Nuclear cardiology: an overview of radioisotope techniques used in the
diagnosis of cardiovascular disorders

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Short title: Nuclear cardiology: an overview of radioisotope diagnostic techniques

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**Abstract**

Cardiovascular diseases are the most common cause of death in patients over 60 years old. Imaging methods of a pivotal role in cardiological diagnostic processes are echocardiography, magnetic resonance, multi-row-detector computed tomography, coronary angiography, and radioisotope tests. In this paper, we summarize the techniques of nuclear medicine (positron emission tomography, single-photon emission computed tomography, radionuclide ventriculography) that could be implemented in the cardiovascular diagnostic algorithms. Despite being acknowledged and positioned in a few cardiological guidelines, these imaging methods are still underestimated by practitioners. Nevertheless, noninvasive diagnostic tools are of increasing potential and should be implemented whenever possible. We discuss the usefulness of particular techniques in the management of patients with obstructive and non-obstructive coronary artery disease, including assessment of myocardial perfusion, contractility, viability, and detection of unstable atherosclerotic plaques. Radioisotope imaging can also be valuable in the diagnosis of infective endocarditis, as well as cardiac sarcoidosis and amyloidosis. Apart from presenting the theoretical principles of nuclear cardiology, this paper also provides three case reports illustrating a practical implementation of these imaging modalities.

**Keywords:** cardiac metabolism, cardiac perfusion, nuclear cardiology, positron emission tomography, single-photon emission computed tomography
Introduction

Cardiovascular diseases (CVDs) are the leading cause of death patients over 60 years old in Poland [1]. Therefore, there is an increased interest in diagnostic techniques that allow a noninvasive detection of CVDs and are helpful in the decision-making process for optimal management.

One of the most frequently noninvasive imaging methods used in cardiology is echocardiography allowing for visualization of cardiac anatomy and function, both at rest and stress. Other noninvasive methods used in cardiology imaging are multi-row detector computed tomography (MDCT) and cardiac magnetic resonance (CMR). Apart from the multidimensional visualization of the heart anatomy, MDCT is particularly useful in the calcification assessment, whereas CMR - with better spatial resolution than MDCT— in the myocardial viability [2].

In contrast to the methods listed above, that focus on cardiac anatomy, the imaging tools used in nuclear cardiology are mostly dedicated to the functional assessment based on radioisotopes uptake by the cardiac structures. This allows the evaluation of the myocardial perfusion, metabolism and viability, adrenergic innervation, radionuclide ventriculography and intracardiac leakage (both left-right and right-left). Although nuclear cardiology methods are acknowledged and recommended by experts in the European Society of Cardiology (ESC) guidelines [3,4], its clinical value seems to be still underpowered most probably by limited availability and inadequate experience of cardiologists in the real-life setting.

This article aims to summarize the acknowledged methods of nuclear cardiology as well as its novel diagnostic possibilities potentially useful in noninvasive clinical management. We also aim to present a practical aspect of nuclear medicine by describing three patients undergoing selected procedures, which were helpful in the decision-making process.
Myocardial perfusion scan

Myocardial perfusion scan (MPS) is one of the most widely used techniques in nuclear cardiology. It allows clinicians to detect coronary artery disease (CAD) and to assess the functional significance of previously diagnosed lesions in coronary vessels before the introduction of invasive management [5]. MPS can be determined using single-photon emission computed tomography (SPECT) and positron emission tomography (PET). In both cases, hybrid imaging might be performed, i.e. complementing the SPECT or PET examination with CT [6].

The most popular tracer used in MPS is methoxyisobutylisonitrile/sectamibi (MIBI) labeled with technetium 99 ($^{99m}$Tc). The $^{99m}$Tc-MIBI chelate is administered intravenously to patients undergoing SPECT imaging [6]. Intracellularly MIBI accumulates in the mitochondrial cristae; therefore, its uptake is dependent on the function of the cell organelle. MIBI is a molecule with positive electrical potential, which in combination with the negative electrical potential of the mitochondrial membrane, allows the accumulation of the radioisotope and significantly reduces the reverse diffusion (only 5% within 6 hours) [7]. However, the $^{99m}$Tc-MIBI is a non-specific radiotracer – it accumulates in muscular tissue, liver, spleen and thyroid gland, and only 1.5% of the administered $^{99m}$Tc-MIBI accumulates in the myocardium [8].

