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REVIEW ARTICLE

Current Role of Myocardial Blood Flow Quantification with PET/CT in the Management of Coronary Artery Disease

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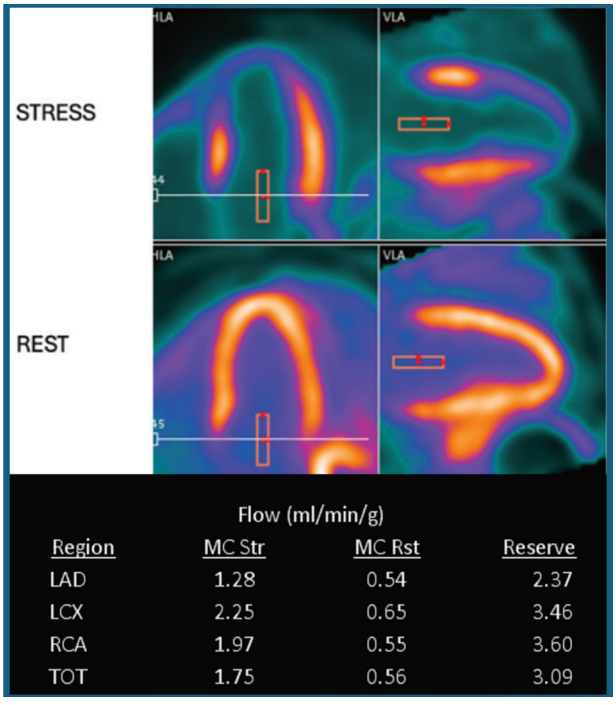
Central Illustration: Current Role of Myocardial Blood Flow Quantification with PET/CT in the Management of Coronary Artery Disease



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Abstract

The ability to measure myocardial blood flow (MBF) offers significant advantages in interpreting the phenomena underlying myocardial ischemia. Nuclear cardiology using hybrid positron emission tomography/computed tomography (PET/CT) systems allows accurate measurement of MBF using noninvasive techniques. Short- or very short-lived radiopharmaceuticals are now available, as well as standardized analytical models and software for clinical use. The incremental value of quantitative measurement of MBF in the pathophysiologic assessment of ischemic heart disease compared with anatomic variables or qualitative or semi-quantitative assessment by single-photon emission computed tomography (SPECT) with gamma-emitting

Keywords

Myocardium; Blood Circulation; Positron Emission Tomography Computed Tomography.

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tracers will be analyzed. The clinical role of MBF, myocardial flow reserve (MFR), and coronary flow capacity (CFC) will be clarified. However, the widespread availability of this technology is limited by the need for on-site cyclotron tracer production or the purchase of expensive radionuclide generators. The ability to obtain quantitative measurements using newer SPECT with cadmium-zinc-telluride technology and technetium-labeled tracers may offer the possibility of extending MBF measurement to most nuclear cardiology units in the near future.

Introduction

The purpose of this short manuscript is to provide clinical cardiologists with some simple considerations to promote the knowledge of a diagnostic tool, namely, quantitative measurement of coronary blood flow, or rather, myocardial blood flow (MBF), which is not widely known and practiced, even in the cardiology departments of reputable and experienced hospital institutions. This is due to lack of availability of adequate facilities on account of its usability, high costs, and complicated execution that requires biochemical, mathematical, and physical knowledge.

Mechanisms of myocardial ischemia

Myocardial ischemia is caused by a complex set of factors that can have a cascading progression with the aim of limiting the consequences of the discrepancy between the metabolic demands related to cardiac work and the supply of oxygen and metabolic substrates.

Cardiac function is maintained by considerable energy expenditure, considering that myocardial mass, which represents 0.5% of total body mass, requires 12% of total body energy. Cardiac metabolism is predominantly aerobic and relies mainly on the oxidation of free fatty acids by the Krebs cycle and glucose by glycolysis. Oxygen consumption is related to cardiac work, which in turn depends on myocardial mass and left ventricular shape and size, preload, afterload, heart rate, and inotropic status. The discrepancy between metabolic demand and oxygen supply results in the ischemic phenomenon with impairment of the tricarboxylic acid cycle, consequent reduced production of ATP, accumulation of hypoxanthine and lactic acid resulting in metabolic acidosis, reduced production of nitric oxide (a potent vasodilator at the prearteriolar vascular structure), and increased production of endothelin, which determines vasoconstriction of epicardial arteries, further impairing MBF.

MBF

Oxygen delivery to the myocardium is dependent on coronary blood flow, which increases 2-fold or more during exercise (up to 4- to-10-fold in trained athletes). It should be noted that nearly complete oxygen extraction is observed under basal conditions; therefore, increased flow is the only useful mechanism for increasing oxygen delivery.

Blood is supplied to the myocardium by the coronary arteries, which run along the epicardial surface without significant resistance to flow; however, they can constrict or dilate under the influence of nervous and humoral (endothelin) stimuli. Branches from the epicardial vessels penetrate the myocardium to the subendocardial layers. Significant pressure drop occurs in these branches. Maximum resistance to coronary flow occurs in vessels with diameters between 300 μm (prearterioles) and 100 μm (arterioles).

