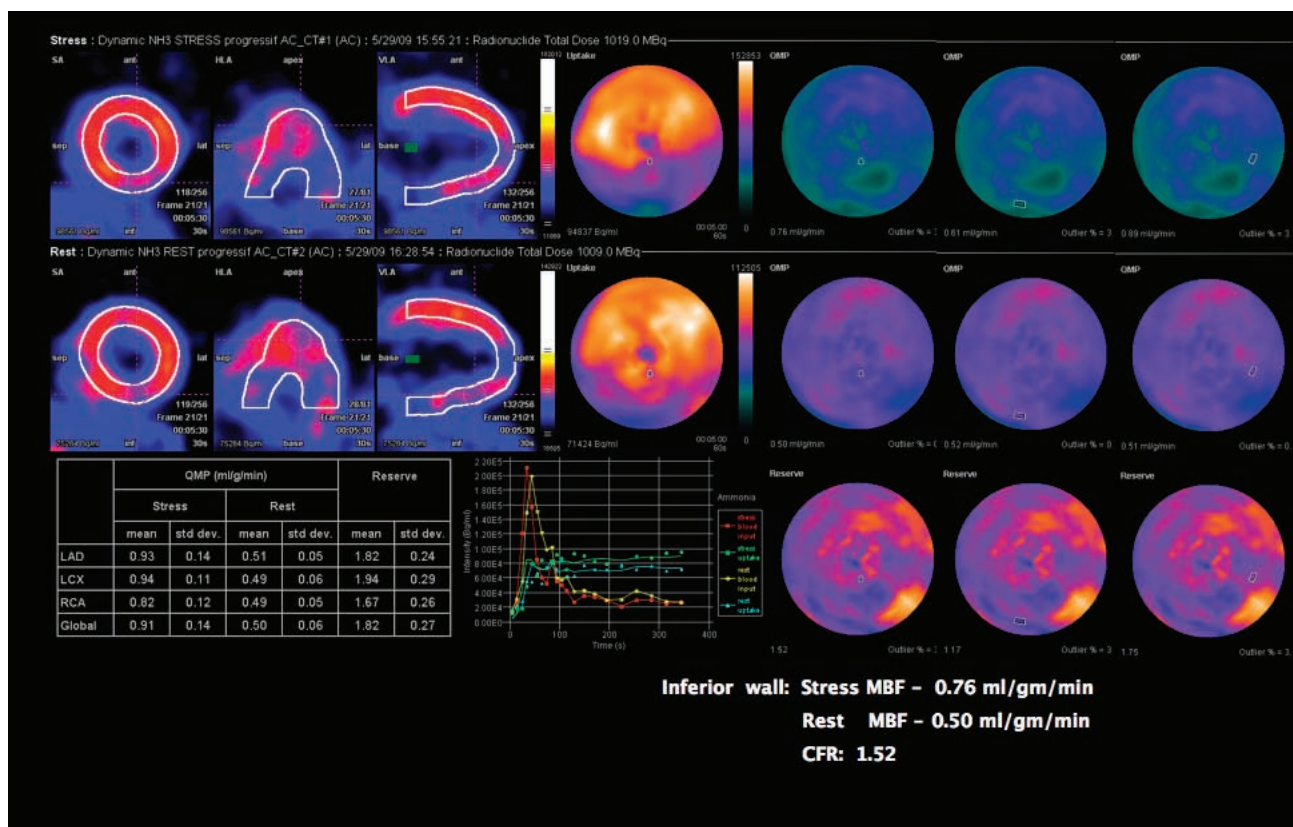


### 3.3 Clinical Examples

A few illustrative examples help explain the impact of flow quantification in CAD diagnosis. The first case (Figures 10, 11), a 78-year-old female with obesity and hypertension, presented with recent onset respiratory distress and signs of heart failure, but no chest pain. List-mode  $^{13}\text{NH}_3$  PET/CT was performed to identify hemodynamically obstructive CAD as a possible cause for cardiac failure. The MPI study shows a fixed perfusion defect in the inferobasal wall that is suggestive of infarction. The apico-inferior and inferolateral walls also show reversible ischemia. In addition, there is a mild post-stress LV dilatation, suggesting