The MPS consists of two parts: rest and stress. The physical stress (treadmill or cycle ergometer) or pharmacological agent, i.e. dobutamine, adenosine, dipyridamole (adenosine disintegration inhibitor), or regadenoson (selective adenosine A2A receptor agonist) may be used during the test. Agents causing coronary dilation and passive myocardial congestion (adenosine, dipyridamole and regadenoson) are preferred over dobutamine. Regadenoson is characterized by a better safety profile, particularly in patients with bronchial asthma or chronic obstructive pulmonary disease [9]. The nuclear medicine specialist chooses the
method and order of the study stages based on the individual medical history, available data, and the results of previous examinations.

A patient should be fasting for at least 8 hours before the planned MPS test. Unless there are contraindications, medications that may affect the course of the exercise test (beta-blockers, blockers of calcium channels, and long-acting nitrates) should be discontinued 48 hours before the examination. Long-acting theophylline derivatives (an adenosine antagonist), as well as coffee and tea (as a natural source of theophylline), should be avoided.

**Evaluation of myocardial perfusion**

An intravenously injected radiotracer accumulates in the heart muscle proportionally to the blood flow (Figure S1). The H\textsubscript{2}\textsuperscript{15}O freely diffuses through the cell membrane and therefore is characterized by a linear relationship between flow and radiotracer extraction. In contrast to this, the uptake of other radioisotopes decreases with increasing flow. This phenomenon is called a "roll-off" effect and may lead to misinterpretation of the result, because small stenosis of the coronary artery may not show a significant change in radiotracer accumulation and thus may not be detected [10]. Figures 1 and 2 demonstrate the basis of an interpretation of MPS studies.

Normal radiotracer distribution in myocardium indicates a very low probability of myocardial ischemia. If there is an area of decreased radiotracer accumulation during the stress study, which entirely or partially resolves during the rest, it is a reversible perfusion defect. It indicates stress-related ischemia and is associated with hemodynamically significant stenosis of a coronary artery supplying a particular myocardial region. If there is no difference in the stress and rest studies and decreased radiotracer accumulation remains the same, it is a fixed perfusion defect. This is typically related to a previous ischemic episode and may indicate both post-infarction scars as well as hibernated myocardium. The molecular mechanism of MIBI cellular uptake is strictly related to mitochondrial function and integrity;
therefore, its distribution may be insufficient to distinguish between these two conditions.

Inflammatory diseases, including myocarditis, may also alter perfusion due to local inflammation and necrosis. The absence of MIBI uptake requires further verification with myocardial viability PET scans with glucose analog radiolabeled with fluorine 18 \((^{18}\text{F})-^{18}\text{F-fluorodeoxyglucose (^{18}\text{F-FDG)})\) [11,12]. MPS with \(^{99}\text{Tc-MIBI}\) presents approximately 87% sensitivity and 73% specificity [6].

A myocardial perfusion SPECT study performed with ECG-gating provides additional data on the left ventricle function (end-diastolic volume, end-systolic volume, ejection fraction, myocardium mass, as well as regional wall motion). Functional data delivered by gated SPECT may improve the detection of three-vessel disease or left main stem disease. If needed, the assessment of myocardial stunning may be performed, with a temporary reduction of the myocardial contractility observed only during the stress, but not at rest, stage [13,14].

Gated SPECT has also been used in the assessment of left ventricle contraction synchrony. This method enables precise myocardial activation tracing and may detect disturbances in this process associated with mechanical contraction asynchrony. Scientists postulate that mechanical asynchrony is related to left ventricle dysfunction (ejection fraction reduction) to a greater extent than perfusion defect size [10,15,16].

PET has superior image quality compared to SPECT. It is due to better radiotracer properties used in PET technique and better spatial resolution (4-7 mm for PET vs. 12-15 mm for SPECT), which allows to detect even minor perfusion defects. In addition to the better spatial resolution, PET has a superior character of temporal resolution. This feature enables a more precise evaluation of radiotracer activity in the coronary arteries and myocardium. Moreover, in PET imaging, absolute myocardial perfusion may be calculated (milliliters per gram of tissue per minute), whereas in SPECT only the relative myocardial perfusion can be
assessed. Therefore, \(^{18}\)F-FDG-PET is believed to be a more accurate diagnostic tool in assessing a myocardial perfusion [17].

