

# Non invasive assessment of coronary microvascular dysfunction

Frans Visser

Stichting CardioZorg-Parkstad Kliniek Amsterdam, Amsterdam, The Netherlands

Correspondence: F.C. Visser, Stichting CardioZorg-Parkstad Kliniek Amsterdam, Burgemeester Roëllstraat 24–26, 1064 BP Amsterdam, The Netherlands.  
E-mail: visser51@gmail.com

### Abstract

Microvascular abnormalities of the coronary circulation are present in several cardiac disorders, are associated with risk factors, and may be present in systemic disease. For the diagnosis and quantification of microvascular dysfunction, non invasive imaging techniques can be used. This paper will highlight the roles of exercise ECG, single photon emission computed tomography, echocardiography, cardiac magnetic resonance imaging, positron emission tomography, and computed tomography.

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**Keywords:** Microvascular disease, exercise ECG, SPECT, echocardiography, cardiac magnetic resonance imaging, positron emission tomography, computed tomography

### Introduction

It has long been recognized that microvascular abnormalities are present in several cardiac disorders. Studies have shown that dysfunction may be present in coronary artery disease, after myocardial infarction, in hypertrophic and dilated cardiomyopathy, in syndrome X, in congenital disease, in non compaction cardiomyopathy, and in systemic disease. Moreover, risk factors such as age, hypertension, diabetes mellitus, hypercholesterolemia, and smoking are all associated with microvascular dysfunction.

Almost all non invasive imaging techniques have been used to identify microvascular dysfunction in a variety of cardiac disorders. In this paper, the use of exercise ECG, single photon emission computed tomography (SPECT), echocardiography, cardiac magnetic resonance (CMR), positron emission tomography (PET), and computed tomography will be discussed.

### Exercise ECG

Exercise ECG has mainly been used in patients with syndrome X, which is characterized by anginal complaints, an abnormal exercise ECG, and normal or near-normal coronary arteries at coronary angiography. Typically, these patients show ST-segment depression during exercise testing (for a recent review, see [1]). An example is given in *Figure 1*.

The major advantage of the exercise ECG is that it is inexpensive and readily available. However, quantification of the extent of microvascular dysfunction is not possible.

### SPECT

Stress–rest perfusion SPECT imaging with thallium-201 or technetium-99m isonitriles has been used to demonstrate microvascular dysfunction in various cardiac diseases: for example, in patients with syndrome X



Figure 1. Example of an exercise ECG in a 54-year-old man with anginal complaints. Exercise stress testing showed ST-segment depression in the precordial lateral leads and ST-segment elevation in lead aVR. Angiography revealed normal coronary arteries.

[2], after percutaneous coronary intervention (PCI) [3], in dilated cardiomyopathy [4] and hypertrophic cardiomyopathy [5], and in patients with a metabolic syndrome [6]. All the studies showed reversible perfusion defects in these patients. Interestingly, the perfusion abnormalities have prognostic significance, except in patients with syndrome X, who have a normal prognosis. These differences may be explained by the differences in the underlying disease.

The use of SPECT is limited by the dose of radiation, limiting the number of studies – for example after a therapeutic intervention. More importantly, perfusion imaging is a semi quantitative technique in which perfusion images of different territories are compared. Attempts have been made to quantify the perfusion, but these have not yet been tested in clinical practice [7].

Examples of SPECT images from patients with reversible perfusion defects, despite the presence of normal coronary arteries, are shown in Figure 2.

## Echocardiography

Using echocardiography, there are three distinct approaches to the detection of microvascular dysfunction.

## Stress echocardiography

Similar to exercise ECG and SPECT perfusion imaging, stress echocardiography can be used to detect microvascular dysfunction in patients with syndrome X [8]. In response to stress provoked by dobutamine or adenosine, patients show new regional wall motion abnormalities.

## Direct Doppler imaging of the coronary arteries

The Doppler technique directly visualizes the coronary artery, by either transthoracic or transesophageal echocardiography. It enables resting flow and flow after vasodilatation to be obtained, giving the flow reserve of the coronary artery [9]. It has been validated in patients with syndrome X, and in those with dilated and hypertrophic cardiomyopathy. In these groups of patients, a lower flow reserve was found compared with that in control individuals. Figure 3 shows an example of Doppler-derived images.

