Physiologic Evaluation of Coronary Circulation.  
Role of Invasive and Noninvasive Techniques

Jaume Candell-Riera, Josep Martín-Comín, Javier Escaned and Jesús Peteiro

For many years, the evaluation of the extent and severity of coronary artery disease has been mainly anatomical, carried out by coronary angiography. However, this technique has methodological limitations and interobserver variability is considerable. Quantification of coronary reserve with pressure guidewires and intracoronary Doppler now provides more precise physiologic evaluation of coronary circulation. Myocardial perfusion single proton emission computed tomography and echocardiography, combined with stress and/or pharmacological challenge testing, though they are only semiquantitative techniques, also offer appropriate complements to coronary angiography in the functional evaluation of coronary patients. The aim of this paper is to discuss the clinical value of these techniques.

Key words: Coronary circulation. Catheterization. Scintigraphy. Echocardiography.

INTRODUCTION

The anatomic classification of the extension of coronary artery disease to one, two, and three vessels has been used routinely in the prognostic assessment of patients with ischemic heart disease and in the selection of patients for revascularization. However, this criterion is too simple and not free of limitations. In 1986, Plotnick noticed that patients with three-vessel coronary artery disease did not constitute a homogeneous population. He remarked that clinical decisions based only on the number of vessels exemplify a unidimensional approach to a multidimensional problem, and demanded «less anatomy and more physiology» in the assessment of ischemic heart disease. In an attempt to overcome these limitations, different systems for scoring coronaryography have been devised, but subjective assessment of the coronary stenoses continues to be subject to considerable interobserver variability. This variability can be considerable although quantitative programs are used. Topol and Nissen warned in 1995 of the excessive concern of cardiologists for «coronary luminology,» in spite of the dissociation often existing between coronaryography and clinical manifestations. The use of intracoronary ultrasound is also just a morphometric approach to the study of the coronary arteries.

At present, more credence is conceded to knowledge of the functional repercussion of a specific coronary stenosis that can be studied in the course of catheterization by assessing coronary reserve using...
pressure guide wires, intracoronary Doppler, myocardial perfusion SPECT, echocardiography, and the conventional electrocardiographic exercise stress test. However, the anatomofunctional correlation of coronary lesions is not always optimal, since different factors, such as the methods used, interpretation criteria, provocation maneuvers, and the patient’s treatment can influence the results of these studies. This motivated Ellestad\(^{16}\) to affirm recently that the time has come to seek a new gold standard for re-evaluating the effectiveness of noninvasive tests.

It is interesting that the invasive techniques used for the assessment of coronary physiology have used as a gold standard noninvasive functional studies such as tomographic radionuclide scans of myocardial perfusion and stress echography, which are not exactly characterized as techniques that allow absolute quantification of coronary flow. The only noninvasive technique that allows quantitative assessment is positron-emission tomography, but it is highly complex and expensive, so its use is strictly limited even in centers that are equipped with the technique. It can be affirmed that the cardiologist currently has more possibilities for measuring anatomic parameters invasively (quantitative coronary angiography, intravascular ultrasound) than for quantifying absolutely functional parameters by invasive (intravascular pressure guide wire and Doppler) and noninvasive means (tomographic perfusion radionuclide scan, stress echocardiography, contrast echocardiography). As will be seen later, the values obtained from the studies of functional parameters are only semiquantitative, the result of comparing the most affected coronary regions with less affected or normal areas.

However, in clinical practice the cardiologist often has the problem of assessing the true importance of a single stenosis that is considered moderate in the coronaryography, or as a preliminary step to considering partial or total revascularization in a coronary patient with multivessel disease. The practice of percutaneous coronary intervention (angioplasty or stent) has increased enormously in the last decade. Initially, percutaneous revascularization techniques were not performed during diagnostic catheterization, but at the present, in order to reduce the aggressiveness of the procedure for the patient, avoid vascular complications, and reduce costs, revascularization is increasingly performed during the same procedure. Therefore, it is not uncommon that the cardiologist ordering a diagnostic coronaryography indicates on the order that revascularization may be performed, depending on the result of coronaryography. Incomplete percutaneous revascularization has been recognized as a reasonable strategy in many patients with multivessel disease; and it is known that total revascularization is performed in only 10% of these patients using percutaneous coronary interventionist techniques (angioplasty, stent). It is in such cases that previous knowledge of the location of the most functionally stenotic coronary artery, the so-called culprit lesion or the lesion responsible for the clinical manifestations of the patient or the most severe ischemia, is extremely important.

In this article, after a brief description of the physiology of the coronary circulation, the current status of invasive and noninvasive studies that can help cardiologists to make functional assessments will be described.

**PHYSIOLOGY OF CORONARY CIRCULATION**

Before approaching in detail the different techniques for functionally assessing the coronary circulation, it is advisable to briefly review some physiological facts that are fundamental for correctly interpreting the results of these studies. The coronary circulation it common described in terms of analogies with simple electrical or hydraulic circuits. In fact, these models are far from capable of integrating the complexity of the phenomena that occur during the cardiac cycle.