The number of arterioles and capillaries per unit of myocardial mass is extremely high, with frequent branches and anastomoses (which promote the reduction of red blood cell flow velocity, increasing O_2 exchange at reduced distance from cells). Most capillaries are not used at rest, but they form a reserve when arteriolar vasodilation requires an increase in coronary flow.

Coronary flow occurs almost exclusively in diastole, because the vessels are almost completely occluded by ventricular contraction during systole.

Myocardial flow control occurs at the level of resistance vessels located at the prearteriolar and arteriolar levels. The most widely accepted hypotheses[1-4] about myocardial flow control would involve two sites, the first located at the prearteriolar level and responsible for myogenic and neurogenic reactivity. Nitric oxide-mediated vasodilation probably occurs at this level. At the arteriolar level, vasodilation is probably induced by the oxygen-sensitive release of endogenous adenosine by cardiomyocytes. Since flow is determined by the pressure/resistance ratio, it is evident that the reduction in resistance resulting from arteriolar vasodilation can only partially compensate for a drop in perfusion pressure related to epicardial coronary artery stenosis or atherosclerosis at the level of the prearterioles.

The ischemic phenomenon in the clinical scenario

As mentioned above, ischemia is a metabolic phenomenon that cannot be quantified by flow dynamics alone. In daily clinical practice, we do not

have a direct tool to verify and measure myocardial ischemia, since the only scientifically uncontroversial tool would be the measurement of lactic acid concentration at the level of the coronary sinus, which is obviously not available for diagnostic work-up. A coronary lesion assessed by computed tomography (CT) angiography or invasive coronary angiography, which may result in a flow deficit detected by myocardial stress/resting single-photon emission computed tomography (SPECT), does not necessarily cause ischemia at a given workload, if oxygen delivery remains sufficient to balance metabolic demands. Conversely, microvascular disease can produce ischemia even in the absence of coronary lesions of the epicardial arteries and without perfusion defects on SPECT, if the flow reduction is balanced in the three coronary districts. The results of the EVINCI study appear paradigmatic in this direction.[5] In the detection of significant coronary artery disease by noninvasive anatomical and functional imaging, the best diagnostic accuracy results are achieved by CT angiography, with sensitivity 91% and specificity 91% (a result that is not surprising in relation to the fact that both techniques measure the same anatomical data), followed by positron emission tomography (PET) and SPECT with perfusion tracers, with sensitivity of 76% and 68%, specificity 89% and 71%, respectively. Stress echocardiography has a high specificity of 93%, but a sensitivity of only 39%; from a pathophysiological point of view, this result is very interesting, because alterations in ventricular mechanics during stress echocardiography require the presence of metabolic acidosis determined by a tissue increase in lactic acid concentration, thus real ischemia, whereas coronary lesions can generate non-ischemic flow alterations not detected by stress echocardiography in most patients. A message of equivalent pathophysiologic significance can be hypothesized by analyzing the results of major clinical trials[6] comparing the efficacy of optimized medical therapy versus mechanical revascularization. Both strategies are essentially equivalent from a prognostic point of view, but with completely different mechanisms. Percutaneous coronary intervention and coronary artery bypass graft directly affect normalization of coronary flow, whereas nitrates, beta blockers, calcium channel blockers, and vasodilators minimally affect coronary flow, but they prevent ischemia by limiting cardiac work through a reduction in preload by acting on venous tone and afterload through peripheral vasodilation, and they control catecholamine stimuli and inotropic function. As a summary of this introduction, we can conclude that, while it is true that we do not have a direct tool for quantifying the ischemic phenomenon, it is also true that a severe, measurable, and quantifiable reduction in maximal myocardial flow is a very useful surrogate of ischemia and a sensitive index of its severity.

Measurement of MBF by PET/CT imaging

Dynamic positron emission tomography/computed tomography (PET/CT) acquisition with a perfusion tracer remains the reference standard for quantitative measurements of MBF.

The measurement methodology requires experience both in the choice of tracers and in the execution of acquisition and processing procedures. Although they are relatively standardized, there are multiple sources of error that can invalidate results.

Choice of radiopharmaceuticals

The choice of radiopharmaceuticals depends essentially on local availability. The most commonly used PET agents for myocardial perfusion are: nitrogen-13 ammonia ($^{13}NH_3$), rubidium-82 (^{82}Rb), and oxygen-15-labeled water (^{15}O-H_2O). Fluorine-18 flurpiridaz (^{18}F-Flu) is a very promising agent that is almost ready for clinical use, but it is still in the authorization pathway by government agencies.