Potential problems with this technique include the difficulty of obtaining adequate images, including

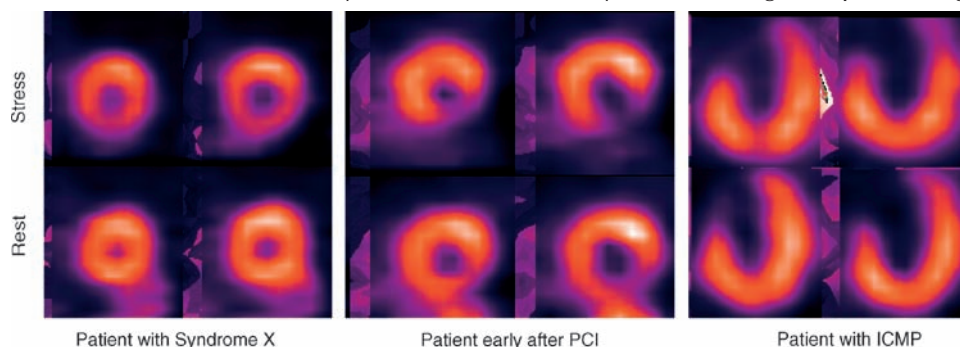


Figure 2. Examples of stress–rest perfusion single photon emission computed tomography in patients with reversible perfusion defects despite the presence of normal coronary arteries, indicating microvascular disease. ICMP, idiopathic dilated cardiomyopathy; PCI, percutaneous coronary intervention.

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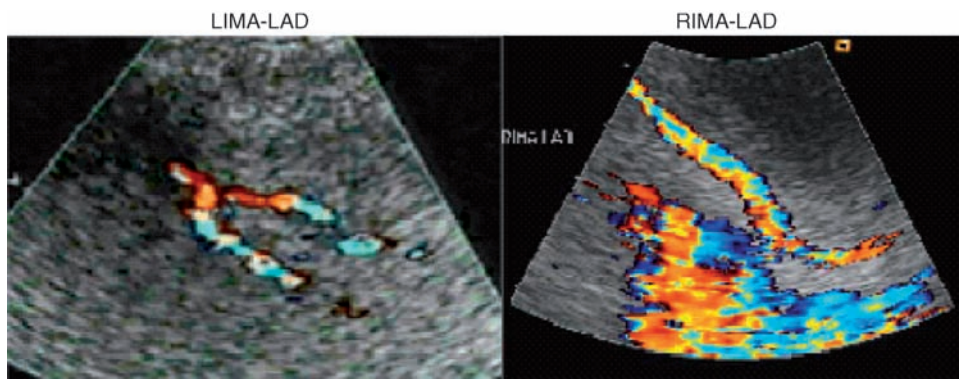


Figure 3. Examples of Doppler-derived images of bypass grafts on the left anterior descending coronary artery (LAD). LIMA, left internal mammary artery; RIMA, right internal mammary artery. (From Voci et al [9], with permission.)

through-plane motion and the angle between the probe and the coronary artery, and the ability to observe only proximal coronary arteries.

### Use of contrast agents to visualize perfusion

The third means of identifying microvascular dysfunction uses contrast agents. Microbubbles have been used, in particular, to assess the presence of no-reflow of the infarct area after primary PCI [10]. After intravenous or intracoronary injection, the microbubbles enter the coronary circulation and the myocardium becomes opacified. The opacification of the myocardium is diffuse and uniform in normal individuals (Figure 4), whereas, in those with microvascular obstruction, the myocardial area shows no or slow opacification.

An interesting approach is quantification of the wash-in rate of the bubbles as a measure of coronary flow. For this purpose, an interesting intervention is used: at a certain time point, the bubbles are destroyed by a high-energy acoustic wave, and subsequent

refilling of the myocardium by the bubbles is followed by echocardiography. From this wash-in rate, the coronary flow can be calculated and – from resting and adenosine-induced hyperemia – the flow reserve [11]. Although initial studies were promising, later studies showed a large variation in data [12], necessitating further refinement of the technique.

### Cardiac magnetic resonance imaging

Cardiac magnetic resonance can be used to assess wall motion during stress. However, this approach is cumbersome, and wall motion can be assessed more readily by means of echocardiography. The most widely used application of CMR imaging involves the use of contrast agents. Directly after injection of gadolinium chelates, myocardial perfusion can be measured, in a similar fashion as with echocardiography. Figure 5 shows an example of lack of opacification of the septal area after the injection of gadolinium benzyloxypropionictetra-acetate (BOPTA) in a patient after infarction.