Heart function is highly dependent on the maintenance and modulation of coronary blood flow. The myocardium, particularly the subendocardium, is the tissue with the highest baseline aerobic demands in the body (8-10 ml O\(_2\)/min/100 g vs 0.15 ml O\(_2\)/min/100 g in the skeletal muscle). The three main determinants of this demand are wall stress, inotropic state, and heart rate.\(^{17,18}\)

**Coronary blood flow is influenced by extravascular compression.** Throughout the cardiac cycle, variations in intramyocardial and intracavitary pressure modify coronary vascular resistance drastically.\(^{19}\) Coronary blood flow is modulated by variations in the resistance of the vascular bed. Whereas blood flow is predominantly diastolic in the left coronary artery, in the right coronary artery there is also systolic blood flow due to the low extravascular compression exerted by the right ventricle and atria.\(^{19,20}\)

During cardiac systole, retrograde flow takes place in the coronary arteries and antegrade flow in the coronary veins. As a result of the extravascular compression resulting from systole, the microcirculatory and intramural vascular bed empties in two directions, retrogradely in the arterial direction and anterogradely in the venous direction, which causes a 180° phase difference in the flow in the coronary arteries and venous sinus.\(^{17,21-23}\)

During diastole, part of the antegrade flow fills the intramyocardial microcirculatory bed. Although coronary blood flow is fundamentally diastolic, during protodiastole epicardial blood flow and myocardial perfusion dissociate because the blood flow dissipates...
in a capacitance phenomenon, as filling the intramural branches and microcirculation milked during systole are filled.21,24

In baseline circumstances, the relation between blood pressure and flow in the coronary arteries is not linear. If the only situation considered from now on is analogous to the mid end-diastole, that is to say, a situation in which extravascular compression is minimal and constant and there are no variations in coronary conductance, coronary blood flow remains stable over a broad range of pressures. This phenomenon receives the name of coronary self-regulation and is the result of intrinsic myogenic tone, a response by the smooth muscle cells of the coronary arterioles to pressure variations.17,21,25,27 Coronary self-regulation is only effective within the range of pressures indicated: when the perfusion pressure falls below this pressure, coronary blood flow decreases.

During maximum coronary hyperemia, the relation between coronary blood pressure and flow is linear. In contrast to the situation just described, complete vasodilation of resistance vessels induced by a maximum physiological or pharmacological hyperemic stimulus (increased myocardial metabolism) establishes a fixed relation between coronary perfusion pressure and blood flow. The slope of this relation is influenced by the resistance of the system: the lower this slope (conductance) is, the greater the resistance of the system will be.21,28 The pressure-flow relation during maximum hyperemia constitutes a ceiling of expected coronary flow values for different perfusion pressures.29

The increase in blood flow from the self-regulation to the maximum hyperemia situation constitutes an indicator of the functional state of the coronary system. This concept constitutes the coronary flow reserve, a functional indicator of the state of coronary circulation that is widely used in diagnostic techniques.17,21,25,27,29 In figures 1 through 3 this principle is illustrated schematically. It is important to remember that in normal conditions the coronary reserve is transmurally heterogeneous: in the subendocardium, the coronary reserve is smaller because there is a greater baseline degree of arteriolar vasodilation as a result of greater subendocardial metabolic requirements.15

The presence of epicardial stenosis causes a loss of energy associated with blood flow that is expressed as a fall in effective perfusion pressure. Stenoses cause two types of resistance, one related with friction (f) and the other related with turbulence and the...
dispersion of blood flow after passing the stenosis (s). The transtenotic pressure gradient, ΔP, has a nonlinear relation with the f and s components and flow, Q, in accordance with the expression ΔP=fQ+sQ^2. The resistive components of friction and turbulence are influenced by characteristics of the blood (viscosity and density) and the geometry of the stenosis (reduction of luminal area, length, and the inflow and outflow angles).26,29,30 The complex interrelation between these factors contrasts with the simplicity of the indices of angiographic severity commonly used in clinical practice (e.g., the percentage of luminal diameter), and illustrates the limitations of angiography for evaluating the functional repercussions of stenosis.31

Coronary self-regulation compensates for the fall in blood pressure caused by stenosis in order to maintain constant coronary blood flow. The mechanism of self-regulation, which in physiological conditions adjusts microcirculatory resistance to myocardial energy requirements, has a chronic compensatory function in response to the fall in intracoronary pressure secondary to stenosis. As the stenosis increases in severity, sustained arteriolar vasodilation increasingly compromises the self-regulatory function to maintain an adequate myocardial blood flow. In other words, the compensatory function of coronary self-regulation in a stenotic vessel is at the expense of reducing coronary reserve. The compromised coronary reserve is first evident in the subendocardium, where baseline arteriolar vasodilation is greater due to higher energy demands.

The hemodynamic effect of a stenosis is manifested in the smaller slope of the pressure-flow relation. The diagnostic utility of the coronary reserve concept derives from this finding. The potential increase in coronary blood flow from a given pressure at baseline to maximum hyperemia (that is, the coronary reserve) decreases in the presence of stenosis. This effect is quantifiable in absolute terms if measurements obtained at baseline and in hyperemia are available. In addition, because adjacent vascular beds have a conserved coronary reserve, the induction of maximum hyperemia tends to increase the heterogeneity of myocardial perfusion, a phenomenon that constitutes the basis for different diagnostic techniques. In this sense, pure arterial vasodilators (adenosine, papaverine, dipyridamole) administered systemically, enhance the heterogeneity of regional and transmural myocardial perfusion (inducing the theft phenomenon when the vessel of the epicardial layers dilate). Dobutamine exhausts the coronary reserve in the stenotic vessel as a result of metabolically increasing myocardial demand (it increases contractility and myocardial oxygen consumption more than physical exercise) and specifically inducing vasodilation of the microcirculation (doses of 30-40 μg/kg/min produce overall coronary vasodilation similar to that of adenosine administered systemically).32 Finally, physical exercise is the most physiological stimulus, since it combines metabolic stimuli with neural modulation of the coronary circulation.