They differ in relation to their physical characteristics (half-life and positron range, which affects resolution) and physiologic properties, for instance, the extraction fraction (percentage of tracer extracted from the blood to the myocardium) and retention fraction of the tracer into the myocardium. Extraction fraction and retention fraction of an ideal radiopharmaceutical are 100% for both parameters, but this is not actually the case for any of the tracers, requiring appropriate settings of calculation algorithms. In particular, the extraction fraction is not linear in currently available PET tracers, leading to underestimation of MBF at high flows.[7] Table 1 summarizes the basic properties and physical characteristics of the most widely used myocardial perfusion PET agents. However, it should be kept in mind that the factor of non-linear extraction of flow tracers with underestimation of high flows does not have a great clinical impact, since the population generally evaluated is predominantly elderly or, in any case, subjects with suspected ischemic heart disease, far from a population of athletes for whom this limitation could have a real clinical significance.

$^{13}NH_3$ represents the best compromise in terms of imaging resolution and quality, half-life, ease of

Table 1 – PET tracers used for myocardial perfusion imaging

Tracer	Half-life	Production	First-pass myocardial extraction	Kinetics	Limitations
^{15}O-water	2.1 min	On-site cyclotron	100%	Diffusion	Requires cyclotron, complicated administration, sub-optimal imaging
^{13}N-ammonia	10 min	On-site cyclotron	80%	Diffusion/active transport	Requires cyclotron
^{82}Rubidium	72 s	Generator	70%	Na+/K+ cotransporter	Expensive, sub-optimal imaging
^{18}F-flurpiridaz	110 min	Centralized radiopharmacy	94%	Mitochondrial complex	Long half-time for same day procedure

administration, and availability of commercial software for processing, but it has the major limitation of requiring an on-site cyclotron for production. This limitation is overcome by the use of ^{82}Rb, produced by commercially available generators. The cost of generators is particularly high, and it can only be covered in cases of availability of fully dedicated PET/CT for nuclear cardiology; in addition, the positron emitted by ^{82}Rb has high energy with reduced resolution and imaging quality compared to $^{13}NH_3$. Finally, its extraction fraction is the lowest of the PET tracers with underestimation of high flows. ^{15}O-H_2O requires the presence of a cyclotron at a very short distance from the site of administration, with suboptimal imaging, but it offers the advantage of a 100% myocardial extraction factor, making it a useful tool for pathophysiological assessments. Fluorine-18 flurpiridaz, when commercialized, will represent an available solution for most PET/CT centers, with high-quality imaging, possibility of being used with physical as well as pharmacological stress, and, finally, a myocardial extraction factor only slightly lower than that of ^{15}O-H_2O.

Methodology

Patient preparation requires fasting for at least 4 to 6 hours, avoidance of xanthines (caffeine, theophylline, theobromine, i.e. coffee, tea, chocolate, cola) for at least 12 hours, ideally 24 hours, prior to the examination. Perfusion PET is usually performed in the same rest-stress sequence, with the advantage that the time interval between the two scans can be extremely short due to the short half-life of the tracers, without the need to subtract residual activity after the first scan. After positioning the patient on the PET/CT scanner, vasodilator pharmacologic stress (regadenoson, adenosine, dipyridamole) is performed simultaneously with dynamic image acquisition to record the entire sequence of radiopharmaceutical transit through the central circulation and to derive dynamic tracer concentrations at the left ventricular outflow tract (input function) and myocardial walls (Figure 1). A simultaneous ECG is also recorded. All data, after quality control to avoid artifacts (incorrect injection, patient motion), are processed with attenuation-corrected (by CT) reconstruction of dynamic (for flow measurements), static, and gated images. The latter two obtain images of ventricular perfusion and kinetics, like those of SPECT studies, with better resolution and counting statistics.

The advantage of PET in nuclear cardiology imaging is the ability to measure the concentration of radioactivity in the human body quantitatively and with 3D technology. The amount of tracer extracted from the myocardium after injection is quantified relative to the concentrations in the aorta measured in a region of interest located in the outflow tract of the left ventricle (input function). Flow calculation is performed using widely validated and standardized commercial software based on relatively complex algorithms, the description of which is beyond the scope of this paper. The two most used models for ^{82}Rb and $^{13}NH_3$ are the tissue compartment model and the simplified retention model. Both models have the same conceptual property of normalizing late phase myocardial activity to account for the total amount of tracer delivered by the arterial blood.[8] MBF is assessed both for the entire left ventricle and at the segmental level, using a 17-segment model, and for vascular territories, at rest and after pharmacological stress, usually with vasodilators. Figure 1 summarizes the method of selecting