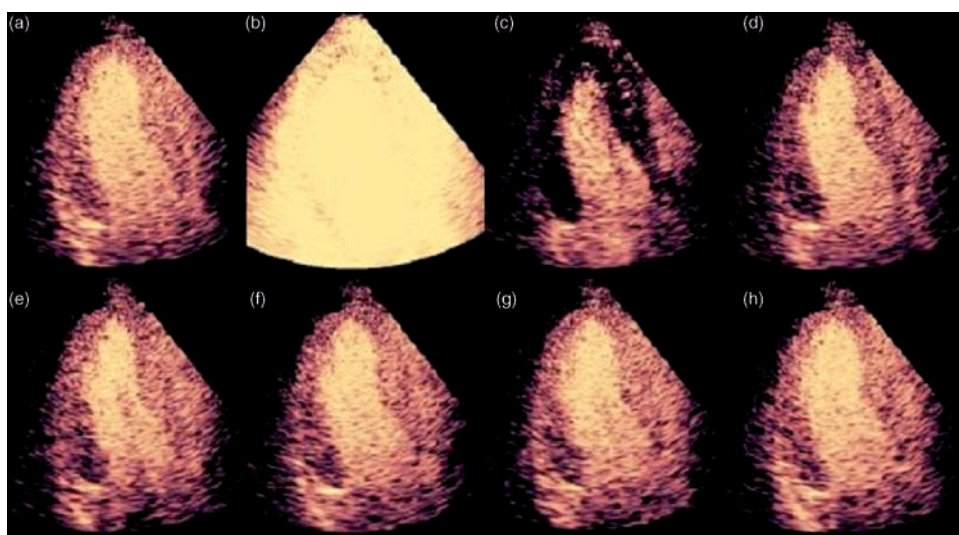


Figure 4. Example of opacification of the myocardium in a normal volunteer, visualized using contrast agents. (From Dijkmans et al [11], with permission.)

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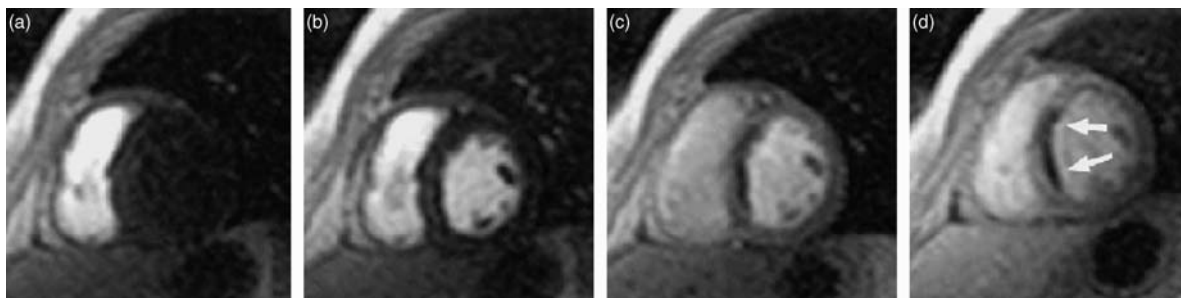


Figure 5. Patient with an anteroseptal infarction with a perfusion defect in the septal area (indicated by arrows) despite reperfusion therapy. (From Schneider et al [13], with permission.)

The time course of distribution of the contrast agent can be quantified by CMR, yielding the coronary flow or perfusion reserve [14]. There are several methodologies available to quantify coronary flow using first-pass perfusion, and the optimal approach remains to be defined. Nevertheless, in patients with syndrome X, a clear reduction in the perfusion reserve has been reported [15].

After injection, gadolinium chelates enter the interstitial space; in areas with microvascular dysfunction, a slow wash-in and wash-out can be observed. This technique is called late enhancement, and is widely used to assess viability and microvascular dysfunction after myocardial infarction [16]. However, late enhancement has also been observed in patients with hypertrophic and dilated cardiomyopathy, and in those with myocarditis. The relationship between microvascular dysfunction and late enhancement, and its clinical significance, thus need further investigation [17].

## PET imaging

Flow imaging with PET is considered the gold standard for the assessment of perfusion. Using the flow tracers [ $^{15}\text{O}$ ]H $_2$ O, [ $^{13}\text{N}$ ]ammonia, and rubidium-82, flow can be quantified, and has been widely validated in animal experiments and in humans. It has been extensively studied for use in assessing microvascular dysfunction in coronary artery disease, after myocardial infarction, in hypertrophic and dilated cardiomyopathy, in syndrome X, in congenital and systemic disease, and in non compaction cardiomyopathy (for a review, see [18]). Moreover, the technique has been used in the study of different therapeutic interventions.

