Estimation of coronary flow reserve: Can SPECT compete with other modalities?

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Detection of early changes of arteriosclerosis is important for the early treatment and prevention of coronary artery disease. The measurement of coronary flow reserve (CFR) is becoming recognized as an important indicator of the physiological significance of coronary stenoses and several other cardiac pathophysiological conditions, which may provide early detection of arteriosclerosis both regionally and globally. CFR is defined as the ratio of coronary flow under maximal drug-induced hyperemia to baseline flow. Gould and Lipscomb[1] originally recognized the importance of measuring CFR in clinical practice and first defined the relationship between CFR and stenosis severity. As stenosis severity increased, they observed a greater impairment of CFR without a change in resting flow. Resting flow was not reduced until the stenosis surpassed 85% diameter narrowing. The analysis of the impairment of relative or absolute CFR has allowed the detection of subcritical coronary stenoses. Therefore the measure of relative or absolute CFR has become an important physiological parameter for detection and management of ischemic heart disease. Routine clinical single photon emission computed tomography (SPECT) imaging provides a simple noninvasive method for the assessment of relative regional CFR.[2] However, true quantitation of CFR has thus far been limited to other modalities such as positron emission tomography (PET). Evidence is accumulating that high-resolution, accurate measures of CFR can be obtained and may be significantly more valuable than the relative CFR measures that can be obtained with current clinical SPECT methods. It is anticipated that modified SPECT acquisition and processing will be able to provide absolute CFR measures.

Measures of coronary reserve can be obtained with a variety of methods.[3,4] The most widely used invasive method is to attach an intravascular Doppler ultrasound transducer or pressure transducer to the end of an angioplasty guidewire system and place the system into the coronary artery of interest.[5] Average or peak velocity is measured at baseline and after administration of an intracoronary bolus of adenosine with the Doppler systems. This approach can give vessel-specific coronary flow velocity reserve (CFVR). Fractional flow reserve measurements are derived from the pressure systems, which measure the gradient of pressure across a stenosis during maximal vasodilation. Noninvasive methods include transthoracic ultrasound, magnetic resonance imaging (MRI), PET, and possibly SPECT. PET with oxygen 15 water is the noninvasive gold standard for obtaining quantitative regional blood flows; regional CFR is computed by the stress-rest ratio of flows calculated by quantitative, compartmental analysis. The measurement of CFR has also been performed by means of PET with nitrogen 13 ammonia[6,7] and with rubidium 82.[8] Transthoracic ultrasound CFVR measurements of the left anterior descending coronary artery compare well with CFR measurements obtained by PET.[9] Contrast MRI has also been shown to have potential for providing accurate estimates of regional CFR noninvasively,[10,11] possibly with a resolution high enough to distinguish subendocardial CFR from subepicardial CFR.[12] The MRI techniques have yet to be well validated. Global CFR measurements are also of value and can be obtained through methods that use injection of contrast or velocity-encoded cine MRI.[13] The velocity-encoded cine MRI method is used to measure blood flow velocities in the coronary sinus at rest and at hyperemia. Measures of coronary reserve that use transesophageal echocardiography,[14] inert gas,[15] thermodilution,[16] suction Doppler,[17,18] angiography,[19] or fast computed tomography[20] have also been reported.

Measures of coronary reserve can be quite different depending on the modality used. For example, CFVR (a velocity measurement), fractional flow reserve (a pressure measurement), and CFR (a flow measurement) all are used as indices of coronary reserve. Invasive tech-

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niques most often measure coronary reserve as the ratio of coronary flow velocity under maximal drug-induced hyperemia to baseline flow, so it is often denoted as CFVR. PET calculates CFR from estimates of flow (in milliliters per gram per minute) at rest and at stress through use of compartmental analysis of a flow tracer; it is assumed that the extraction fraction is constant over the flow range analyzed.[21] In some cases a Patlak plot (a graphical technique) is used to calculate the CFR measurements, thus avoiding computation-intensive nonlinear estimation techniques.[22] Gould and Lipscomb[1] originally distinguished stenosis flow reserve from myocardial flow reserve, the former being a regional index and the latter a global index of coronary reserve. Pijls and De Bruyne[23] proposed the concept of fractional flow reserve based on regional intracoronary pressure measurements using pressure-tipped catheters after maximal dilation of the coronary vessels. In the literature it is common to find the term CFR to be used for both coronary flow reserve and coronary flow velocity reserve.