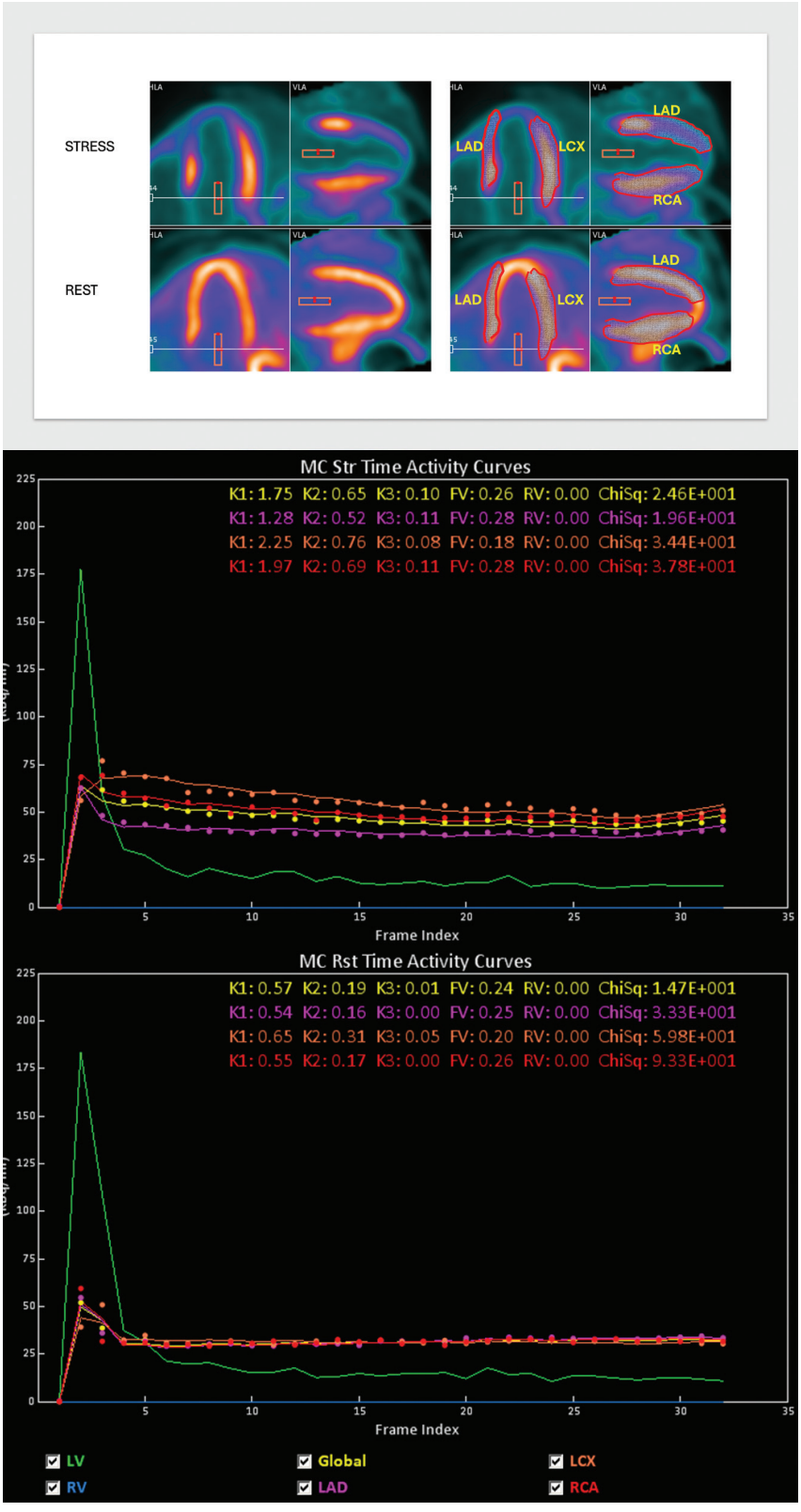

Figure 1 – Top: ROI selection of the left ventricular output track (input function) and myocardial regions according to the distribution of the coronary territories (LAD, RCA, LCX). Bottom: Time-activity curves for input function, whole left ventricle, and standard territories assigned to coronary territories: LAD, LCX, and RCA regions. See text for further information.
LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; ROI: region of interest.

the vascular region of interest (rectangle at the base of the ventricle) by which the input function is assessed. Its placement is particularly critical because flow at the aortic level is laminar, and off-center placement results in underestimation of flow. The curves represent the dynamic phase at the level of the input function (left ventricle, green), global myocardium (yellow), left anterior descending artery (LAD, purple), right coronary artery (red), left circumflex artery (orange). Based on the analysis of the curves in Figure 1, it is possible to conclude that the trend of the four myocardial curves is basically superimposable at rest, while significant differences are shown during vasodilation with relative reduction in the area of the LAD. Flow is measured in ml/min/gr of tissue. Normal values at rest are 0.7 to 0.9 ml/min/gr for $^{13}NH_3$, and slightly lower values are found for ^{82}Rb. During stress-induced hyperemia, flow increases at least twofold. The ratio of hyperemic to resting flow is defined as myocardial flow reserve (MFR), which is greater than 2 in normal subjects. Depending on the tracer, model, and commercial software, corrections are applied to compensate for the myocardial extraction factor of the tracer, which is never linear, apart from ^{15}O-H_2O, with respect to the increase in flow, especially for particularly high flows. MFR measures the ability of the myocardial vasculature to respond to increased energy demands. This index combines the effects of epicardial coronary structural lesions and microvascular dysfunction, which is characterized by impaired arteriolar vasodilatation that can lead to ischemia even in the absence of obstructive coronary artery disease: INOCA (ischemia with no obstructive coronary arteries).[9] Figure 2 shows the results of the case presented in Figure 1. The top image displays the basal and hyperemic MBF and MFR values, global and by individual coronary district. The bottom image displays, in the right column, the polar maps of perfusion at rest and after stress and the map of the reversibility of the stress perfusion defect detectable in the LAD distribution territory. The center column displays the evaluation of MBF and MFR according to a color scale, and the right column shows flow values in ml/min/gr in the 17 segments. In this case, it is interesting to note that, despite impaired hyperemic flow in the LAD territory, the MFR appears normal. This finding is determined by the fact that MFR is the result of the ratio of hyperemic MBF to basal MBF, and the normal MFR result is determined by downregulation of basal flow in this patient. The message is particularly important because MFR should never be evaluated alone, but always in combination with hyperemic MBF. We can also observe the opposite when MFR is low despite normal hyperemic flow, in cases of resting vasodilation with MBF higher than normal, as is often observed in subjects with myocardial hypertrophy.