**Myocardial viability assessment**

Nuclear imaging with PET and SPECT is particularly useful in cardiac muscle viability assessment. According to recent guidelines on myocardial revascularization, myocardial viability assessment is crucial in patients with chronic total occlusion of coronary arteries and severely depressed left ventricular systolic function. Preserved viability encourages coronary artery bypass grafting or percutaneous coronary intervention before cardiac transplantation or implantation of devices that mechanically assist circulation [3]. As mentioned above, the MPS performed with SPECT is unable to differentiate post-infarction scar from the hibernated myocardium. This is caused by the fact that \(^{99m}\)Tc-MIBI accumulates neither within the scar nor in the hibernated cardiomyocytes, as they both present a mitochondrial dysfunction disabling the uptake of the radiotracer. Nonetheless, as hibernated cardiomyocytes still use anaerobic metabolism and utilize glucose, they can accumulate \(^{18}\)F-FDG. Perfusion and metabolism comparison (\(^{99m}\)Tc-MIBI and \(^{18}\)F-FDG uptake) enable the identification of viable myocardium. If \(^{18}\)F-FDG uptake is observed in the areas representing weak or absent MIBI uptake, it is indicative of hibernation and the viable myocardium (perfusion-metabolism mismatch). The absence of both MIBI and \(^{18}\)F-FDG uptake confirms a scar (perfusion-metabolism match) – Figure 3, Table 1 [18-20]. Images obtained from \(^{18}\)F-FDG PET are able to determine the viability of dysfunctional myocardial regions (sensitivity 88%, specificity 73%, PPV 82%, NPV 83%) and predict recovery of global contractile function after revascularization [21].
Coronary microvascular dysfunction

Coronary microvascular disease (MVD) encompasses functional changes of coronary microvasculature disabling a proper vasodilatation and augmentation of coronary blood flow required during exercise [22]. Coronary flow reserve (CFR) measured in PET (defined as the ratio between myocardial blood flow calculated in ml/min/g at stress and at rest) quantifies a general coronary vasomotor function integrating hemodynamic effect of epicardial stenosis, diffuse atherosclerosis and MVD. Depending on the study protocol a normal values of CFR ranges between 1.4 – 2.7. PET-derived CFR measurements correlate with the biomarkers characteristic for MVD and may enhance understanding and better management of symptomatic patients. This is particularly helpful in risk stratification, since MVD is common among patients with chest tightness and a long term prognosis in MVD is similarly poor when compared to the patients with obstructive coronary disease [23-25].

Unstable atherosclerotic plaques evaluation

Unstable atherosclerotic plaque refers to a plaque that has a large necrotic lipid core, and the thickness of the connective tissue cap does not exceed 65 μm. Within the plaque, there is an intense inflammatory process dominated by macrophages and lymphocytes T. Very often also neovascularization and hemorrhages inside the plaque are observed [26]. Because of high glucose consumption of vascular macrophages, $^{18}$F-FDG PET/CT is used in imaging of inflammation process for a long time. An association between the $^{18}$F-FDG uptake, macrophage burden, and gene expression of CD68 was also confirmed in the study evaluating atherosclerotic plaques in the carotid arteries [27]. Subsequently, a study by Tarkin JM et al. proved superiority of $^{68}$Ga-DOTATATE over $^{18}$F-FDG in differentiating stable and unstable coronary plaque found in CT imaging, as higher uptake of $^{68}$Ga-DOTATATE was observed in the culprit coronary and carotid lesions. The researches confirmed in the histopathological
examinations that $^{68}\text{Ga-DOTATATE}$ was present in CD68-positive, macrophage-rich carotid plaques [28].

Studies have shown that PET/CT scan with sodium fluoride ($^{18}\text{F-NaF}$), used in musculoskeletal system diseases, may be even more beneficial in the assessment of atherosclerotic plaque biology. An increased accumulation was seen in ruptured and high-risk plaques with significantly higher sensitivity than $^{18}\text{F-FDG}$ in terms of coronary artery atherosclerosis, due to the lack of physiological uptake of $^{18}\text{F-NaF}$ by the myocardium [29,30]. In assessing unstable atherosclerotic plaque $^{68}\text{Ga-DOTATATE}$ and $^{18}\text{F-NaF}$ PET are superior to $^{18}\text{F-FDG}$ PET studies.