Microcirculatory dysfunction is also manifested the smaller slope of the pressure-flow relation. This is important for the correct interpretation of diagnostic techniques based on coronary reserve, and explains the development of techniques for the specific assessment of epicardial and microcirculatory resistance.33-36 Many clinical entities that cause remodeling of the coronary microcirculation also participate in the development of epicardial stenoses, such as diabetes mellitus, arterial hypertension, smoking, and hypercholesterolemia, as well as heart transplant vasculopathy.26,36 Likewise, microcirculatory resistance can increase in relation to alpha-adrenergic stimulation (e.g., in relation to physical exercise or mental stress),37 during acute myocardial ischemia,38 or as a result of microembolization (platelet or thrombotic aggregates, particles resulting from rotational atherectomy).39

Another important observation for diagnostic techniques is that microcirculatory dysfunction reduces the gradient of transtenotic pressure in an epicardial stenosis that, as discussed above, is dependent on coronary blood flow. This phenomenon can lead to an incorrect interpretation of diagnostic tests that are based on the Bernouilli formula or measurement of the translesional gradient.35,40 This again explains the importance of tests that allow
independent assessment of the severity of an epicardial stenosis and the state of microcirculation.

**INVASIVE METHODS FOR THE PHYSIOLOGICAL ASSESSMENT OF CORONARY CIRCULATION**

The techniques of intracoronary physiological assessment described below arise from the possibilities, made available by technological advances, to make the same observations used to clarify the pathophysiology of ischemic heart disease experimentally for clinical purposes, and to develop noninvasive techniques for detecting ischemia. By virtue of its invasive character, intracoronary physiological assessments are always made with previous knowledge of the coronary anatomy and in a highly selective way. Studies are made of individual vessels or the stenosis itself, which allows the assessment of patients with single or multivessel disease. Since these interventions are percutaneous, their results contribute to decision-making and the assessment of the final results during such interventions.

**General aspects of physiological assessment in the hemodynamics laboratory**

Although various invasive techniques have been used for the physiological assessment of coronary circulation in hemodynamics laboratories, the instruments most used at present are very small caliber solid guide wires equipped with speed or pressure sensors. Guide wires with velocity sensors provide reliable information about the mean speed of coronary blood flow, based on spectral analysis of the radiofrequency signal obtained. Guide wires equipped with pressure sensors provide measurements of intracoronary pressure with a high frequency response. In both cases, in contrast with previously used techniques, the low profile of guide wires (0.16 mm²) produces negligible interference with the measurements obtained. Doppler guide wires allow good quality recordings to be obtained at baseline and during hyperemia in most cases. Occasionally, the increase in blood flow with the induction of hyperemia can change the position of the guide wire, causing signal loss and making it necessary to reposition the guide wire. In contrast, pressure guide wires do not have to be positioned and provide stable pressure signals that do not change during the induction of hyperemia. Measurements of intracoronary pressure are combined with those of aortic pressure obtained with the catheter guide wire.

Many of the techniques that will be describe require pharmacological induction of maximum coronary hyperemia. The agents most often used are adenosine (or adenosine triphosphate) and papaverine. Adenosine can be administered by the intracoronary (20-40 µg bolus) or intravenous route (140-160 µg/kg/min), although the intravenous route is preferable for the purpose of guaranteeing complete, sustained hyperemia during measurements. It must be used with caution in patients with bronchial hyperreactivity, cardiac conduction disorders, and severe kidney failure. Its effect can be antagonized by concomitant xanthine treatment. Papaverine administered in an intracoronary bolus (12 mg in the left coronary and 8 mg in the right) provides a stable maximum hyperemia lasting approximately 1 min. Finally, although it is not generally used in calculations of coronary reserve, the administration of maximum doses of dobutamine (30-40 µg/kg/min) is also associated with maximum coronary hyperemia.

**Coronary reserve indices**

**Coronary flow velocity reserve**

Doppler guide wires make it possible to calculate an index equivalent to classic, or volumetric, coronary reserve, the coronary flow velocity reserve (CFVR), which is the ratio between intracoronary mean velocity in baseline conditions and after pharmacological induction of maximum hyperemia. CFVR does not discriminate between the effect on coronary reserve of epicardial stenoses or microcirculatory disorders. Its usefulness in the hemodynamic assessment of epicardial stenoses has been studied widely. The most relevant papers in this field are listed in Table 1, with the type of test used to detect ischemia used as a reference. The cutoff point for determining the hemodynamic relevance of these studies varies, with CFVR <2 generally being accepted as indicative of abnormal coronary reserve. The main limitation of the concept of CFVR is its dependency on values obtained with respect to the baseline flow velocity, which can be modified by many factors, including sex, blood pressure, and heart rate. For this reason, a model has been proposed to adjust CFVR measurements to the baseline speed and age of the patient, a concept designated corrected coronary flow velocity reserve.