Clinical application of PET measurements of MBF

The integration of maximal MBF and coronary flow reserve (CFR) has been evaluated by Gupta et al. in a comprehensive assessment of patients with known or suspected stable coronary artery disease.[10] As shown in Figure 3, the researchers divided the population of more than 4000 patients into 4 quadrants according to whether the values of hyperemic MBF and MFR (also defined as CFR) were concordantly normal or abnormal or discrepant, with thresholds of maximal MBF < 1.8 mL/min/gr and CFR < 2. In patients with known or suspected coronary artery disease, the association of concordant abnormal CFR and hyperemic MBF is a strong independent predictor of cardiovascular mortality (red circles). MFR is a stronger predictor than absolute maximum MBF, beyond traditional cardiovascular risk factors, including hemodynamic stress (rate-pressure product), myocardial scar/ischemia, left ventricular ejection fraction, and post-scan revascularization. Discordant abnormal MFR and normal hyperemic MBF or the opposite, normal MFR and abnormal MBF, identify patients at intermediate risk of cardiovascular death. The importance of the relationship between hyperemic MBF and MFR has been systematized by Johnson and Gould through the concept of coronary flow capacity (CFC).[11]

Using the graph in Figure 4, whose ordinate (CFR) and abscissa (stress MBF) values should be set according to the radiopharmaceutical and specific modeling, algorithm, and processing software used, it is possible to categorize the risk of ischemia. If the hyperemic MBF is normal, the risk of ischemia is low regardless of the MFR value. Substantially reduced flow, both basal and after exercise, is compatible with scar, even in the presence of residual vasodilator potential. The risk of ischemia is low, with only minimally or mildly reduced CFC, but increases with moderately reduced CFC; the risk of definite ischemia occurs when both MFR and hyperemic MBF are severely reduced. Myocardial steal is observed in the presence of low MBF and no MFR. These observations reinforce the concepts expressed in the introduction, namely, that the metabolic phenomena leading to ischemic damage occur when CFC is severely

Flow (ml/min/g)			
Region	MC Str	MC Rst	Reserve
LAD	1.28	0.54	2.37
LCX	2.25	0.65	3.46
RCA	1.97	0.55	3.60
TOT	1.75	0.56	3.09