CLINICAL SIGNIFICANCE OF MEASURING CFR

Measurements of CFR are useful in assessing the functional significance of coronary artery stenosis[24] and have been used as an endpoint of coronary intervention.[25] CFR measurement is also a more sensitive predictor of major cardiac events than coronary angiography.[26] Elevated cardiovascular risk status[27] is associated with decreases in CFR. A number of conventional coronary artery disease risk factors, such as age, hyperlipidemia, and family history, are directly related to CFR. In a study that measured CFR by O-15 water PET, it was found that CFR decreased and coronary vascular resistance increased in relation to the number of risk factors.[27] In particular, patients with hypercholesteremia and anatomically normal coronary arteries show a decreased CFR, as measured by N-13 ammonia PET.[7] The decrease seems to be related to both the plasma concentration of total cholesterol and the duration of the hypercholesterolemic state. It has been suggested that reduced CFR may be due to an abnormality in the regulation of coronary flow.[28]

CFR also decreases in patients with hypertension. Hypertrophied hearts in hypertensive subjects have a decreased CFR, elevated minimal coronary vascular resistance, and a reduction in capillary density.[29] These findings suggest that the total cross-sectional area of the vessels (the area responsible for flow resistance) does not increase in proportion to the muscle mass during hypertension-induced left ventricular hypertrophy.

CFR is also attenuated in patients with diabetes.[30] It has been demonstrated that both reduced maximal coronary vasodilatation and impairment in the regulation of coronary flow occur in response to increases in myocardial demand in patients with diabetes mellitus.[30] These microvascular abnormalities may lead to myocardial ischemia in the absence of coronary atherosclerosis. This can contribute to adverse cardiovascular events in patients with diabetes.

LIMITATIONS OF THE CFR MEASUREMENT

Global CFR is a useful indicator of cardiovascular disease, but in practice vessel-specific or region-specific CFR measurements are desired.[4] Analysis of relative perfusion may also be insufficient because more global disease processes such as hyperlipidemia, hypertension, valvular disease, and diabetes may impair CFR diffusely without regional stress-induced flow heterogeneity. Unfortunately, regional myocardial dysfunction associated with infarction or regional ischemia may also impair CFR in remote regions with no presence of coronary stenosis.[31,32] This impairment in CFR in territories remote from regional dysfunction may be due to alterations in remote regional metabolism, or in the mechanics associated with regional ischemic dysfunction, or possibly a coexisting diffuse microvascular disease.

A number of disease processes may impair vascular reserve in small, isolated nontransmural regions of the myocardium. Current approaches for assessment of CFR are unable to distinguish the differences between subendocardial and epicardial CFR. Numerous investigators have demonstrated important transmural gradients in vascular reserve, which may be explained in part by regional differences in the microcirculation or mechanical forces that occur during cardiac contraction. An increase in contractility increases intramyocardial tissue pressures, especially in the subendocardium. This increase compresses the subendocardial vessels more forcefully and compromises subendocardial perfusion. Concurrent effects in the epicardium may be quite different. Current approaches to assessment of CFR cannot effectively identify CFR changes in the endocardium and epicardium, although the ability to measure CFR selectively in the subendocardium may be possible with recent advancements in MRI.[12]

Another important issue that arises when applying vasodilators is determining whether maximum vasodilatation has been achieved.[4] Usually a single average dose of an agonist is administered based on previous experience, but this may be unreliable because some patients need more than the average dose for maximum vasodilatation to occur. If regional measurements of CFR are desired, it may be possible to deploy a vasoactive agonist that acts on only part of the circulation. Agents such as nitroglycerin tend to dilate larger or intermediate-sized vessels, whereas adenosine tends to dilate smaller vessels (<50 μm). Differential

effects of vasoactive agents on the arterial or venous components may also be important and could affect kinetics of tracers used to estimate changes in vascular reserve. These potential confounding effects remain undefined.

Finally, it can be difficult to interpret a decrease in CFR because it could be due to a host of regional and global pathophysiological processes, such as coronary steal,[33] and may not simply reflect regional coronary stenosis as originally defined.