**Relative coronary flow velocity reserve**

As mentioned, coronary reserve and, therefore, CFVR provide combined information on the epicardial (stenosis) and microcirculatory components of the vessel studied. The potential coexistence of both anomalies can lead to problems in clinical decision-making. The concept of relative coronary flow velocity reserve (CFVR-r) provides a solution for this problem. CFVR-r is the ratio between the CFVR obtained in a stenotic vessel and CFVR in a non-
stenotic reference vessel (Figure 4). CFVR-r can have a maximum value of 1, corresponding to the complete absence of hemodynamic relevance in the problem stenosis. Below 0.60-0.65 (Table 1), the problem stenosis would be considered hemodynamically significant regardless of the presence of microvascular dysfunction.47,49 This technique offers the advantage of providing simultaneous information on the state of the microcirculation (CFVR<2 in the reference vessel indicates that the subject has microcirculatory dysfunction). The limitations of the method are the assumption that microcirculation presents a similar degree of impairment in the two territories in which CFVR measurements are made and the need for a non-stenotic reference vessel, which impedes its application in patients with multivessel disease.

Myocardial fractional flow reserve

Information can be obtained relative to the coronary flow reserve in accordance with intracoronary pressure measurements. The principle on which this technique is based derives from the pressure-flow relation in the coronary tree. This relation is linear during hyperemia, so it is evident that the proportion between two intracoronary pressures is identical to the proportion between the two coronary flows corresponding to these pressures. If this concept is applied to pressures proximal (Pa) and distal (Pd) to a stenosis, we will be able to calculate the percentage fall in coronary flow caused by the stenosis: For example, Pd/Pa ratio=0.5 will be interpreted as a 50% reduction in coronary blood flow caused by the stenosis in relation to a non-stenotic situation (in which case there would be no difference between Pa and Pd, and Pd/Pa=1). The Pd/Pa ratio obtained during maximum hyperemia constitutes the

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Technique</th>
<th>PCO</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVFC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller et al42</td>
<td>33</td>
<td>SPECT</td>
<td>2.0</td>
<td>82</td>
<td>100</td>
</tr>
<tr>
<td>Joye et al43</td>
<td>30</td>
<td>SPECT</td>
<td>2.0</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>Deychak et al44</td>
<td>17</td>
<td>SPECT</td>
<td>1.8</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Heller et al45</td>
<td>55</td>
<td>SPECT</td>
<td>1.7</td>
<td>81</td>
<td>87</td>
</tr>
<tr>
<td>Danzi et al46</td>
<td>30</td>
<td>Stress echo</td>
<td>2.0</td>
<td>91</td>
<td>84</td>
</tr>
<tr>
<td>Verbene et al47</td>
<td>37</td>
<td>SPECT</td>
<td>1.9</td>
<td>67</td>
<td>86</td>
</tr>
<tr>
<td>Abe et al48</td>
<td>46</td>
<td>SPECT</td>
<td>2.0</td>
<td>88</td>
<td>95</td>
</tr>
<tr>
<td>Chamuleau et al49</td>
<td>127</td>
<td>SPECT</td>
<td>1.7</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>Relative CFVR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbene et al47</td>
<td>37</td>
<td>SPECT</td>
<td>0.65</td>
<td>78</td>
<td>89</td>
</tr>
<tr>
<td>Chamuleau et al49</td>
<td>127</td>
<td>SPECT</td>
<td>0.60</td>
<td>48</td>
<td>91</td>
</tr>
<tr>
<td>FFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pijs et al54</td>
<td>45</td>
<td>Ergo+SPECT+stress echo</td>
<td>0.75</td>
<td>88</td>
<td>100</td>
</tr>
<tr>
<td>Abe et al58</td>
<td>46</td>
<td>SPECT</td>
<td>0.75</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>Chamuleau et al49</td>
<td>127</td>
<td>SPECT</td>
<td>0.74</td>
<td>65</td>
<td>85</td>
</tr>
<tr>
<td>Diastolic FFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abe et al49</td>
<td>46</td>
<td>SPECT</td>
<td>0.76</td>
<td>96</td>
<td>100</td>
</tr>
</tbody>
</table>

N indicates sample size; PCO, optimal cutoff point; CVFR, coronary velocity flow reserve; FFR, myocardial fractional flow reserve.
CFVR, FFR provides very similar values under different hemodynamic conditions. Unlike CFVR, FFR provides very similar values under different hemodynamic conditions. This cutoff point is based on other studies summarized in Table 1. A modification of FFR is the diastolic FFR, which is characterized by using the ratio of pressures obtained only during diastole. This technique, aside from demonstrating the highest sensitivity for the detection of inducible ischemia, can potentially avoid the interference of systolic phenomena that affect calculations based on mean pressures.

FFR has characteristics that deserve detailed analysis. In the first place, it is a specific technique for the hemodynamic assessment of stenoses, so it cannot be applied to coronary arteries without epicardial revascularization. The information that FFR provides is relative to a theoretical hemodynamic situation in which the stenosis to be studied does not exist, an characteristic that makes it especially useful for assessing the need for percutaneous revascularization. FFR evaluation provides combined information on anterograde flow through the stenosis and on collateral circulation in the myocardial territory dependent on the artery to be studied: in vessels with important collateral support, the relative effect of stenosis on the perfusion of the territory is smaller and FFR values are higher. Unlike CFVR, FFR provides very similar values under different hemodynamic conditions. Finally, although it does not contribute information on the state of coronary microcirculation, FFR measurements are dependent on the state of the microcirculation. Since the transtenotic pressure gradient is a function of coronary flow, attenuation of the hyperemic response by microcirculatory impairment will be associated with higher FFR values than those obtained in cases of normal microcirculation. From a practical viewpoint, this may not constitute a limitation of the technique: the finding of a normal FFR value in a stenosis with important underlying microcirculatory involvement would make it possible to anticipate a small percentage increment in myocardial blood flow if this vessel is revascularized.