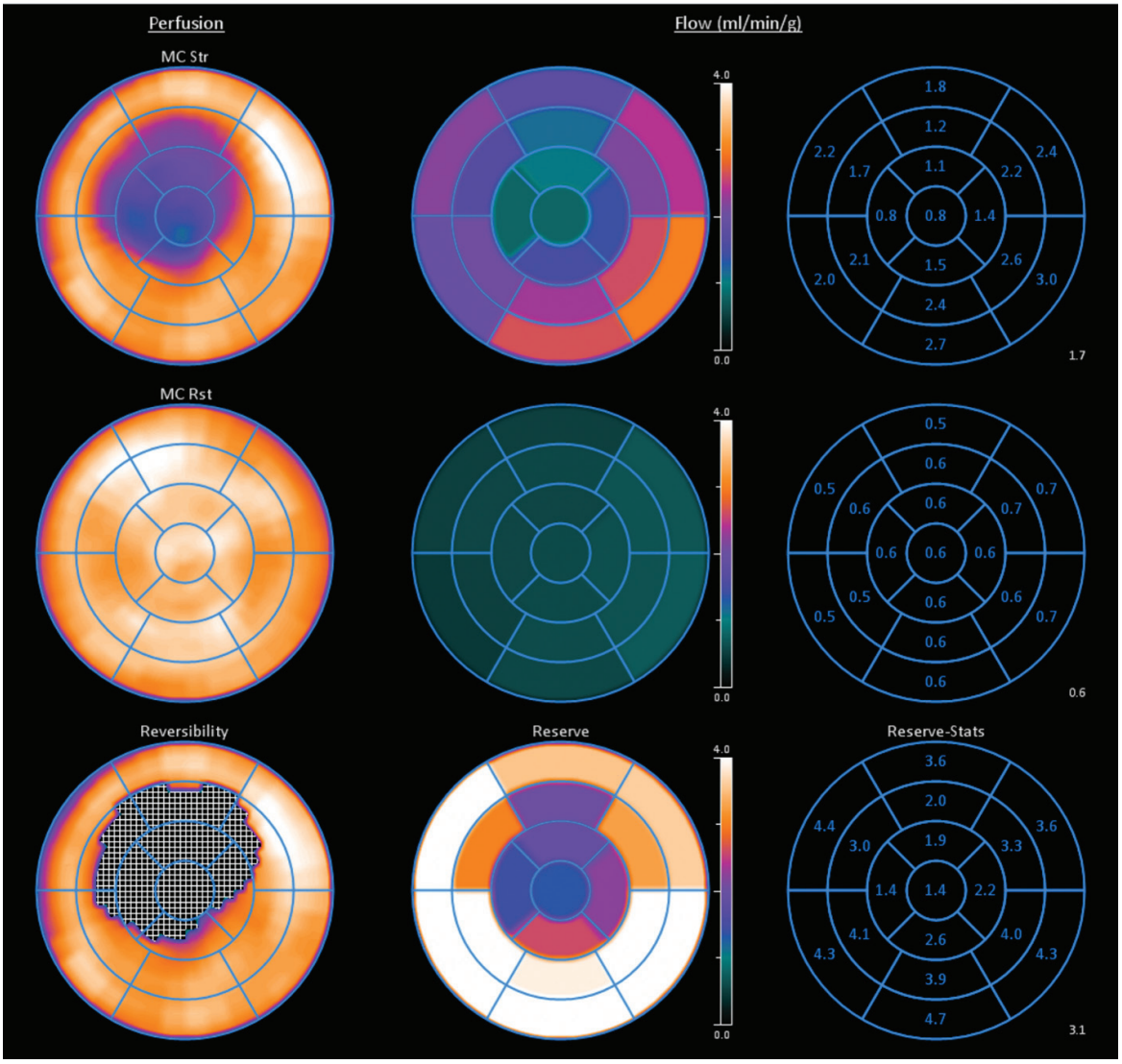

Figure 2 – Top: MBF and CFR measured at rest and after hyperemia. Bottom: Segmental assessment of perfusion at rest and after exercise and MBF and MFR values expressed as a color scale and as absolute values.
LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; TOT: total.

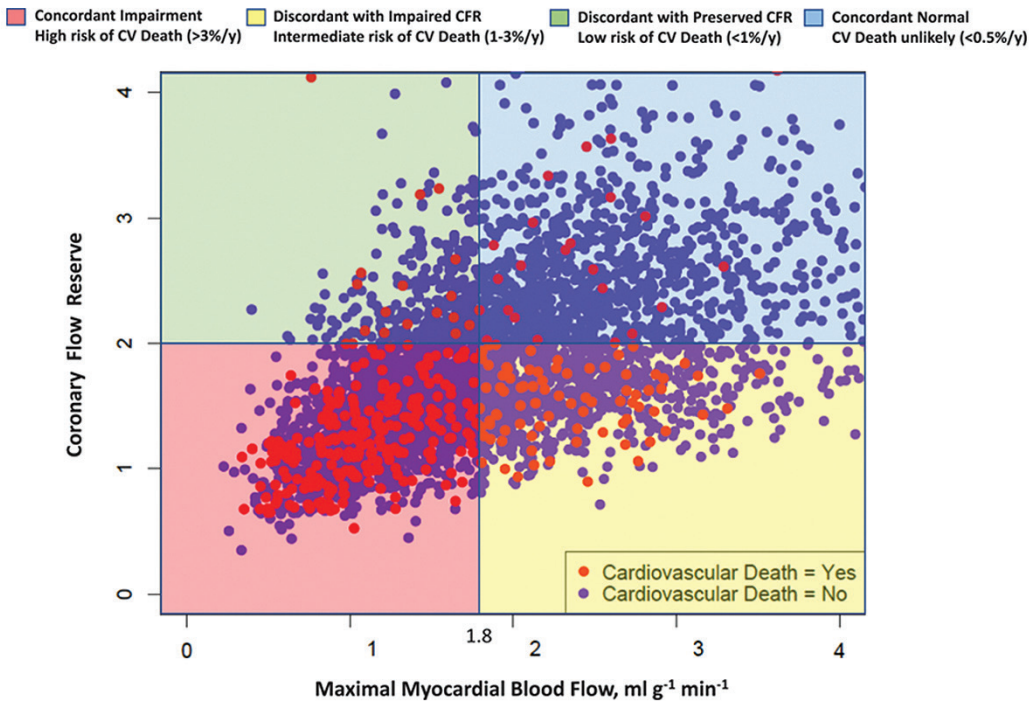

Figure 3 – Scatter plot of CFR and maximal MBF by cardiovascular death. Concordant and discordant impairment of CFR and maximal MBF identify unique prognostic phenotypes of patients. Reprinted with permission from Gupta et al.[10]
CFR: coronary flow reserve; CV: cardiovascular.

compromised. The definition of ischemia as a simple perfusion defect detectable by qualitative analysis alone (or worse, as an anatomical lesion of the coronary arteries) is not correct from a pathophysiological point of view and could be a harbinger of decision-making errors with erroneous indications for mechanical revascularization. In contrast, reduced CFC in the absence of detectable coronary artery disease in the epicardial coronaries is a fingerprint of microcirculatory pathology that merits careful clinical evaluation and appropriate medical therapy.