CURRENT STATE OF THE ART AND FUTURE POTENTIAL OF STATIC AND DYNAMIC SPECT METHODS

In this issue of the Journal, Sugihara et al present a noninvasive method of obtaining CFR using planar and SPECT imaging with technetium 99m tetrofosmin. The approach is a "microsphere" method; it is assumed that the tracer sticks in the myocardial tissue so that myocardial flow can be calculated (in milliliters per minute per gram) as the ratio of the counts in the tissue over the integral of the arterial concentration of the tracer up to the time of the SPECT measurement. Serial planar imaging is performed to obtain images of the first transit through the pulmonary artery, which is used to give a measure of the arterial concentration. SPECT is performed to provide counts in the region of interest. The method is performed both at rest and under induced stress. For the stress study, Tc-99m tetrofosmin is injected after infusion of dipyridamole. The increased ratio of the myocardial blood flow (MBF_{IR}) is calculated from the rest and stress studies as follows: $MBF_{IR} = [(RMCs \times PACr)/(RMCr \times PACs) - 1] \times 100$, where RMCr and RMCs are counts (as measured by SPECT) in a myocardial region at rest and stress, respectively, and PACr and PACs are the area under the time-activity curve of the measured first transit counts (as measured by dynamic planar imaging) in the pulmonary artery at rest and stress, respectively.

This is an interesting and simple way to calculate CFR and to include the changes of arterial input function and myocardial uptake during stress. With this method the CFR is calculated noninvasively and the values are given in percentages. Sugihara et al report a mean MBF_{IR} of 46.9% ± 22.8% in healthy subjects. This corresponds to a CFR measurement of 1.47. Their results showed that the mean MBF_{IR} of infarcted regions and that of ischemic regions were both significantly decreased: 8.3% ± 12.2% and 11.2% ± 11.9%, respectively, which correspond to CFRs of 1.08 and 1.11, respectively. They point out that the results obtained from their method are lower than those found with PET. The reasons for this could be due, in large part, to the limited extraction of Tc-99m tetrofosmin at high blood flow. Another factor is the accuracy of the input function; tetrofosmin's interaction with red blood cells and plasma proteins may create difficulty in obtaining the true input. Validation of the accuracy of the input and the CFR estimates by an established technique is needed before considering this approach for clinical use. The authors also found that the MBF_{IR} decreased according to the heart rate at rest. Others have pointed this out as a limitation to obtaining an accurate measure of CFR.[34]

Another approach to calculation of CFR is to use dynamic cardiac SPECT.[35] The methods are similar to those used in dynamic PET, which are well established, having been developed over a number of years. Wash-in and wash-out kinetic parameters are estimated for regions in the heart from a sequence of dynamic reconstructed images by quantitative compartmental analysis of Tc-99m teboroxime kinetics to measure changes in response to adenosine-induced coronary vasodilatation. We have calculated both regional and global CFR measurements in canines and in patients using the ratio of the wash-in for adenosine-induced coronary vasodilatation (stress) to the wash-in at baseline flow (rest) as the CFR measurement. Our regional measurements for 2 subjects diagnosed as normal ranged from 1.6 to 2.3, with a global measurement of 1.9. Our results show that a patient with 2-vessel disease had regional CFRs ranging between 1 and 1.2, with a global CFR of 1.09, and a patient with 3-vessel disease had regional CFRs ranging between 0.64 and 1.2, with a global CFR of 0.94 (unpublished results, 2000). These results are similar to those of Sugihara et al but are somewhat lower than those previously reported by Chiao et al.[36] They reported global CFR measurements (ratio of wash-in Tc-99m teboroxime at stress to that at rest) in healthy individuals that ranged from 1.19 to 3.87, with a mean of 3.44 ± 1.07. On the other hand, PET studies using N-13 ammonia give even greater values, as high as 4.3 ± 1.6.[37]

What Would Be the Best Tracer for CFR Measurement With SPECT?