advanced disease. The integrated calcium score study shows a very high coronary calcification (greater than 2000) with the predominant calcification in the right coronary artery (RCA) and left circumflex arteries. A standard evaluation of the stress-rest images suggests that there is predominant inferior and inferolateral wall ischemia. However, the MBF values suggest ischemia throughout the entire LV myocardium, with the most severe flow abnormality in the inferobasal, inferior and inferolateral wall.

Figure 11 Data courtesy of the University of Geneva, Geneva, Switzerland



The inferobasal wall, which shows the most severe perfusion abnormality, shows peak stress MBF of 0.61 ml/g/min with resting flow of 0.50 ml/g/min. This suggests a non-transmural infarct since the resting flow is better preserved as compared to what is expected in a transmural infarction. A portion of the apico-inferior segment shows peak stress MBF of 0.76 ml/g/min and a resting MBF of 0.50 ml/g/min, which implies reversible ischemia. The anterior and lateral wall also shows a decreased stress MBF of approximately 0.90 ml/g/min with a resting flow similar to the inferior wall. These results suggest there is a

moderate reversible ischemia in the anterior wall and septum, as well as the lateral wall, along with the severely ischemic inferolateral wall. Thus, the MBF estimation suggests triple-vessel disease with a predominant involvement of the inferior segments, while a relative evaluation was pointing to involvement of the RCA and possibly the left circumflex. The patient underwent coronary angiography, which showed triple-vessel disease: occlusion of the RCA, 95 percent occlusion of the left circumflex lesion and 75 percent LAD lesion. The MBF values were consistent with the stenosis estimation from coronary angiography.

Another example (Figures 12 and 13) shows a 69-year-old morbidly obese patient, with hypertension and type-2 DM, who presented with exertional dyspnoea and atypical chest pain. A stress-rest  $^{13}\text{NH}_3$  PET MPI exam showed reversible perfusion defect in the inferior wall. Average stress and rest RCA MBF were almost the same at 1.2 ml/gm/min (lower limit of normal 2.0 ml/gm/min) and 1.19 ml/gm/min, respectively. MBF at the area of the inferior wall with the lowest perfusion showed stress MBF of 0.99 ml/gm/min with a resting MBF of 1.36 ml/gm/min. The resting MBF in this region was higher than that at the peak

stress flow with a CFR of 0.73, which suggested severe (>90%) RCA stenosis. The average peak stress left anterior descending (LAD) MBF was 1.58 ml/gm/min, which was slightly lower than normal, but resting MBF (0.95 ml/gm/min) and CFR (1.88) were normal. Coronary angiography demonstrates a 90 percent to 99 percent occlusion of the proximal RCA. The LAD showed 50 percent to 70 percent stenosis, which was not considered flow limiting, and the minor reduction in peak stress MBF was attributed to microvascular dysfunction. The proximal RCA stenosis was successfully stented.