**Methods not based on the concept of coronary reserve: slope of the diastolic pressure-flow relation in hyperemia (coronary conductance) and coronary resistance**

In the introduction to the elementary principles of coronary physiology, the relation between coronary blood pressure and flow is emphasized as one of the best ways to approach coronary function. This principle was developed by Mancini et al. to be used as a diagnostic application designated as the instantaneous hyperemic diastolic pressure-flow slope (i-HDPFS) using only measurements obtained in mid end-diastole. As commented above (Figure 3), during protodiastole there is no relation between pressure and flow due to the capacitance of intramyocardial vessels and microcirculation. Experimental studies have shown a good correlation between the severity of epicardial stenoses and the degree of subendocardial conductance measured with radiospheres. The method has been adapted for clinical use with guide wires fitted with pressure microsensors and flow velocity by Mario et al. The principle of i-HDPFS is similar to that of the hemipressure time used in the assessment of mitral stenosis with Doppler echocardiography. It has the advantage of not needing baseline reference measurements because data are collected only during maximum hyperemia. The main limitation of i-HDPFS is the technical difficulty of obtaining the measurement. There are no commercial systems for
the measurement of this variable, and in clinical studies, the poor quality of the Doppler signal has made it impossible to perform this calculation in 20% of cases. Controversy exists regarding its dependence on changes in preload, heart rate, and cardiac contractility.61,63

A second approach is to calculate coronary resistance from mean values of coronary pressure and flow velocity, expressed in absolute terms64 or as a ratio between resistance in baseline conditions and hyperemia.64 In spite of their limited diffusion, these techniques have demonstrated their potential for identifying histological changes in microcirculation64,65 and for observations about their role in different coronary syndromes.38,66

A growing amount of information is available on the safety not only of intracoronary maneuvers with pressure and flow guide wires,67 but also on decision-making about revascularization based on intracoronary physiological data obtained with these techniques.56-79

**NONINVASIVE METHODS FOR THE PHYSIOLOGICAL ASSESSMENT OF CORONARY CIRCULATION**

As discussed in the previous section, the techniques of intracoronary physiological assessment described have been validated by noninvasive functional studies of the coronary circulation: myocardial tomographic radionuclide perfusion scanning (SPECT; single-photon emission computed tomography) and echocardiography. In the hospital setting, half of the indications for noninvasive studies are requested for the functional assessment of a specific coronary stenosis or for the detection of the culprit lesion, after practicing diagnostic coronariography, which indicates that in many cases this last study alone is not sufficient to make an integral assessment of coronary patients.

**Radionuclide study of myocardial perfusion**

The most recent innovation in nuclear cardiology is positron-emission tomography (PET). This technique uses isotopes with a very short mean life (min/s) and high energy (511 KeV), which is why tissue attenuation is minimal. PET allows the quantitative and noninvasive determination of coronary blood flow60,61 in an exact way. The isotopes most used for the absolute quantification of coronary blood flow are $^{13}$N-ammonium and $^{82}$Rb. A good correlation has been observed between coronary blood flow determined by radionuclide scan and by microspheres. On the other hand, PET can be used to assess the viability of the myocardium by the combined use of metabolic radionarkers like $^{18}$F-FDG, whose uptake depends on cellular integrity, and perfusion radionarkers like $^{13}$N-ammonium or $^{82}$Rb. Clinical experience with PET in cardiology is limited because it is an expensive technique, of limited availability, whose diagnostic performance remains to be determined.

For these reasons, the assessment of myocardial perfusion in clinical practice is usually made by myocardial perfusion scan using single-photon emission computed tomography, or SPECT, which is a technique with which broad experience is available (Figure 6). Myocardial perfusion studies were initiated in the 1970s using thallium chloride ($^{201}$TlCl) as the radiomarker. Thallium-201 is a monovalent cation of behavior similar to the potassium that penetrates the cell by active uptake (Na pump) and passive diffusion. Myocardial uptake is proportional to coronary flow and peaks at approximately 20 min. Once the peak value is reached, so-called redistribution takes place, a process by which intra and extracellular concentrations balance out and $^{201}$Tl circulates from high-uptake to low-uptake zones. This means that the post-stress study must be acquired quickly (within 10 min of radiomarker administration) and before redistribution begins.

In addition to $^{201}$Tl, there are currently two other perfusion radionuclide markers available for clinical use: $^{99m}$Tc-sestamibi (MIBI; methoxy-isobutylisonitril) and $^{99m}$Tc-tetrofosmin. These agents have different advantages over $^{201}$Tl. Unlike $^{201}$Tl, they penetrate the cell by passive diffusion and do not present appreciable redistribution. This means that they must be administered in two doses, one for the stress study and the other for the study at rest. Although the efficiency of extraction is greater for
that determined by echocardiography the ejection fraction determined by gated-SPECT and good correlation having been demonstrated between coronary perfusion and cardiac function (Figure 7), a Gated-SPECT enables the simultaneous assessment of dividing the cardiac cycle into 8 or 16 segments. The acquisition of SPECT synchronized with the ECG consists of synchronizing the onset of dipyridamole, adenosine and dobutamine, basically. treadmill or bicycle, or pharmacological stress: dobutamine stimulation.