Ideally, one would like a tracer with physiological characteristics that match the detector capabilities and one that can be tagged with the appropriate single photon radionuclide. In PET, O-15 water and N-13 ammonia are most often used for measuring CFR, but there have been some reports of the use of Rb-82.[8] O-15 water is preferred because of its high extraction and linearity of uptake with flow, even at high flows associated with pharmacologic stress. However, an additional inhalation of O-15 carbon monoxide, which tags to hemoglobin, is needed to better delineate blood pool from myocardial tissue. The turnover of O-15 water in tissue is too fast for any SPECT system to be able to resolve, and its photon

flux would saturate a SPECT system. In SPECT the results of Chiao et al[36] show that wash-in and wash-out estimates of Tc-99m teboroxime for the entire left ventricular myocardium changed significantly in response to coronary vasodilatation. Therefore quantitative compartmental analysis of Tc-99m teboroxime kinetics provides a sensitive indicator for changes in estimates of wash-in in response to adenosine-induced coronary vasodilatation. Our results corroborate these findings. In addition, we have shown that dynamic imaging of teboroxime with compartment modeling provides a better measure of flow than can be obtained from static imaging of thallium 201,[38] or for that matter, static imaging of Tc-99m teboroxime.[39] These studies show that both Tl-201 uptake and Tc-99m teboroxime wash-in parameters correlate significantly with flow, but defect contrast is better evaluated with wash-in parameters obtained from dynamic Tc-99m teboroxime data and compartmental modeling methods. Preliminary dynamic cardiac SPECT patient studies have been performed with Tl-201.[40,41] The results indicate that dynamic cardiac SPECT imaging with Tl-201 could potentially be useful for measuring CFR, but it does not have as large a range of flow values for which the extraction fraction remains linear as a function of flow. Technetium 99m–labeled bis (N-ethoxy, N-ethyl dithiocarbamato) nitrido technetium(V) (Tc-99m N-NOET) is another radiotracer with high extraction that could be used for dynamic cardiac SPECT imaging. It is a neutral compound like Tc-99m teboroxime, with slower myocardial clearance, which potentially makes this agent a better alternative for dynamic cardiac SPECT imaging than either Tl-201 or Tc-99m teboroxime.

There are several possible tracers that can be used as chemical "microspheres." The agent Tc-99m tetrofosmin was used by Sugihara et al and showed promising initial results. Tc-99m tetrofosmin has an extraction fraction lower than that of another commonly used diffusible radiotracer, Tc-99m sestamibi. It was suggested in the article by Sugihara et al that Tc-99m sestamibi is also a possible tracer for calculating CFR with use of this microsphere technique. Iodorotenone[42] is another potential agent that has an even higher extraction fraction than these commonly used compounds, and it may also be a useful tracer for calculating CFR.

What is the Best Technique and Equipment Overall for Noninvasive Evaluation of CFR?

For calculation of CFR with dynamic imaging, the camera used ideally should be a multidetector or ring system but such systems are not available for cardiac imaging. However, multi-gamma camera systems have the mechanical stability and control hardware that allow 360° acquisitions of data in 5 to 10 seconds and include transmission devices that enable accurate attenuation correction. Single-detector SPECT systems may also produce positive results when coupled with new techniques for data analysis. The standard single-gamma camera configuration for SPECT has been supplanted at many institutions by dual- or triple-detector systems, with dual-detector systems being most commonly purchased by health care providers. However, single-detector systems are still the most common in clinical inventories because of the significant number that have been acquired by institutions over the last 15 years. The microsphere method presented by Sugihara et al for calculating CFR may be the ideal method for these single-detector SPECT systems. It remains uncertain whether this approach will be comparable to dynamic SPECT approaches or dynamic PET.

What is the Best Technique for Data Analysis?

In dynamic cardiac SPECT the principle of tracer kinetics is used to extract kinetic parameters of compartment models that describe the pathways and dynamic behavior of tracers in cardiac tissue. Over the last few years, significant work has been accomplished in improving the analysis of dynamic cardiac SPECT data, which are commonly reconstructed into a dynamic series of 3-dimensional reconstructed images from which regions of interest (ROIs) are specified and time-activity curves are generated. These time-activity curves are input into a nonlinear estimation program[43] that estimates the compartment model kinetic parameters. The ROIs are usually drawn by hand, but semiautomatic programs can improve reproducibility. The possibility of performing dynamic cardiac SPECT imaging with the use of a single, slowly rotating camera is enticing because such scanners are both inexpensive and widely deployed. Unfortunately, when a slowly rotating camera is used to image a distribution of emission sources, the activities of which vary significantly during the time taken for the camera to complete a revolution, the angular projections obtained are inconsistent. Consequently, application of conventional tomographic reconstruction algorithms yields a single, inaccurate reconstructed image that is "blurred over time," which leads to biases in the estimated kinetic parameters. A better approach to analyzing dynamic cardiac SPECT data is to estimate the ROIs or kinetic parameters directly from the projection data of the sinotimogram using an accurate model of the data acquisition of the spatial and temporal distribution of the radiopharmaceutical within the SPECT field of view.[35,44,45] This reduces bias by more accurately modeling the change in the concentration of the radiopharmaceutical from sampled projection to sampled projection, thus improving the temporal resolution.