These concepts were confirmed by Bober et al.,[12] who showed that regions with severely reduced CFC on PET showed significant improvement in quantitative MBF after revascularization, whereas regions without reduced CFC showed no improvement in perfusion after the same procedure. In a recent retrospective prognostic evaluation, Gould et al. demonstrated, in a 10-year follow-up of a population of more than 5000 patients, that severely reduced CFC predicted higher rates of death, myocardial infarction, stroke, and revascularization procedures than PET parameters such as MFR or hyperemic MBF.[13]

New perspectives

Quantitative assessment of MBF by PET/CT remains the gold standard, but it requires the use of short-lived radiotracers that are expensive and not widely available. SPECT technology using traditional dual-head SPECT or SPECT/CT allows semi-quantitative estimation of myocardial perfusion, but does not yet allow absolute MBF measurements. Conversely, SPECT with gamma-emitting perfusion tracers is a low-cost technology and is therefore widely used.[14-22] The introduction of SPECT with CZT technology (cadmium-zinc-telluride solid-state detectors) allows dynamic SPECT acquisition after tracer infusion, providing data on input function and myocardial uptake with a methodology very similar to quantitative PET. Algorithms for the analysis of absolute MBF and MFR ratio (ratio of stress to resting MBF) are currently available from the leading cardiac CZT vendors. Several studies have recently documented the feasibility of MBF/MFR measurements using CZT technology in comparison with various reference standards, including fractional flow reserve by invasive coronary angiography[15,17,19] and PET/CT with $H_2{}^{15}O$, $^{13}NH_3$, ^{82}Rb (Figure 5).[14,16,18,20-22]

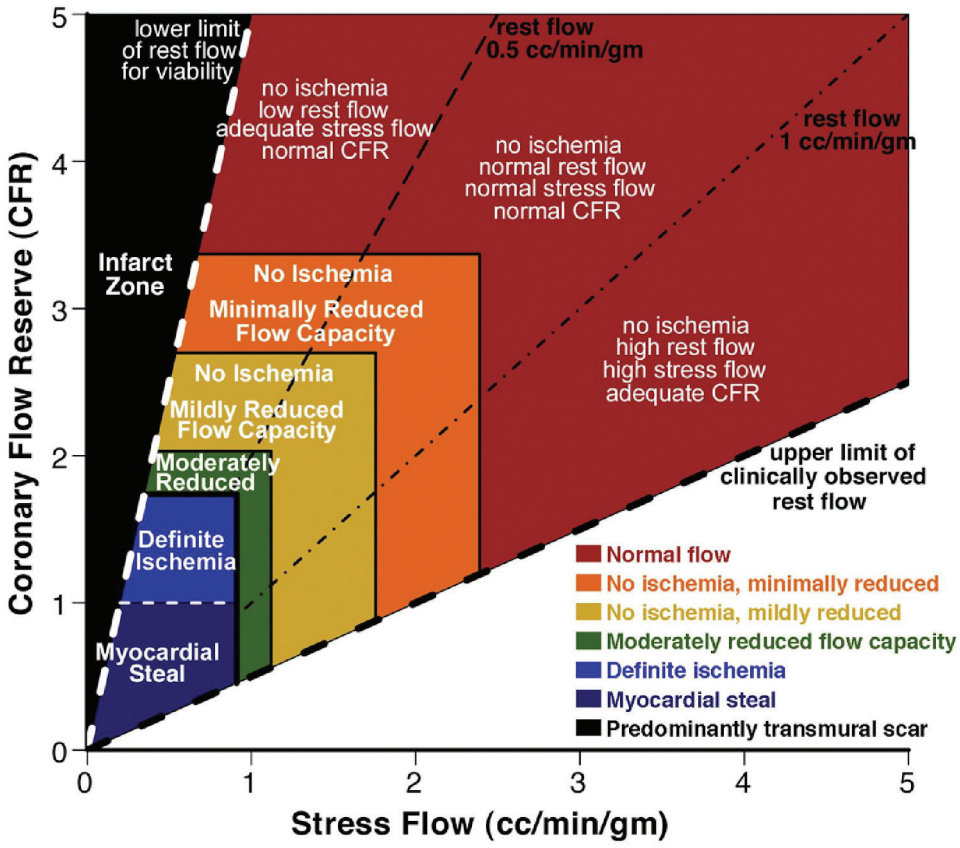

Figure 4 – Diagram of CFC; see text for description. Reprinted with permission from Johnson and Gould.[11]
CFR: coronary flow reserve.