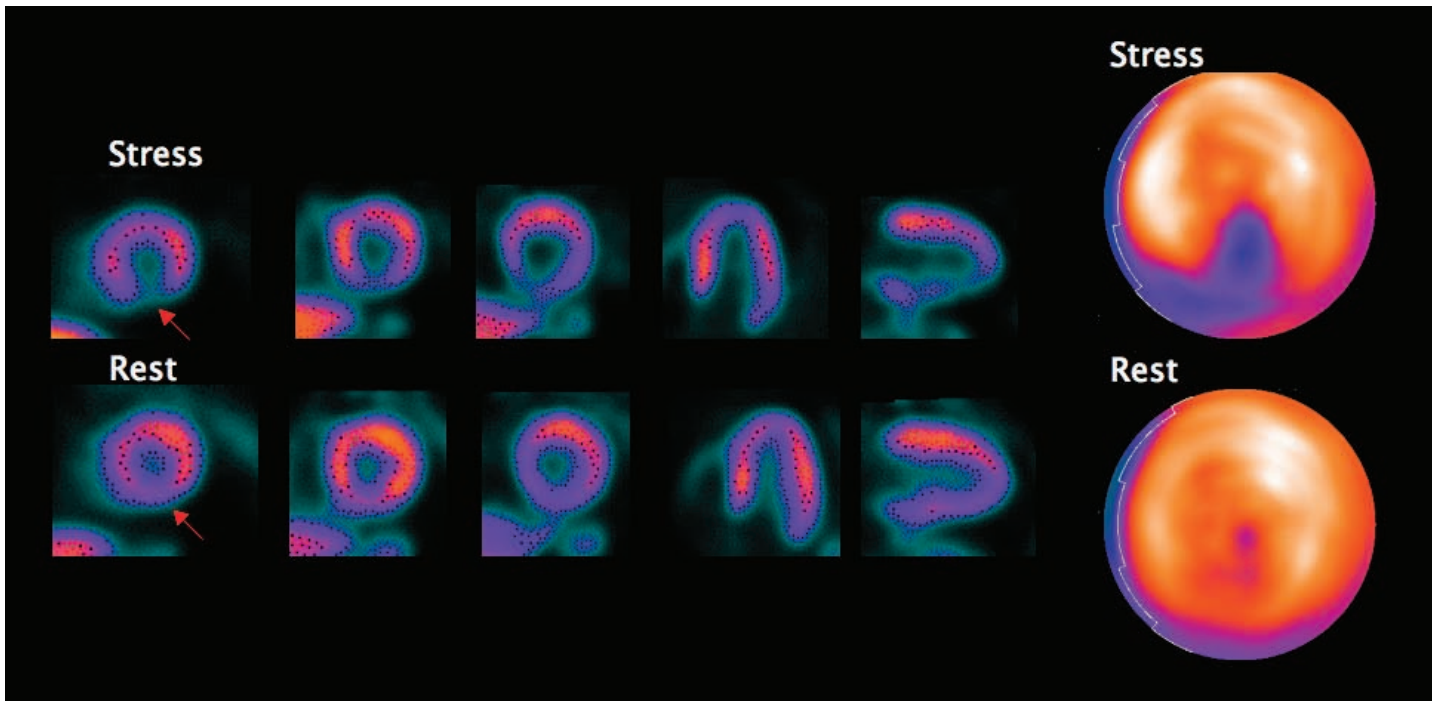
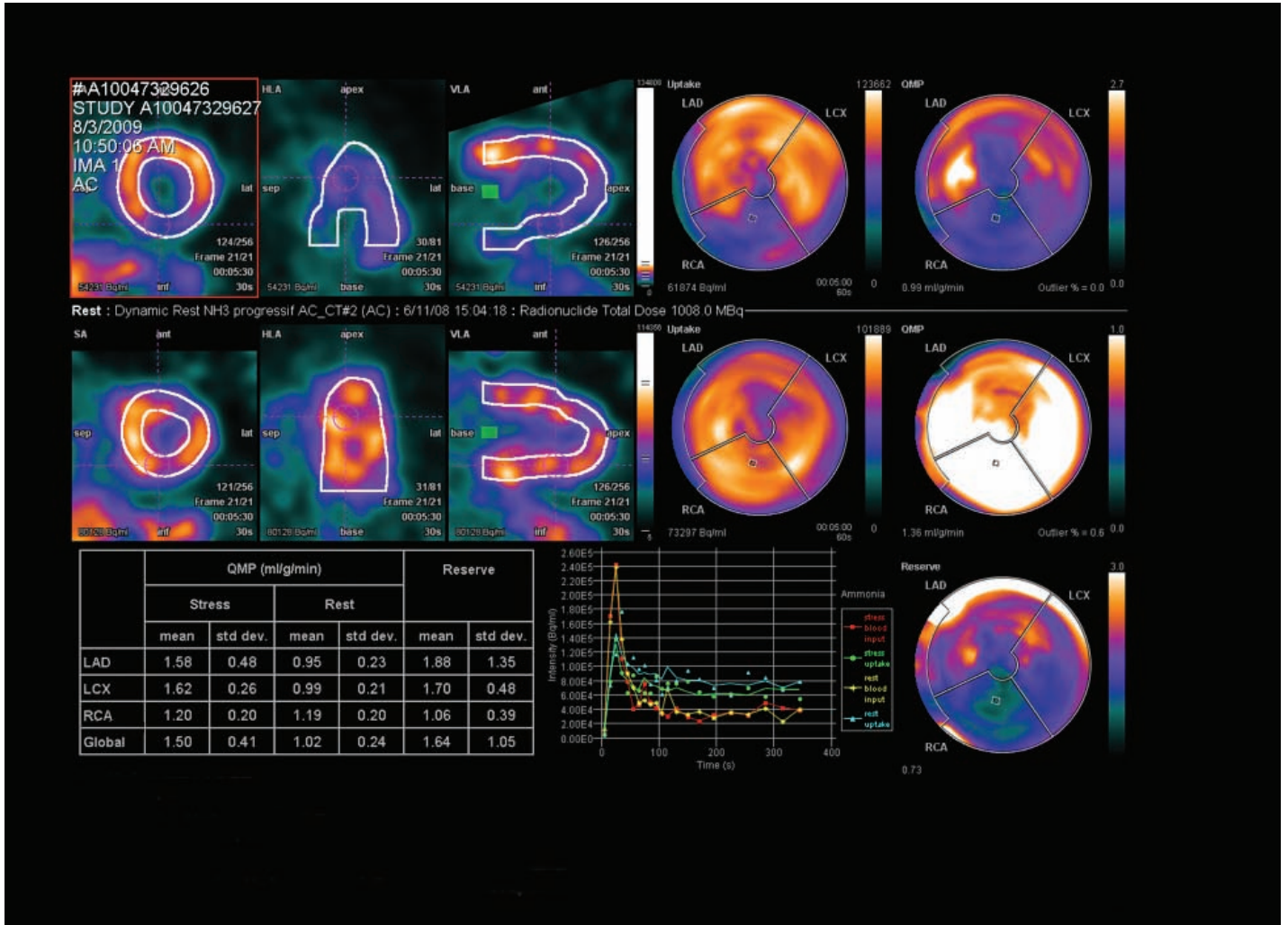