**Radionuclide ventriculography**

Radionuclide ventriculography is used in the left ventricle function assessment. It utilizes $^{99m}\text{Tc}$ that binds to hemoglobin, producing “radionlabelled blood pool” [31,32].

When ECG gating is used, changes in blood pool radioactivity can be tracked, both with SPECT or dynamic methods and it allows the calculation of the left ventricle volumes and ejection fraction (Figure 4). SPECT imaging also enables a regional wall motion evaluation by tracking the endocardium movement. Radionuclide ventriculography is one of the most accurate techniques to evaluate left ventricle ejection fraction. Due to anatomical conditions, right ventricle evaluation is much more complicated and is not commonly used [31].

**Adrenergic system imaging**

Use of catecholamine analog – metaiodobenzylguanidine (mIBG) labeled with Iodine 123 (m$^{123}\text{IBG}$) – enables the assessment of the function of the adrenergic heart system. The analysis is based on the assessment of presynaptic m$^{123}\text{IBG}$ uptake by the heart adrenergic system. The measurements are performed at two-time points, enabling the visualization of a
flushing effect. Obtained values provide information about the integrity of the heart adrenergic system and its activity. The test is used primarily in patients with heart failure as it may help to predict the response to the applied treatment, i.e. cardiac resynchronization therapy or ablation of atrial fibrillation [33-38].

**Infective endocarditis imaging**

In recent years, the occurrence of infective endocarditis (IE) is significantly higher. According to the ESC guidelines, the gold standard for imaging patients with IE remains echocardiography [4]. However, patients after implantation of prosthetic valves and cardiac implantable electronic devices (CIEDs) are those in whom the use of conventional imaging methods and microbiology results are inconclusive. In this setting, SPECT/CT with indium 111 (\(^{111}\)In) or \(^{99m}\)Tc labeled leukocytes is most commonly used. The implementation of SPECT/CT with \(^{99m}\)Tc labeled hexamethylpropyleneamine oxime (\(^{99m}\)Tc-HMPAO) is particularly useful in patients with a prosthetic valve. It shows an abnormal uptake of radiotracer around the prosthesis in case of endocarditis. Moreover, it is recommended as an additional diagnostic tool (2b class recommendation) in patients with CIEDs with clinical suspicion of IE, negative echocardiography, and positive results of blood cultures [39-42].

\(^{18}\)F-FDG PET/CT study has been introduced in the modified Duke’s criteria for IE diagnosis. Despite the low sensitivity obtained in native valves (< 40%), this technique has shown a significant accuracy (sensitivity 87%, specificity 92%) in prosthetic valve IE (PVE) or CIEDs. The introduction of this method to the diagnostic process enhanced the sensitivity of the modified Duke’s criteria from 52% to 91% and therefore has been incorporated in the diagnostic algorithm proposed in the 2015 ESC guidelines [4].

A spatial resolution of the PET method limits the possibility of imaging areas smaller than 5 mm. At the same time, due to the high physiological activity of \(^{18}\)F-FDG, it is
impossible to visualize septic emboli in the brain. Moreover, it is not possible to distinguish between an aseptic postoperative inflammatory process and infection in the first three months after cardiac surgery. Also $^{18}$F-FDG PET does not differentiate thrombi, soft atherosclerotic plaque, primary cardiac tumors, postoperative inflammatory infiltrates, and reaction to a foreign body [4,43,44].

One of the disadvantages of scintigraphy with labeled leukocytes compared to PET/CT is the lower spatial resolution and its limited value in non-bacterial infections (the majority of leukocytes labeled are neutrophils) [44].