Other markers are under study, but not available commercially. They have characteristics similar to those mentioned, for instance, Tc-teboroxime, and, more recently, Tc-NOET and agonists of the adenosine-A2A receptors. There are various protocols for the acquisition of SPECT (stress-rest in one day, two days, etc.) and single detector and multimodulator (with two or three detector heads) gammacameras. The response of the heart to stress can be evaluated with the effort stress test using a treadmill or bicycle, or pharmacological stress: dipyridamole, adenosine and dobutamine, basically. The acquisition of SPECT synchronized with the ECG has been introduced recently (gated-SPECT). This technique consists of synchronizing the onset of acquisition with the R-wave signal in the ECG and dividing the cardiac cycle into 8 or 16 segments. Gated-SPECT enables the simultaneous assessment of coronary perfusion and cardiac function (Figure 7), a good correlation having been demonstrated between the ejection fraction determined by gated-SPECT and that determined by echocardiography and contrast ventriculography. The combined assessment of myocardial thickening and contractility provided by gated-SPECT helps to differentiate defects due to artifacts from those due to ischemia, as well as the myocardial contractile reserve by means of low-dose dobutamine stimulation. The latest innovation in this context has been the correction of attenuation, a method for correcting the attenuation of tissues surrounding the heart.

SPECT allows the study of myocardial perfusion by assessing the homogeneity/heterogeneity of the distribution of the radionuclide marker in the myocardium. In the healthy subject, the images obtained post-stress or at rest demonstrate homogeneous activity in the left ventricular myocardium. Any zone of hypoactivity must be considered pathological and must be assessed, especially the changes observed between the image obtained in stress and at rest (Figure 8). When assessing the precision of SPECT for the diagnosis of coronary artery disease, it has been observed that there are no significant differences in results according to the sex or age of the patients, and that the sensitivity and specificity values are about 90-95%. It is necessary to take into account that are diverse non-atherosclerotic causes that can give rise to perfusion defects: the X syndrome, coronary spasm, coronary ectasia, coronary fistula, and hypertrophic cardiomyopathies.

**Diagnosis of multivessel disease**

The diagnosis of multivessel disease by means of the radionuclide perfusion scan is based principally on the detection of reversible perfusion defects in more than one coronary region (Figure 9) and other indirect signs, such as transitory ischemic left ventricular dilation and post-effort pulmonary radionuclide uptake. The association of these indicators of severe ischemia in the radionuclide perfusion scan with signs of severity in the electrocardiogram improves the
results of both tests considered separately.\textsuperscript{107-109} After reviewing thousands of patients included in studies in which SPECT and effort or pharmacological echography was performed, it has been concluded that effort SPECT is more sensitive but less specific than stress echography for the diagnosis of coronary artery disease.\textsuperscript{110,111}

Assessment of the myocardium at risk

The term «myocardium at risk» is generally used to define the extension of the myocardium threatened by diseased coronary arteries. However, in fact it should refer to the amount of myocardium that could be infarcted if the most stenotic coronary artery was occluded.\textsuperscript{112} Correlations between different quantitative tomographic radionuclide scanning methods for the assessment of the extension of perfusion defects are very acceptable, as demonstrate by the results of Ceriani et al.\textsuperscript{113} which compared three quantitative methods for assessing the myocardium at risk by means of SPECT.\textsuperscript{114-116} The correlations between tomographic radionuclide quantification and different coronarographic qualifications of the entire myocardium at risk are significant although not optimal.\textsuperscript{117-120} They improve progressively as the coronarographic score becomes more complex (r=0.48 for the Califf method, r=0.59 for the modified Gensini method, and r=0.65 for a coronarographic score in which the presence of collateral circulation is also assessed).\textsuperscript{117}

In coronarography, the role of collateral circulation can be underestimated.\textsuperscript{120-122} In fact, the best correlations are obtained with the coronarographic score that takes into account the existence of collateral circulation in cases in which an occluded coronary artery exists. Although it is known that not always is the most stenotic artery responsible for future infarction, it would be more logical to use the term myocardium at risk to define the extension of the myocardium that can be infarcted if the coronary artery with the most severe lesion were to be occluded.\textsuperscript{121-124} The best correlation (r=0.85) between the myocardium at risk obtained by SPECT and that determined by coronarography (considering circulation collateral) is obtained when assessing the culprit lesion.\textsuperscript{117} It is logical that this is the case, considering that tomographic radionuclide perfusion does not allow absolute quantification of the coronary flow, offering information only about the most hypoperfused region with respect to the least hypoperfused region.

Detection of the culprit lesion

Myocardial radionuclide perfusion scan is very useful in indicating partial revascularization procedures in patients with chronic coronary arterial disease.\textsuperscript{125-127} since in these cases what we aim to detect is the coronary stenosis that induces ischemia, the so-called «culprit lesion». This term is used as a synonym for the coronary lesion that causes symptoms in patients with ischemic heart disease.\textsuperscript{128,129} Some authors have relied on coronarography\textsuperscript{129} and others on radionuclide perfusion scan\textsuperscript{128} to detect the culprit lesion before performing a partial revascularization. The first possibility occurs generally in patients with unstable angina, and the second in stabilized patients.

The myocardial region with the greatest hypoperfusion in stress is assessed better in short-axis sections, because these images visualize in combined form the four basic regions of the left ventricular myocardium (anterior, septal, inferior, and lateral). In these images, the relative perfusion of these regions can be compared and the most severely affected region determined with respect to the radionuclide scan (Figure 9). The assessment of myocardial ischemia by radionuclide perfusion scan correlates well with CFVR, relative CFVR, FFR, and diastolic FFR (Table 1). Consequently, in cases in which the significance of a certain coronary stenosis is inconclusive,\textsuperscript{130,131} perfusion tomographic radionuclide scan can be very useful for assessing the severity of ischemia.

