

Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal



Journal of Clinical and Basic Cardiology 2001; 4 (Issue 2), 135-138

Assessment of Vascular Reactivity with Positron Emission Tomography

Pirich Ch

Homepage:

www.kup.at/jcbc

**Online Data Base Search
for Authors and Keywords**

Assessment of Vascular Reactivity with Positron Emission Tomography

Ch. Pirich

Positron Emission Tomography (PET) is the most advanced scintigraphic imaging technique developed for *in-vivo* assessment of cardiac (patho)physiology and biochemistry. The currently available PET technology allows the measurement of regional tracer activity with high spatial and temporal resolution. During recent years several radiopharmaceuticals have been developed to study myocardial perfusion enabling accurate diagnosis and risk stratification of coronary artery disease (CAD). The quantitative assessment of myocardial blood flow at rest and under stress conditions and the calculation of (regional) coronary flow reserve by N-13 ammonia, Rb-82 or O-15 water PET is the most sensitive means to detect any abnormal vasoreactivity which has already been found at very early stages of the atherosclerotic process before any angiographic or clinical evidence of CAD. Importantly, available flow tracers provide also quantitative information on the haemodynamic effects of any local, invasive (angioplasty) or systemic (risk factor modification) intervention supporting the use of PET methodology for drug research and evaluation in clinical cardiology. *J Clin Basic Cardiol 2001; 4: 135–138.*

Key words: PET, flow, coronary artery disease

For more than 10 years, positron emission tomography (PET) has been the most sophisticated scintigraphic imaging technique targeting on *in-vivo* quantification of cardiac (patho)physiology and biochemistry. Since its introduction into clinical medicine the use of PET has been rather restricted due to its limited availability and high costs. The role of clinical PET is being redefined due to (1) the increasing amount of data from clinical trials on its relevance for patient management and (2) better availability of this technique. This overview will focus on the current role of clinical applications of PET imaging in coronary artery disease (CAD) with a perspective on future developments.

Measurements of Myocardial Blood Flow

a) Blood flow tracers

Blood flow tracers (Table 1) can be classified based on their physiologic behavior. Oxygen-15 water for example represents a freely diffusible tracer, which washes in and out of myocardial tissue as a function of blood flow. The first pass extraction of O-15 water in the heart is neither diffusion limited nor is O-15 water tissue extraction affected by any metabolic pathways. Oxygen-15 water represents an almost ideal tracer for the assessment of myocardial blood flow over a wide flow range [1–3]. The time course of tissue O-15 activity can be modeled by a single tissue compartment using the blood pool activity as the input function. The second group of flow markers are tracers, which are retained in myocardial tissue proportional to myocardial blood flow. For these

radiopharmaceuticals the initial tracer extraction (first pass extraction) and their tissue retention are important factors defining their suitability as blood flow tracers. N-13 ammonia is highly extracted by myocardial tissue in the form of N-13 ammonia [4]. Within the tissue the tracer can either back-diffuse into the vascular space or be trapped in the form of N-13 glutamine whereby the relative activity retained in myocardial tissue following extraction varies from 60 % to 80 % [4, 5]. The rate limiting step for the tissue retention of N-13 ammonia is the glutamine synthetase reaction. This metabolic pathway is energy dependent and can be altered by extreme pathophysiological conditions (pH, ischaemia) as well as pharmacological interventions inhibiting transaminations. Ionic tracers among which rubidium-82 is most common, display similar tracer kinetics to thallium-201 [6]. Initial extraction of these compounds ranges between 50 to 70 %. For both N-13 ammonia retention and ionic tracer extraction, a nonlinear relationship exists between blood flow and tissue tracer extraction. With increasing flow rates the transport of radiopharmaceuticals into the cell or their metabolic trapping (N-13 ammonia) becomes rate limiting, resulting in reduced net tissue retention fraction. Such a nonlinear relationship between tracer tissue uptake and blood flow restricts the ability to quantitate myocardial perfusion based on tissue tracer concentration, alone, which is why correction factors or mathematical models were introduced to compensate for the known decrease of tracer extraction fraction at higher flow states [7, 8].