Figure 12 Data courtesy of the University of Geneva, Geneva, Switzerland

Figure 13 Data courtesy of the University of Geneva, Geneva, Switzerland



#### 4.0 Conclusion

Although standard, cardiac gated stress MPI is the mainstay of cardiovascular imaging<sup>13</sup>, *syngo* MBF, an alternative imaging methodology provided by Siemens *syngo* MBF PET/CT cardiac workflow, is potentially “game changing.”

The Biograph PET/CT and the *syngo* MBF application provide for non-invasive assessment of MBF and CFR with <sup>82</sup>Rb and <sup>13</sup>NH<sub>3</sub> using one- and two-tissue compartment tracer kinetic models. Siemens seamlessly integrates the compartment kinetic analysis of PET data, without complexity, into the clinical workflow using

state-of-the-art PET/CT scanners, acquisition modes, reconstruction methods, and kinetic analysis for quantitative MBF and CFR quantification and review.

*syngo* MBF is a commercially available user-friendly software for quantification of MBF and CFR. Using *syngo* MBF, the average cardiac PET/CT user would be able to perform quantitative studies on a regular basis, which can improve diagnostic confidence in a wide range of coronary artery disease states, especially in multivessel disease.

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1 Rb will be validated for use with *syngo* MBF in Nov 2010.

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