An exciting development is the combination of PET and computed tomography in one imaging device. Computed tomography makes it possible to visualize the coronary tree, whereas PET provides perfusion data. An example is given in Figure 6.

The major disadvantage of PET is its limited availability, which is related to the cost. In view of the increasingly widespread installation of PET-computed tomography devices nowadays, it is pro-

bable that costs will become lower. A second disadvantage of the technique, of course, is that radiation is also involved; however, this is a fraction of that associated with conventional SPECT imaging.

## Computed tomography

The technique of computed tomography is the latest development in assessing microvascular dysfunction. As mentioned above, the coronary arteries can be visualized non invasively, and cardiac computed tomography is mainly used for this purpose, to assess the presence of coronary artery disease and calcification. Moreover, with the additional use of iodine contrast agents, myocardial perfusion can also be visualized. As with echocardiography and CMR, the contrast agent can be followed over time after injection, and early and late imaging may show perfusion defects (Figure 7).

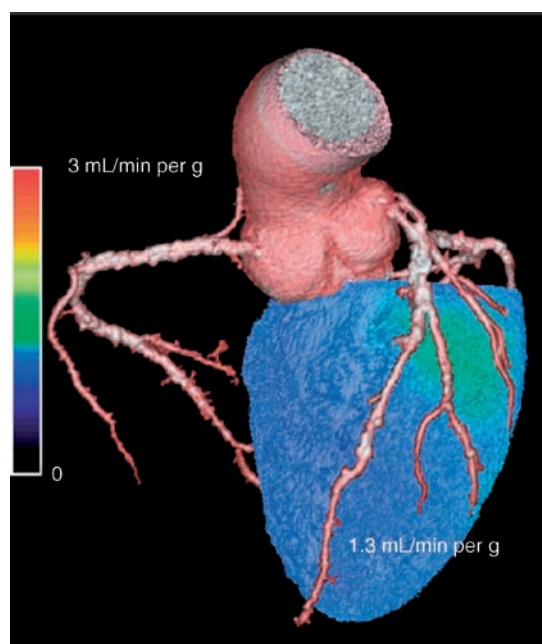


Figure 6. Fusion display of the coronary arteries and flow assessment by [ $^{15}\text{O}$ ]H $_2$ O positron emission tomography, showing a uniform reduction in maximal flow during infusion of adenosine. (From DeKemp et al [18], with permission.)

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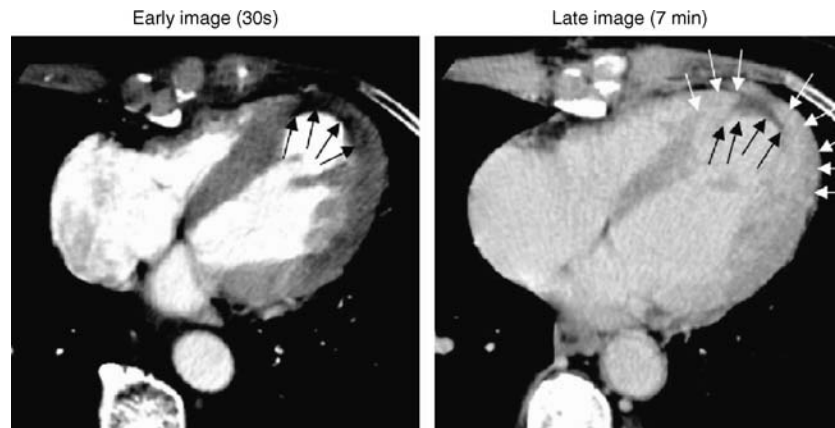


Figure 7. Example of early and late computed tomography imaging. The arrows indicate a region with hypoperfusion. (From Koyama et al [19]. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

Quantification of perfusion imaging is possible with contrast computed tomography, but awaits further validation in larger studies [20]. Computed tomography has excellent spatial resolution, but its role relative to established techniques needs to be assessed. Its major disadvantage is the high dose of radiation that is used, but that may be reduced in future.

### Summary

Microvascular dysfunction can be diagnosed with a variety of cardiac imaging tools, from simple techniques such as the exercise ECG to advanced devices such as PET-computed tomography. As microvascular dysfunction is becoming a more and more important target, large validation and therapeutic intervention studies can be expected. ■

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