CONCLUSION

SPECT can obtain CFR measurements, both globally and regionally. Positive SPECT results, as well as positive PET results, depend upon the tracer having a constant extraction fraction over the flow range being studied. SPECT approaches will probably not be as accurate as dynamic PET for estimation of CFR because spatial and timing resolution is poorer. Also, the radiopharmaceuticals may not track flow as effectively as O-15 water. The method presented by Sugihara et al is simpler than dynamic cardiac SPECT with compartment modeling; however, the technique works only for radiopharmaceuticals that act like microspheres. It is important that the extraction remain constant over a large flow range. The microsphere method also relies on not having any wash-out from the tissue from the time of injection to the time of measurement. Dynamic cardiac SPECT works best with radiopharmaceuticals that have high extraction. These radiopharmaceuticals are not as fast as the ideal flow tracer O-15 water. However, because of the inadequate timing resolutions of commercial SPECT systems, it would be virtually impossible to image such flow tracers.

Research is still needed in the following areas. (1) Further studies should be done to determine what mechanisms govern maximal coronary vasodilation. (2) There should be a determination of how these new SPECT approaches can be evaluated and tested in human beings. It has yet to be determined whether use of the coronary flow or pressure wire would be better. Perhaps comparison to dynamic PET imaging alone would be sufficient. (3) Systematic studies should be done to define the distribution of absolute CFR in both normal and abnormal hearts and to determine how the common factors that can diminish CFR affect regional reserve, especially in small subendocardial regions. To truly define coronary vascular reserve, it is essential that subendocardial measurements of CFR be obtainable. (4) Technological advances must be made in order to improve SPECT imaging systems so that they better facilitate dynamic imaging. Current SPECT systems have been limited by low sensitivity, poor resolution, and poor temporal resolution as a result of the necessary mechanical rotation of the detector. However, recent advancements in dynamic cardiac SPECT, drawn from developments in PET, demonstrate that dynamic cardiac SPECT is useful for the extraction of physiologic values of perfusion[38] in a manner similar to that of dynamic PET. These systems allow volumetric imaging but do not require sampling at rates of less than 5 seconds because of the lack of sufficient statistical data.

The future success of SPECT imaging as a means of determining CFR will depend on these technological advances as well as the development of new radiopharmaceuticals and data analysis approaches that can easily be applied in a clinical setting. These new SPECT approaches must be competitive with other noninvasive techniques both in accuracy (in eliciting these subtle changes in CFR) and in cost.

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References

1. Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. Am J Cardiol 1974;34:48-55.
2. Heller LI, Cates C, Popma J, Deckelbaum LI, Joye JD, Dahlberg ST, et al. Intracoronary Doppler assessment of moderate coronary artery disease: Comparison with ^{201}Tl imaging and coronary angiography. FACTS Study Group. Circulation 1997;96:484-90.
3. Marcus ML, Wilson RF, White CW. Methods of measurement of myocardial blood flow in patients: a critical review. Circulation 1987;76:245-53.
4. Hoffman JI. Problems of coronary flow reserve. Ann Biomed Eng 2000;28:884-96.
5. Doucette JW, Cori PD, Payne HM, Flynn AE, Goto M, Nassi M, et al. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. Circulation 1992;85:1899-911.
6. Masuda D, Nohara R, Tamaki N, Hosokawa R, Inada H, Hirai T, et al. Evaluation of coronary blood flow reserve by ^{13}N-NH_3 positron emission computed tomography (PET) with dipyridamole in the treatment of hypertension with the ACE inhibitor (Cilazapril). Ann Nucl Med 2000;14:353-60.
7. Yokoyama I, Ohtake T, Momomura S, Nishikawa J, Sasaki Y, Omata M. Reduced coronary flow reserve in hypercholesterolemic patients without overt coronary stenosis. Circulation 1996;94:3232-8.
8. Gould KL, Goldstein RA, Mullani NA, Kirkeeide RL, Wong WH, Tewson TJ, et al. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. VIII: Clinical feasibility of positron cardiac imaging without a cyclotron using generator-produced rubidium-82. J Am Coll Cardiol 1986;7:775-89.
9. Saraste M, Koskenvuo JW, Knuuti J, Toikka J, Laine H, Niemi P, et al. Coronary flow reserve: measurement with transthoracic Doppler echocardiography is reproducible and comparable with positron emission tomography. Clin Physiol 2001;21:114-22.
10. Al-Saadi N, Nagel E, Gross M, Schnackenburg B, Paetsch I, Klein C, et al. Improvement of myocardial perfusion reserve early after coronary intervention: assessment with cardiac magnetic resonance imaging. J Am Coll Cardiol 2000;36:1557-64.
11. Germain P, Roul G, Baruthio J, Jahn C, Coulbois PM, Dumitresco B, et al. Myocardial flow reserve parametric map, assessed by first-pass MRI compartmental analysis at the chronic stage of infarction. J Magn Reson Imaging 2001;13:352-60.
12. Schwitter J, Nanz D, Kneifel S, Bertschinger K, Buchi M, Knusel PR, et al. Assessment of myocardial perfusion in coronary artery disease by magnetic resonance—a comparison with positron emission tomography and coronary angiography. Circulation 2001;103:2230-5.
13. Koskenvuo JW, Sakuma H, Niemi P, Toikka JO, Knuuti J, Laine H, et al. Global myocardial blood flow and global flow reserve measure-