Rb-82 and N-13 ammonia are the tracers most commonly used. At the beginning most of the studies employed visual data analysis, as it has been clinical routine for Tl-201 and Tc-99m-SPECT imaging [4, 9]. The next step was the introduction of semiquantitative analysis [10–13]. Quantification of myocardial blood flow of attenuation corrected PET images by the use of volumetric approaches has opened up the spectrum for the clinical use of myocardial perfusion imaging [14].

b) Clinical applications of blood flow measurements in coronary artery disease

Measurements of myocardial blood flow at rest and under stress conditions allow the non-invasive determination of

Table 1. Tracers for routine cardiac PET studies

Radionuclide	Half-life	Radiopharmaceutical	Application
Rb-82	76 sec	Rubidium	Blood flow
O-15	2 min	Water	Blood flow
N-13	10 min	Ammonia	Blood flow
C-11	20 min	Acetate	Blood flow
F-18	110 min	Deoxyglucose	Oxygen consumption Glucose metabolism

From the Department of Nuclear Medicine, University Hospital of Vienna, Austria

Correspondence to: Christian Pirich, MD, Professor, Department of Nuclear Medicine, University Hospital Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria; E-mail: christian.pirich@akh-wien.ac.at

coronary flow reserve (CFR) [15]. CFR has been measured accurately, reproducibly, and non-invasively by N-13 ammonia, Rb-82 and O-15 water PET. Stress can be evoked by exercise, physically (cold pressure test) or pharmacologically. Most studies employed pharmacological stress using dipyridamole or adenosine. Resting myocardial blood flow reaches about 60–100 ml/100g/min in healthy subjects and is unchanged only in patients with mild to moderate coronary stenosis, while calculating CFR from rest and stress studies is a very sensitive means to detect vascular abnormalities [8, 16–21]. In fact, stenosis severity has been linked to the restriction in myocardial blood flow under stress and correlated with the decrease in CFR [19–21]. Even a 30 % to 40 % diameter stenosis has been associated with a reduction in CFR [19]. It is notable, that the extent of the reduction in CFR may be rather variable due to local vascular factors such as lesion geometry and concomitant changes in microvasculature and flow-dependent endothelium-mediated epicardial vasodilation [19, 22]. However, Demer et al. have demonstrated a close agreement between the severity of perfusion defects in PET and angiography [23]. These data underline that myocardial perfusion imaging with PET is more sensitive than SPECT leading to a 10 % gain in diagnostic accuracy. No differences in sensitivity could be found between the different tracers used. Thus, N-13 ammonia and Rb-82 PET have been shown to detect CAD with comparable sensitivity [23]. An improved sensitivity as compared to SPECT and the high accuracy has led to the assumption that rest-stress PET perfusion imaging might be more cost-effective in diagnosing patients with a low or intermediate likelihood of CAD as compared to conventional rest-stress myocardial perfusion scintigraphy.

Flow measurements with PET allow not only the documentation of a restricted CFR in patients with cardiovascular risk factors [17, 18, 24] and a familial history of CAD [16] but also the monitoring of therapeutic interventions (Table 2). Primary and secondary prevention studies have impressingly demonstrated an improvement in coronary events after intense risk factor modification [25–27]. The reduction in “hard” end points has been attributed to the stabilization of lipid-rich plaques, prevention of their formation, improvements on the microvasculature and flow-mediated vasodilation (endothelial function) rather than on stenosis regression [28, 29]. From several observations it seems rather plausible that both changes in microvasculature and flow-mediated vasodilation, an endothelium-dependent function, could be assessed by PET perfusion imaging. An improvement in CFR could be documented by PET imaging in patients with manifested CAD after a 4-week therapy with simvastatin, a mem-

ber of the HMG-CoA reductase inhibitor family [22]. The fact that improvements had been only seen in the stenosed vessel area led to the conclusion that mainly changes in flow-mediated vasodilation but not in the microvasculature were responsible for the documented improvement in CFR. Lipid lowering with fluvastatin, another synthetic HMG-CoA reductase inhibitor induced an improvement in CFR after 6 months of lipid lowering therapy while no effects were seen after 3 months of therapy [30]. It is interesting that the improvement in CFR relates to the observed statistical clinical benefit in lipid lowering trials after about 9 months. Altogether, these findings suggest that PET perfusion imaging might serve as a surrogate marker of cardiac vascular function. However, prospective studies are needed to determine whether (quantitative) perfusion imaging with PET provides prognostic impact in patients at increased risk for CAD.

c) PET and other new imaging modalities: competitive or additive?