**Cardiac sarcoidosis**

Cardiac sarcoidosis (CS) may be an incidental diagnosis, albeit it may lead to multiple complications, including advanced heart block, cardiomyopathy and arrhythmias. Advanced imaging modalities like CMR or PET show similar accuracy in the diagnosis of CS compared to autopsy studies. Combining $^{18}$F-FDG PET/CT study with perfusion in SPECT/CT is particularly useful, as the co-occurrence of multiple uptake areas associated with the matching perfusion abnormalities seen in SPECT/CT gives a high probability of an accurate diagnosis [45]. There have been attempts to assess the therapeutic and prognostic factors using $^{18}$F-FDG PET/CT. Among 137 studied patients, a pathologic right ventricular $^{18}$F-FDG uptake occurred more frequently in a group of patients with cardiovascular events compared to those without (46% vs. 6%). Another study suggested that high total cardiac metabolic activity (up to 900 MBq of $^{18}$F-FDG) in relationship with right ventricular uptake of radiotracer were significant risk factors of worse prognosis in patients with CS [46], thus using 18F-FDG PET is more suitable in assessing CS than SPECT/CT imaging.
Cardiac amyloidosis

Cardiac amyloidosis (CA) is currently more often diagnosed pathology owing to the advanced diagnostic methods. There are two most common types of cardiac amyloidosis: light-chain amyloidosis (AL) and transthyretin amyloidosis (ATTR), both with distinct therapeutic management and prognosis. Echocardiography and CMR play a crucial role in the diagnostic process, however, the differentiation between CA subtypes remains problematic. Radionuclide scintigraphy with $^{99m}$Tc labeled diphosphonopropanodcarboxylic acid ($^{99m}$Tc-DPD), pyrophosphate ($^{99m}$Tc-PYP) or methylendiphosphonic acid ($^{99m}$Tc-MDP) has been found useful in identifying patients with ATTR. Increased uptake of $^{99m}$Tc-DPD in the myocardium with decreased or absent uptake in the bones suggest the ATTR type [47]. In the study performed on a group of 1217 patients who underwent either $^{99m}$Tc-DPD or $^{99m}$Tc-PYP SPECT examinations, negative results excluded ATTR in 99%, with the specificity of 86% [48]. Correlation of positive bone scintigraphy test with a negative result of monoclonal protein in the blood or urine increased specificity to 100% [49].

Future directions

Radiotracers labeled with $^{18}$F, e.g. $^{18}$F-flurpiridaz used in MPS PET/CT, can be introduced in the diagnostic evaluation of coronary artery disease. In 86 patients who underwent coronary angiography, the sensitivity of PET was higher compared to the results obtained with SPECT (78.8% to 61.5%; $P = 0.02$); with statistically similar specificity (PET: 76.5% to SPECT: 73.5%, $P = \text{ns}$). The published results showed that $^{18}$F-flurpiridaz-PET MPS was safe and qualitatively better than SPECT MPS in CAD diagnostics [50].

Recently Mood JB et al. assessed an absolute MBF and myocardial flow reserve (MFR) in rest and pharmacologic stress in 231 patients. These data were compared with CAD severity quantified by invasive coronary angiography on a per-patient and per-vessel basis.
They found that stress MBF per-vessel accurately identified the obstructive disease and, along with MFR, progressively declined with an increasing coronary atherosclerotic burden. The study confirmed the incremental diagnostic value of stress MBF and MFR in the diagnostic workup of CAD. Therefore, 18F-flurpiridaz PET is a promising modality in myocardial blood flow measurements [51].

There have been attempts for noninvasive evaluation of myocardial hypoxia. This phenomenon can be present in ischemic heart disease, including microvascular circulation disorders or myocardial hibernation and cardiac hypertrophy. PET/CT with $^{18}$F-fluoromisonidazole ($^{18}$F-MISO) or $^{18}$F-fluoronitroimidazole ($^{18}$F-FAZA) demonstrate a real-time data reflecting the biodistribution of radiopharmaceuticals [52,53].

**Conclusion**

The use of noninvasive nuclear medicine methods in the diagnosis of cardiovascular diseases in recent decades has become the subject of greater interest. Improved access to the specialized equipment, as well as the introduction of new radiotracers, allow addressing multiple clinical questions, with coronary artery disease being one of the most investigated ones. Emerging methods may also be applied in the management of endocarditis, hypertrophic cardiomyopathy or heart failure.