ments by MRI and PET are comparable. J Magn Reson Imaging 2001;13:361-6.
14. Iliceto S, Marangelli V, Memmola C, Rizzon P. Transesophageal Doppler echocardiography evaluation of coronary blood flow velocity in baseline conditions and during dipyridamole-induced coronary vasodilation. Circulation 1991;83:61-9.
15. Strauer BE. The concept of coronary reserve. J Cardiovasc Pharmacol 1992;19:S67-80.
16. Ganz W, Tamura K, Marcus MS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow by continuous thermodilution in man. Circulation 1971;44:181-95.
17. Marcus ML, Wright CB, Doty DB, Eastham C, Laughlin D, Krumm P, et al. Measurements of coronary velocity and reactive hyperemia in the coronary circulation of humans. Circ Res 1981;49:877-88.
18. Wilson RF, Laughlin DE, Ackell PH, Chilian WM, Holiday MD, Hartley CJ, et al. Transluminal, subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man. Circulation 1985;72:82-92.
19. De Bruyne BT, Dorsaz PA, Doriot PA, Meier B, Finci L, Rutishauser W. Assessment of regional coronary flow reserve by digital angiography in patients with coronary artery disease. Int J Card Imaging 1988;3:47-55.
20. Wolfkiel CJ, Brundage BH. Measurement of myocardial blood flow by UFCT: towards clinical applicability. Int Card Imaging 1991;7:89-100.
21. Iida H, Takahashi A, Tamura Y, Ono Y, Lammertsma AA. Myocardial blood flow: comparison of oxygen-15-water bolus injection, slow infusion and oxygen-15-carbon dioxide slow inhalation. J Nucl Med 1995;36:78-85.
22. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab 1983;3:1-7.
23. Pijls NHJ, De Bruyne BT. Coronary pressure. Dordrecht: Kluwer Academic; 1997.
24. Sakuma H, Kawada N, Takeda K, Higgins CB. MR measurement of coronary blood flow. J Magn Reson Imaging 1999;10:728-33.
25. Serruys PW, di Mario C, Piek J, Schroeder E, Vrints C, Probst P, et al. Prognostic value of intracoronary flow velocity and diameter stenosis in assessing the short- and long-term outcomes of balloon angioplasty. Circulation 1997;96:3369-77.
26. Ferrari M, Schnell B, Werner GS, Figulla HR. Safety of deferring angioplasty in patients with normal coronary flow velocity reserve. J Am Coll Cardiol 1999;33:82-7.
27. Pitkanen OP, Raitakari OT, Ronnemaa T, Niinikoski H, Nuutila P, Iida H, et al. Influence of cardiovascular risk status on coronary flow reserve in healthy young men. Am J Cardiol 1997;79:1690-2.
28. Seiler C, Hess OM, Buechi H, Suten TM, Krayenbuehl HP. Influence of serum cholesterol and other coronary risk factors in vasomotion of angiographically normal coronary arteries. Circulation 1993;88:2139-48.
29. Marcus ML, Koyanagi S, Harrison DG, Doty DB, Hiratzka LF, Eastham CL. Abnormalities in the coronary circulation that occur as a consequence of cardiac hypertrophy. Am J Med 1983 Sep 26; 75(no. 3A):62-6.
30. Nahser PJ, Brown RE, Oskarsson H, Winniford MD, Rossen JD. Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. Circulation 1995;91:635-40.
31. Wu JC, Yun JJ, Dione DP, Heller EN, Deckelbaum LI, Sinusas AJ. Severe regional ischemia alters coronary flow reserve in the remote perfusion area. J Nucl Cardiol 2000;7:43-52.