Cardiac PET is the gold standard for the assessment of myocardial viability and for the non-invasive quantification of myocardial blood flow even when evaluating new, advanced imaging technologies [31]. The relation between coronary calcification and vascular reactivity is another major field of interest because electron beam computed tomography (EBCT) or ultrafast CT might be promising tools for the initial evaluation of asymptomatic subjects at risk for CAD facilitating risk stratification and, in consequence, the decision making on further diagnostic (scintigraphic) tests and therapeutic interventions [32]. Both exercise treadmill testing and conventional myocardial perfusion imaging with SPECT exhibited a low incidence of abnormal stress tests, which excludes their use as primary screening tests for early detection of CAD. In consequence these tests have limited value in the diagnostic work up of asymptomatic subjects and have been not recommended [33, 34]. Preliminary results might support the use of EBCT as a primary screening tool for the identification of high-risk subjects with subclinical CAD in whom early diagnosis and aggressive treatment seem advisable and cost-effective [32]. However, incertitude persists on the value of EBCT in asymptomatic subjects [35, 36]. Current evidence suggests (1) an increased prevalence of coronary calcium in adolescents and young adults with familial hypercholesterolemia [37, 38], (2) an association between increased coronary artery calcification and the development of clinically manifested CAD [39–40] and (3) an association between the severity of coronary calcification and the frequency of exercise-induced perfusion abnormalities [41]. It is im-

Table 2. Clinical applications of myocardial blood flow studies with PET

Application		Author
<i>Diagnosis</i> (Pre)clinical stage	Conditions with impaired vascular reactivity: positive history of CAD, familial hypercholesterolaemia, diabetes, mental stress	Dayanikli [16], Demer [23], Kao [46], Pitkänen [24], Yokoyama [45]
<i>Definition of extent</i> Risk stratification	Haemodynamic relevance of lesions, area at risk	Beanlands [21], DiCarli [19], Uren [20]
<i>Therapeutic monitoring</i> (Pre)clinical stage	Effects of: • Risk factor modification: hyperlipidaemia, cardiovascular conditioning • Pharmacological therapy (ACE inhibitors, Vitamin C) • Revascularization • Transplantation • Angiogenesis therapy	Gould [48], Guethlin [30], Huggins [22], Czernin [47] Kaufmann [49], Schneider [50], Stewart [51] Wolpers [52], Zhao [53] Udelson [54]

portant to note that the incremental value of EBCT over traditional multivariate risk assessment has not yet been established [42] while this has been the case for SPECT [43]. Taken together with the large evidence from studies using PET methodology, even in asymptomatic subjects it is plausible that the measurement of vasodilator reserve represents the most reliable functional parameter of coronary health.

Perspectives

The unique functional information provided by cardiac PET is increasingly relevant for a more effective management of patients with different cardiovascular diseases. The clinical acceptance, however, will depend on availability, cost and accuracy of scintigraphic information in comparison to other existing or developing alternative imaging modalities.