The agreement between coronarography and
The main advantages of echocardiography with respect to other techniques for investigating ischemia are its low cost, broad availability, absence of radiation, and the possibility of evaluating associated valve dysfunction. Its main limitation derives from the difficulty of making a quantitative analysis. However, this can now be palliated, in part, with new techniques like Doppler tissue studies, the measurement of tissue deformation (strain), and the omnidirectional M-mode. Another limitation is its broad interobserver variability, which has been observed in studies in which the second harmonic was not yet in use.

**Stress echocardiography**

The development of stress echocardiography has also been facilitated by second harmonic imaging, in addition to the availability of software that allows the comparison a posteriori of digitized baseline and stress images. Stress echocardiography has two major clinical applications: the diagnosis of myocardial ischemia and myocardial viability. Provocation maneuvers have been divided by the mode of triggering ischemia. Thus, exercise, dobutamine, and electrical stimulation increase myocardial oxygen demand, and ergonovine reduces demand. Vasodilator drugs like dipyridamole and adenosine produce ischemia by «coronary theft» mechanisms.

The performance of stress echocardiography in the diagnosis of ischemia is based on the concept of the «ischemic cascade». In the presence of ischemia, in first place disturbances in myocardial perfusion occur, which can be detected by radionuclide scan and perfusion echocardiography. Then, disturbances in diastolic function appear, which can be visualized by pulsed transmitral Doppler or M-mode color Doppler and, regionally, by tissue Doppler and studies of strain (tissue deformation). Eventually, disturbances in systolic function that can be detected by stress echocardiography occur (Figures 10 and 11). The, finally, ECG disturbances and angina appear.

Numerous studies have been published on exercise...
echocardiography on the treadmill and ergometric bicycle, reporting a sensitivity of 80% and a specificity of 85-90%. The diagnostic precision is always greater than that of conventional effort tests and generally close to that of radionuclide studies. In exercise echocardiography, regional and overall contractile function are analyzed at baseline and at peak effort or in the immediate postexercise period. Interpretable images are commonly obtained in more than 85% of patients. Limitations to the sensitivity of this technique are the need for special training, particularly when postexercise images are acquired, since there is a narrow «temporal window» for acquiring them, ideally <1.5 min. Other limitations are those of conventional exercise testing: inability to walk and failure to attain an adequate tachycardization.

Comparative studies of exercise, dobutamine, and dipyridamole have demonstrated a greater sensitivity (and similar specificity) of exercise and dobutamine than with dipyridamole, and scant serious undesirable effects. The addition of atropine to dobutamine increases the precision of the test and is
especially useful in the presence of beta-blocker
treatment. Transesophageal stress echocardiography
has been carried out with dobutamine with
considerable diagnostic safety and precision.
Echocardiography with ergonovine can play a role in
patients with suspected Printzmetal angina and
negative results of other tests. Recently, excellent
results have been communicated with transthoracic
echocardiography obtained by oral introduction of a
transesophageal electrical stimulation probe.

Assessment of the coronary reserve
Coronary reserve represents the capacity of the
coronary arteriolar bed to dilate in response to
increased cardiac metabolic needs. It is calculated as
the ratio between the velocity of coronary flow after
the administration of a vasodilator (usually adenosine
or dipyridamole) and in baseline circumstances. The
advantages of adenosine are rapid action and
termination of its effect and almost peak vasodilator
capacity. Its disadvantage is more frequent side
effects. Coronary reserve decreases progressively
when a fixed lesion produces a stenosis of 50%, in
such a way that it is completely suppressed with
lesions of more than 90%. Its usefulness in the
functional study of coronary lesions between 30% and
70% is unquestionable because it is in this range of
angiographic severity that clinical doubts arise.

Transesophageal echography allows the
visualization of the proximal segments of coronary
arteries (generally the left main trunk and the first
centimeters of the circumflex artery and anterior
descending artery), but the latest generation
equipment allows transthoracic visualization of flow
through the distal portion of the anterior descending
artery (Figure 12). This has the advantage of allowing
the coronary reserve to be calculated at that level.
Visualizing the flow of the anterior descending artery
requires experience, as well as the use of modified
planes. The possibility of measuring the distal
coronary reserve is excellent because the reserve
calculated reflects the residual vasodilator capacity of
the vascular bed, which is affected specifically by
proximal lesions of the proximal and middle anterior
descending coronary. Caiati et al, who studied
the coronary reserve with the infusion of adenosine
using pulsed Doppler in the distal section of the
anterior descending artery, reported a sensitivity of
91% and specificity of 76% for detecting stenosis
>75%. The flow signal was optimal without contrast
in half of the patients (55%) and in all of them after
contrast was administered. However, it must be
considered that the coronary reserve is also reduced in
left ventricular hypertrophy, small-vessel disease,
constrictive pericarditis, cardiomypathies, and
transplanted hearts, and left bundle-branch block.

Echocardiography of myocardial perfusion
Myocardial perfusion echocardiography is the
technique that, in combination with vasodilators,
results in the earliest detection of ischemia by
revealing a heterogeneous flow, as radionuclide
techniques do. The main difference with respect to
myocardial radionuclide perfusion scan is that the
thallium or technetium compounds are deposited in
the cardiac cell, indicating cellular integrity or
viability, whereas perfusion echocardiography only
indicates the integrity of the microcirculation.