32. Daher E, Dione DP, Heller EN, Holahan J, DeMan P, Shen M, et al. Acute ischemic dysfunction alters coronary flow reserve in remote nonischemic regions: potential mechanical etiology identified in an acute canine model. J Nucl Cardiol 2000;7:112-22.
33. Billinger M, Fleisch M, Ebedi FR, Meier B, Seiler C. Collateral and collateral-adjacent hyperemic vascular resistance changes and ipsilateral coronary flow reserve: documentation of a mechanism causing coronary steal in patients with coronary artery disease. Cardiovasc Res 2001;49:600-8.
34. Rossen JD, Winniford MD. Effect of increases in heart rate and arterial pressure on coronary flow reserve in humans. J Am Coll Cardiol 1993;21:343-8.
35. Gullberg GT, Huesman RH, Ross SG, Di Bella EVR, Zeng GL, Reutter BW, et al. Dynamic cardiac single-photon emission computed tomography. In: Zaret BL, Beller GA, editors. Nuclear cardiology: state of the art and future directions. St. Louis: Mosby; 1999. p. 137-87.
36. Chiao P-C, Ficaro EP, Dayanikli F, Rogers WL, Schwaiger M. Compartmental analysis of technetium-99m-teboroxime kinetics employing fast dynamic SPECT at rest and stress. J Nucl Med 1994;35:1265-73.
37. Hutchins GD, Schwaiger M, Rosenspire KC, Krivokapich J, Schelbert H, Kuhl DE. Noninvasive quantification of regional blood flow in the human heart using N-13 ammonia and dynamic positron emission tomographic imaging. J Am Coll Cardiol 1990;15:1032-42.
38. Di Bella EVR, Ross SG, Kadrmas DJ, Khare HS, Christian PE, McJames S, et al. Compartmental modeling of technetium-99m–labeled teboroxime with dynamic single-photon emission computed tomography: comparison to static thallium-201 in a canine model. Inv Radiol 2001;36:178-85.
39. Kadrmas DJ, Di Bella EVR, Khare HS, Christian PE, Gullberg GT. Static versus dynamic teboroxime myocardial perfusion SPECT in canines. IEEE Trans Nucl Sci 2000;47:1112-7.
40. Iida H, Eberl S. Quantitative assessment of regional myocardial blood flow with thallium-201 and SPECT. J Nucl Cardiol 1998;5:313-31.
41. Khare HS, Di Bella EVR, Kadrmas DJ, Christian PE, Gullberg GT. Comparison of static and dynamic cardiac perfusion thallium-201 SPECT. IEEE Trans Nucl Sci. In press.
42. Marshall RC, Powers-Risius P, Reutter BW, Taylor SE, VanBrocklin HF, Huesman RH, et al. Kinetic analysis of ^{125}I-iodorotenone as a deposited myocardial flow tracer: comparison with ^{99m}Tc-sestamibi. J Nucl Med 2001;42:272-81.
43. Huesman RH, Knittel BL, Mazoyer BM, Coxson PG, Salmeron EM, Klein GJ, et al. Notes on RFIT: a program for fitting compartment models to region-of-interest dynamic emission tomography data. Report LBL-37621. Berkeley (CA): Lawrence Berkeley National Laboratory; 1995.
44. Reutter BW, Gullberg GT, Huesman RH. Kinetic parameter estimation from attenuated SPECT projection measurements. IEEE Trans Nucl Sci 1998;45:3007-13.
45. Bauschke HH, Noll D, Celler A, Borwein JM. An EM algorithm for dynamic SPECT. IEEE Trans Med Imaging 1999;18:252-61.