References

- Haas F, Haehnel CJ, Picker W, Nekolla S, Martinoff S, Meisner H, Schwaiger M. Perioperative PET viability assessment and peri- and postoperative risk in patients with advanced ischemic heart disease. *J Am Coll Cardiol* 1997; 30: 1693-700.
- Araujo LI, Lammertsma AA, Rhodes CG, McFalls EO, Iida H, Rechavia E, Galassi A, De Silva R, Jones T, Maseri A. Noninvasive quantification of myocardial blood flow in coronary artery disease with oxygen-15-labeled carbon-dioxide: inhalation and positron emission tomography. *Circulation* 1991; 83: 875-85.
- Bergmann SR, Herrero P, Markham J, Weinheimer CI, Walsh MN. Non-invasive quantification of myocardial blood flow in human subjects with oxygen-15 labeled water and positron emission tomography. *J Am Coll Cardiol* 1989; 14: 639-52.
- Iida H, Kanno I, Takahashi A, Miura S, Murakami M, Takahashi K, Ono Y, Shishido F, Inugami A, Tomura N, et al. Measurement of absolute myocardial blood flow with H₂¹⁵O and dynamic positron emission tomography. *Circulation* 1988; 78: 104-15.
- Schelbert HR, Phelps ME, Hoffman EJ, Huang S, Selin CE. Regional myocardial perfusion assessed with N-13 ammonia and positron emission computerized axial tomography. *Am J Cardiol* 1979; 43: 209-18.
- Schelbert H, Phelps M, Huang S, MacDonald NS, Hansen H, Selin C, Kuhl DE. N-13 ammonia as an indicator of myocardial blood flow. *Circulation* 1981; 63: 1259-72.
- Goldstein R, Mullani N, Marani S, Fisher D, Gould K, O'Brien H Jr. Myocardial perfusion with rubidium-82. Effects of metabolic and pharmacologic interventions. *J Nucl Med* 1983; 24: 907-15.
- Czernin J, Muller P, Chan S, Brunken RC, Porenta G, Krivokapich J, Chen K, Chan A, Phelps ME, Schelbert HR. Influence of age and hemodynamics on myocardial blood flow and flow reserve. *Circulation* 1993; 88: 62-9.
- Krivokapich J, Huang S, Phelps M, MacDonald NS, Shine KI. Dependence of ¹³NH₃ myocardial extraction and clearance on flow and metabolism. *Am J Physiol* 1982; 242: H536-H542.
- Go TR, Marwick TH, MacIntyre WJ, Saha GB, Neumann DR, Underwood DA, Simpfordorfer CC. A prospective comparison of rubidium-82 PET and thallium-201 SPECT myocardial perfusion imaging utilizing a single dipyridamole stress in the diagnosis of coronary artery disease. *J Nucl Med* 1990; 31: 1899-905.
- Hicks K, Ganti G, Mullani N, Gould K. Automated quantitation of three-dimensional cardiac positron emission tomography for routine clinical use. *J Nucl Med* 1989; 30: 1787-97.
- Porenta G, Kuhl W, Czernin J, Ratib O, Brunken RC, Phelps ME, Schelbert HR. Semiquantitative assessment of myocardial blood flow and viability using polar map displays of cardiac PET. *J Nucl Med* 1992; 33: 1628-36.
- Laubenbacher C, Rothley J, Sitomer J, Beanlands R, Sawada S, Sutor R, Muller D, Schwaiger M. An automated analysis program for the evaluation of cardiac PET studies: initial results in the detection and localisation of coronary artery disease using nitrogen 13-ammonia. *J Nucl Med* 1993; 34: 968-78.
- Nekolla S, Schlieringer S, Stadler E, Schwaiger M. World wide web and virtual reality markup language extensions in cardiac SPECT and PET data processing. *J Nucl Med* 1996; 37: 172P.
- 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.
- Dayanikli F, Grambow D, Muzik O, Mosca L, Rubenfire M, Schwaiger M. Early detection of abnormal coronary flow reserve in asymptomatic men at high risk for coronary artery disease using positron emission tomography. *Circulation* 1994; 90: 808-17.
- Yokoyama I, Ohtake T, Momomura S, Nishikawa J, Sasaki Y, Omata M. Reduced coronary flow reserve in familial hypercholesterolemia. *J Nucl Med* 1996; 37: 1937-42.
- Yokoyama I, Murakami T, 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.
- DiCarli M, Czernin J, Hoh CK, Gerbaudo VH, Brunken RC, Huang SC, Phelps ME, Schelbert HR. Relation among stenosis severity, myocardial blood flow, and flow reserve in patients with coronary artery disease. *Circulation* 1995; 91: 1944-51.
- Uren NG, Melin JA, DeBruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary artery stenosis. *N Engl J Med* 1994; 330: 1782-8.