**Case presentations**

**Case 1.** A 49-year old patient with suspected CAD and atypical clinical presentation underwent MPS with $^{99m}$Tc-MIBI. Chest pain was originating in the epigastrium and radiating to the back, interscapular region. The patient presented no CAD risk factor except nicotinism in the past. Routine treadmill stress test and transthoracic echocardiography were normal; subsequent coronary angiography revealed a critical stenosis in the proximal left anterior descending artery (Figure 5).
**Case 2.** A 60-year old female with suspected CAD and atypical symptoms underwent the treadmill exercise test. It demonstrated ST-segment depression in leads II, III, aVF suggestive of inferior wall ischemia. In this case, myocardial scintigraphy shown in Figure 6 excludes ischemia and proves ECG-stress to be false positive.

**Case 3.** A 69-year old asymptomatic patient presented four years after successful mitral and aortic valves replacement (biological prostheses). During routine echocardiographic follow up, two abnormal structures were visualized on the mitral prosthesis. Figure 7 demonstrates abnormalities in the $^{18}$F-FDG PET scan that was conclusive of active endocarditis on both prostheses.
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Table 1. Basic patterns of interpretation of myocardial viability [20]

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<th>Parameter</th>
<th>Standard</th>
<th>Hibernation</th>
<th>Necrosis</th>
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<td>present</td>
<td>absence</td>
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<tr>
<td>Glucose metabolism</td>
<td>present</td>
<td>present</td>
<td>absence</td>
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<tr>
<td>Ejection fraction</td>
<td>present</td>
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**Figure 1.** Basic myocardial perfusion scan interpretation. Normal result. In rest conditions, coronary blood flow is even, so radiotracer uptake in myocardium appears to be homogenous. During stress, coronary blood flow increases and, if there is no obstruction related to coronary artery stenosis, radiotracer concentration in myocardium remains uniform.
Figure 2. Basic myocardial perfusion scan interpretation. An abnormal result is related to CAD. Despite coronary artery stenosis, coronary blood flow is still unaltered at rest. In stress, coronary blood flow rises, but due to obstruction caused by atherosclerotic plaque, the area of myocardium supplied by the stenotic artery receives less blood than other areas, so more radiotracer gets accumulated in healthy areas.
**Figure 3.** Myocardial viability interpretation in $^{99m}$Tc-MIBI SPECT and $^{18}$F-FDG PET study.

$^{18}$F-FDG PET - Positron emission tomography with fluorodeoxyglucose, $^{99m}$Tc-MIBI SPECT – single-photon emission positron tomography with $^{99m}$Tc-MIBI
**Figure 4.** The left ventricle function report indicates normal wall thickening and motion along with normal left ventricle volume, ejection fraction, and muscle mass.
**Figure 5.** Myocardial perfusion polar map. Top row – stress images; middle row – rest; bottom row – reversibility. Left column – normalized perfusion; right column – defect blackout maps.

Stress images show significantly lower $^{99m}$Tc-MIBI concentration in the apex, anterior wall, and septum, as well as apical segment of lateral wall indicating severe myocardial ischemia. Rest images show significant radiotracer accumulation improvement. Perfusion defect reversibility is observed nearly in the entire abnormal region covering 44% of left ventricle myocardium.

$^{99m}$Tc-MIBI - methoxyisobutylisonitrile/sestamibi labeled with $^{99m}$Tc
Figure 6. Stress perfusion report - images without and with attenuation correction both present normal myocardial perfusion. Slice-by-slice report.
**Figure 7.** PET imaging of the heart. A) Whole-body maximum intensity projection indicates abnormal uptake corresponding to both prostheses. Despite that, no obvious abnormal $^{18}$F-FDG distribution is observed. B) Maximum intensity projection covering the chest, left/anterior oblique view. $^{18}$F-FDG uptake mainly in mitral valve ring, lesser accumulation in aortic valve ring. C) PET/CT scan, a transmitral plane with auxiliary sections. Intense $^{18}$F-FDG uptake in the mitral valve ring. D) PET/CT scan, a transaortic plane with auxiliary sections. $^{18}$F-FDG uptake in aortic valve ring.

Ao – aorta, AoV – aortic valve, $^{18}$F-FDG - Fluorodeoxyglucose, Ki – kidney, LA – left atrium, Li – liver, LV – left ventricle, Mi – mitral valve, PET/CT – positron emission tomography/computed tomography