Preliminary results are certainly interesting and point to a possible development in this direction, once some methodological problems have been resolved, such as the need to correct for attenuation, which seems to be necessary to obtain MBF values comparable to PET/CT values.[22] In this regard, it should also be noted that there are currently no dedicated cardiac CZT machines with integrated CT; therefore, attenuation correction can only be performed with stand-alone CT scanners. There are whole-body CZTs designed for 3D imaging with integrated CT, which are certainly capable of obtaining high-quality studies, but for the time being this technology has a very limited diffusion.

Recently, Wells et al. published the first multicenter work to evaluate the reproducibility of MBF and MFR measurements at 5 centers in Canada, Germany, Italy, Japan, and Singapore, using equipment from both cardiology CZT equipment companies.[23] The overall correlation between core laboratory and local site was 0.93 (range, 0.87 to 0.97) for MBF at rest, 0.90 (range, 0.84 to 0.96) for MBF at exercise, and 0.84 (range, 0.70 to 0.92) for MFR. The average additional acquisition time varied between sites from 44 to 79 minutes, but this time could be significantly reduced by further refinement of the method.

Additional clinical cases of MBF and coronary reserve measurements are presented in detail in the International Atomic Energy Agency open access atlas.[24]

Conclusion

MBF measurements are the most accurate tool for understanding the pathophysiology of coronary circulation. The complexity and cost of the techniques used to date have limited their use. Preliminary studies with technetium-labeled radiopharmaceuticals and CZT SPECT have paved the way for clinical use. However, there is still a need for further evaluation in multicenter

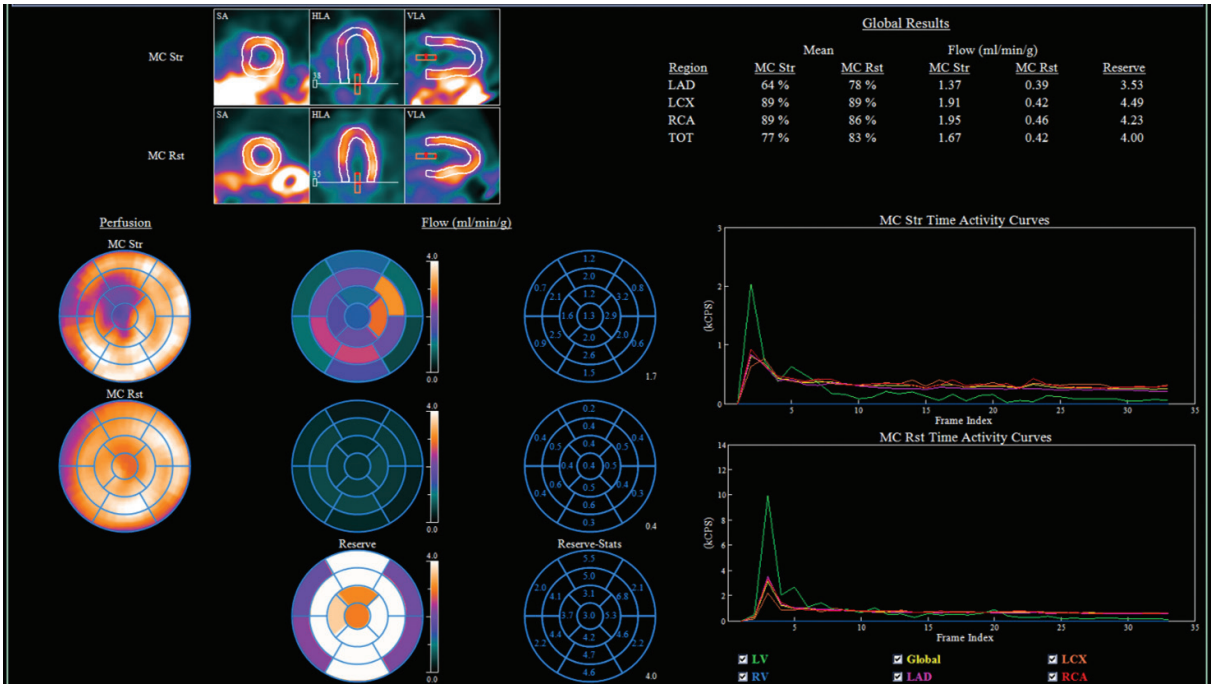

Figure 5 – Same clinical case as Figures 1 and 2, but studied with SPECT technology (cadmium-zinc-telluride SPECT) and SPECT tracer for myocardial perfusion (99mTc-tetrofosmin). The absolute values of coronary flow and reserve, but especially their clinical significance, are absolutely equivalent to those obtained with 13NH3. In particular, the low flow values obtained at rest.

studies with larger patient samples in specific clinical scenarios to validate methods that may open new, cost-effective clinical perspectives in the field of ischemic heart disease.

Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data and writing of the manuscript: Giubbini R; critical revision of the manuscript for intellectual content: Giubbini R, Milan E.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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