At present, contrast agents are available that can be
used intravenously thanks to special characteristics
that allow them to pass the pulmonary barrier without
being destroyed. Nevertheless, it still has not been
established which is the best method for detecting echocontrast in the myocardium. The contrast agents produce a significant amount of bubbles that enter the coronary circulation and expand and compress alternatively when exposed to ultrasound. The detection of these bubbles depends on their capacity to generate two resonance waves of different frequency, in contrast with myocardial tissue. Therefore, if ultrasound are emitted to the myocardium at a frequency of 1.8 mHz, the myocardium itself will not transmit any frequency at 3.6 mHz, but the bubbles will. Therefore, by changing the system reception frequency to 3.6 mHz, the echoes from the bubbles will be visualized without the echoes from the myocardium. The second point to consider is that ultrasound rapidly destroys the bubbles, especially if the so-called «mechanical index» is high. The intermittent imaging system is the system of transmitting and receiving ultrasounds only once every x cycles. The bubbles can be destroyed by the fleeting emission of ultrasounds, but in the meantime new bubbles can be detected enter the system.

At present, numerous problems still exist, due mainly to artifacts. To determine if the echoes originating from the myocardium represent true perfusion or artifacts, the image can be multiplied, as well as intermittent. Multiplication consists of the emission and reception of ultrasound by the system at a moment in the cardiac cycle (image 1), and immediately after, in 30-50 ms (image 2). If «perfusion» is visible in image 1 and not in image 2, it is probably true perfusion, because the bubbles in image 1 will have been destroyed and the time is too short for the myocardium to have filled again. If perfusion is appreciated in both images, it usually should be considered an artifact. Another system for differentiating between true perfusion and artifacts is to change the frequency of the multiple images, passing from emitting and receiving, for example, every 4-5 beats in which perfusion is observed, to emitting and receiving every beat, in which it should not be visible due to the destruction of the bubbles.

Studies made with intermittent and multiple images using dipyridamole\cite{188} or adenosine,\cite{189} and comparing this technique with SPECT and technetium compounds, have obtained similar results. Agreement between methods for the presence or absence of coronary artery disease in each patient was 81-86%. Nevertheless, the agreement between techniques was greater in the territory of the anterior descending artery (81%; K=0.81) and right coronary (76%; K=0.52), and significantly smaller in the territory of the circumflex artery (72%; K=0.40). This is due to the large number of false defects obtained with echocontrast on the lateral face. In effect, due to the angle of incidence of ultrasound on the lateral wall, false defects may be more common in this territory. Spencer et al 190 also demonstrated a greater frequency of perfusion defects with echocontrast in the lateral wall, in the absence of defects in thallium radionuclide scans, with both techniques carried out at rest.

In addition to the system for detecting perfusion by intermittent and multiple images, bubbles can currently be visualized in real-time images. The aim is to work with a very low mechanical index that does not destroy the bubbles. To check if true perfusion is involved, at a given moment an emission with a high mechanical index (flash) will destroy the bubbles present in a true perfusion (Figure 13). The initial results obtained with these techniques seem promising, because they overcome many of the limitations of perfusion echocardiography,\cite{191,192} allowing them to be used, for example, during stress tests.\cite{193,194}

Possible, or future, clinical applications of myocardial perfusion echocardiography are not only the detection of ischemia, but also the detection of viability. Studies that have compared vascular integrity by echocontrast with the inotropic reserve by echodobutamine to predict recovery in coronary patients with ventricular dysfunction have documented a good sensitivity with the echocontrast (80-95%), but a notably lower specificity than with dobutamine echocardiography (50-75% vs 85%).\cite{195,196} Myocardial perfusion echocardiography can also evaluate the non-reflux phenomenon. It is known that approximately 18-25% of patients have impaired microcirculation.
after an effective primary angioplasty or fibrinolysis (TIMI-3), and that these patients do not recover their microcirculatory function during follow-up.\textsuperscript{200,201}

CONCLUSIONS

The intracoronary hemodynamic parameters that reflect the physiology of coronary circulation correlate acceptably with the functional assessment of myocardial ischemia evaluated by myocardial perfusion SPECT and stress echocardiography. However, none of these techniques allows absolute quantification of coronary flow and discrepancies can be observed between them in up to 15\% of patients.

From the review of more than 7000 patients included in 75 studies in which SPECT and other stress or pharmacological stress echography were available, it was concluded that effort SPECT was more sensitive than effort echography for the diagnosis of coronary artery disease, identification of stenotic arteries, and diagnosis of multivessel disease. In a review of 1380 patients from 22 studies in which there was a direct comparison of SPECT and stress echography (effort, dobutamine, adenosine, or dipyridamole),\textsuperscript{111} SPECT was found to be more sensitive but less specific than echography, particularly in the identification and localization of nonsevere coronary artery disease and if vasodilators were used as the provocation maneuver. The greater tradition of radionuclide scans has probably contributed to its selection as the reference method for invasive functional studies,\textsuperscript{42-45,47-49,202} but in practice the indication for each examination depends mainly on the availability and experience with each technique in individual hospitals. The most desirable aim is that each center control its own results insofar as the diagnostic and prognostic effectiveness of the method that it uses. In this sense, different studies have shown that complications in patients with ischemic heart disease correlate more with the number of angiographically stenotic arteries.\textsuperscript{203-208} Therefore, in the future decisions about coronary revascularization must also be based on evidence that a certain coronary stenosis also has objective functional significance.

REFERENCES

16. Ellestad MH. The time has come to reexamine the gold standard when evaluating noninvasive testing. Am J Cardiol 2001;87:100-1.


122. Little WC, Constantinescu M, Applegate RJ, Kutzer MA, Burrows MT, Kahl FR, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with...
121