- Beanlands RSB, Muzik O, Melon P, Sutor R, Sawada S, Muller D, Bondie D, Hutchins GD, Schwaiger M. Noninvasive quantification of regional myocardial flow reserve in patients with coronary atherosclerosis using nitrogen-13 ammonia positron emission tomography. *J Am Coll Cardiol* 1995; 26: 1465-75.
- Huggins GS, Pasternak RC, Alpert NM, Fischmann AJ, Gewirtz H. Effects of short-term treatment of hyperlipidemia on coronary vasodilator function and myocardial perfusion in regions having substantial impairment of baseline dilator reserve. *Circulation* 1998; 98: 1291-6.
- Demer LL, Gould KL, Goldstein RA, Kirkeide RL, Mullani NA, Smalling RW, Nishikawa A, Merhige ME. Assessment of coronary artery disease severity by positron emission tomography: comparison with quantitative arteriography in 193 patients. *Circulation* 1998; 98: 825-35.
- Pitkanen OP, Raitakari OT, Ronnema T, Niinikoski H, Nuutila P, Lida H, Viikari J, Knuuti J. Influence of coronary risk status on coronary flow reserve in healthy young men. *Am J Cardiol* 1997; 79: 1690-2.
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Trial (4S). *Lancet* 1994; 344: 1383-9.
- Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; 335: 1001-9.
- Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; 333: 1301-7.
- MAAS investigators. Effect of simvastatin on coronary atheroma: The Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994; 344: 633-8.
- Brown BG, Zhao XQ, Sacco DE, Albers JJ. Lipid lowering and plaque regression: new insights into prevention of plaque disruption and clinical events in coronary disease. *Circulation* 1993; 87: 1781-91.
- Guethlin M, Kasel AM, Coppenrath K, Ziegler S, Delius W, Schwaiger M. Delayed response of myocardial flow reserve to lipid lowering therapy with fluvastatin. *Circulation* 1999; 99: 475-81.
- Schwittler J, DeMarco T, Kneifel S, von Schulthess GK, Jorg MC, Arheden H, Ruhm S, Stumpe K, Buck A, Parmley WW, Luscher TF, Higgins CB. Magnetic resonance-based assessment of global coronary flow and flow reserve and its relation to left ventricular functional parameters: a comparison with positron emission tomography. *Circulation* 2000; 101: 2696-702.
- O'Rourke RA, Brundage BH, Froelicher VF, Greenland P, Grundy SM, Hachamovitch R, Pohost GM, Shaw LJ, Weintraub WS, Winters WL Jr, Forrester JS, Douglas PS, Faxon DP, Fisher JD, Gregoratos G, Hochman JS, Hutter AM Jr, Kaul S, Wolk MJ. American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *Circulation* 2000; 102: 126-40.
- Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WFC, Froelicher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD, Winters WL Jr, Yanowitz FG. ACC/AHA guidelines for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on exercise testing). *J Am Coll Cardiol* 1997; 30: 260-315.
- Ritchie JL, Cheitlin MD, Garson A Jr, Lewis RP, O'Rourke RA, Ryan TJ, Schlant RC, Winters WL Jr. Guidelines for clinical use of cardiac radionuclide imaging: report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Radionuclide Imaging), developed in collaboration with the American Society of Nuclear Cardiology. *J Am Coll Cardiol* 1995; 25: 521-47.
- O'Malley PG, Taylor AJ, Jackson JL, Doherty TM, Detrano RC. Prognostic value of coronary electron beam computed tomography for coronary heart disease events in asymptomatic populations. *Am J Cardiol* 2000; 85: 945-8.
- Arad Y, Spadaro M, Goodman KG, Lledo-Perez A, Sherman S, Lerner G, Guerci AD. Prediction of coronary events with electron beam computed tomography: 19-month follow-up of 1173 asymptomatic subjects. *Circulation* 1996; 96: 1122-9.
- Gidding SS, Bookstein LC, Chomka EV. Usefulness of electron beam tomography in adolescents and young adults with heterozygous familial hypercholesterolemia. *Circulation* 1998; 98: 2580-3.
- Schmidt HHJ, Hill S, Makariou E, Feuerstein IM, Dugi KA, Hoeg JM. Relation of cholesterol-year score to severity of calcific atherosclerosis and tissue deposition in homozygous familial hypercholesterolemia. *Am J Cardiol* 1996; 77: 575-80.
- Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. *Am Coll Cardiol* 2000; 36: 1253-6.

40. Wong ND, Hsu JC, Detrano RC, Diamond G, Eisenberg H, Gardin JM. Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events. *Am J Cardiol* 2000; 86: 495–8.
41. He ZX, Hedrick TD, Pratt CM, Verani MS, Aquino V, Roberts R, Mahmarian JJ. Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. *Circulation* 2000; 101: 244–51.
42. Detrano R, Wong ND, Doherty T, Shavelle RM, Tang W, Ginzton LE, Budoff MJ, Narahara KA. Coronary calcium does not accurately predict near-term future coronary events in high-risk adults. *Circulation* 1999; 33: 1756–824.
43. Blumenthal RS, Becker DM, Moy TF, Coresh J, Wilder LB, Becker LC. Exercise thallium tomography predicts future clinically manifest coronary heart disease in a high-risk asymptomatic population. *Circulation* 1996; 93: 915–23.
44. Czernin J, Sun K, Brunken R, Bottcher M, Phelps M, Schelbert H. Effect of acute and long-term smoking on myocardial blood flow and flow reserve. *Circulation* 1995; 91: 2891–7.
45. Yokoyama I, Ohtake T, Momomura S, Yonekura K, Woo-Soo S, Nishikawa J, Sasaki Y, Omata M. Hyperglycemia rather than insulin resistance is related to reduced coronary flow reserve. *Diabetes* 1998; 47: 119–24.
46. Kao H, Arrighi JA, Burg M, Cohen I, Zaret BL, Soufer R. Differences in myocardial blood flow response to mental stress in normals compared with minimally-stenosed regions in patients with coronary artery disease. *J Nucl Med* 1999; 40: 86P (Abstract).
47. Czernin J, Barnard RJ, Sun KT, Krivokapich J, Nitzsche E, Dorsey D, Phelps ME, Schelbert HR. Effect of short-term cardiovascular conditioning and low-fat diet on myocardial blood flow and flow-reserve. *Circulation* 1995; 92: 197–204.
48. Gould KL, Martucci JP, Goldberg DI, Hess MJ, Edens RP, Latifi R, Dudrick SJ. Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole on patients with coronary artery disease. *Circulation* 1994; 89: 1530–8.
49. Kaufmann PA, Gneecchi-Ruscione T, di Terlizzi M, Schafers KP, Luscher TF, Camici PG. Coronary heart disease in smokers: vitamin C restores coronary microcirculatory function. *Circulation* 2000; 102: 1233–8.
50. Schneider CA, Voth E, Moka D, Baer FM, Melin J, Bol A, Wagner R, Schicha H, Erdmann E, Sechtem U. Improvement of myocardial blood flow to ischemic regions by angiotensin-converting enzyme inhibition with quinaprilat IV: a study using [¹⁵O] water dobutamine stress positron emission tomography. *J Am Coll Cardiol* 1999; 34: 1005–11.
51. Stewart RE, Miller D, Bowers TR, McCullough PA, Ponto RA, Grines CL, O'Neill WW, Juni JE, Safian RD. PET perfusion and vasodilator function after angioplasty for acute myocardial infarction. *J Nucl Med* 1997; 38: 770–7.
52. Wolpers HG, Koster C, Burchert W, van den Hoff J, Schafers HJ, Wahlers T, Meyer G. Coronary reserve after orthotopic heart transplantation: quantification with N-13 ammonia and positron emission tomography. *Z Kardiol* 1995; 84: 112–20.
53. Zhao XM, Delbeke D, Sandler MP, et al. Nitrogen 13-ammonia and PET to detect allograft coronary artery disease after heart transplantation: comparison with coronary angiography. *J Nucl Med* 1995; 36: 982–7.
54. Udelson JE, Dilsizian V, Laham RJ, Chronos N, Vansant J, Blais M, Galt JR, Pike M, Yoshizawa C, Simons M. Therapeutic angiogenesis with recombinant fibroblast growth factor-2 improves stress and rest myocardial perfusion abnormalities in patients with severe symptomatic chronic coronary artery disease. *Circulation* 2000; 102: 1605–10.