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Research Article

Myocardial Perfusion Scintigraphy in Diagnosic of Coronary Heart Disease

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Abstract

Introduction: Atherosclerosis plays a key role in the etiopathogenesis of cardiovascular diseases. Atherosclerosis is a generalized chronic inflammatory disease of the vascular wall, which results in anatomical and histological changes that, together with functional changes, lead to endothelial dysfunction, narrowing of the arterial lumen, and insufficient blood supply to the tissues. The shift in the incidence of cardiovascular diseases to younger age groups is alarming. The presence of microvascular changes in the myocardium is significant. The high incidence of cardiovascular diseases, especially ischemic heart disease, requires early diagnosis and modern treatment. *Aim:* The aim of the paper is to analyse and point out early diagnosis of coronary heart disease using nuclear medicine methods. *Set of examined patients and methodology:* Using nuclear medicine methods, we try to detect these changes in time and thus prevent the occurrence of acute coronary events. In nuclear cardiology, instead of a large-area scintillation detector, a new type of cardio-gamma camera "Discovery CZT 530c" based on the principle of semiconductor detectors began to be used. The abbreviation CZT stands for semiconductor composition (Cadmium-Zinc-Tellur). The set of respondents consisted of 4270 people examined in the years 2014-2016 by myocardial perfusion scintigraphy. There were 950 diabetic patients in the analysed group of the 4270 examined. *Results:* In the analysed group of 4270 respondents, 61% had negative findings and 39% had positive findings in terms of the presence of ischemic heart disease. In the group of diabetic patients, there was a negative finding in 28% of respondents and a positive finding in 72% of the respondents in the sense of positive ischemic heart disease. Using myocardial perfusion scintigraphy in the diagnosis of functional changes, we confirmed a great benefit in detecting early changes in coronary heart disease, including in the diagnosis of microvascular angina. *Conclusion:* Nuclear medicine methods are of great benefit for the diagnosis of small vessel disease, diabetic cardiomyopathy and cardiac autonomic neuropathy in patients with diabetes mellitus. The new type of cardio gamma camera "Discovery CZT 530c" allows more accurate assessment of myocardial perfusion abnormalities and at the same time the reduction of the radiopharmaceutical dose reduces the patient's radiation load by 50%.

Keywords

Coronary Heart Disease, Radionuclides, Semiconductor Cardio-gamma Camera

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1. Introduction

Atherosclerosis is considered the main cause of cardiovascular diseases. We evaluate atherosclerosis as an immune-inflammatory process, the result of which is damage to the intima. In the beginning, there is endothelial dysfunction, causing the transmigration of lipids into the intima, local platelet aggregation and thrombus formation [1].

An important factor in the development of atherosclerosis is inflammation. Plaque becomes vulnerable when inflammation occurs. The measurement of Lp-PLA2 (*lipoprotein-associated phospholipase A2*) is used to determine inflammation in the plaque. Lp-PLA2 is a vascular-specific inflammatory enzyme, playing a significant role in the formation of unstable plaques, it can be considered as a new prospective biomarker. Increased concentration of LpPLA2 is associated with increased cardiovascular risk [2-4]. There is an opinion that LpPLA2 should have in vivo anti-inflammatory effects due to inhibition of PAI-1 (plasminogen activator inhibitor-1). In vivo the maximum production is mediated precisely by macrophages and foam cells. Histopathological studies show a higher concentration of LpPLA2 in unstable atheromatous plaques with a thin fibrous cap and a large fatty core, which are prone to rupture. It turns out that the concentration of LpPLA2 is related more to the quality of the plaque than to its size. In addition to proatherogenic markers, there are also antiatherogenic markers, which are HDL cholesterol, paraoxonase, cytokines [2-4, 9, 10].

Other new biomarkers include oxLDL (oxidized low-density lipoprotein), ADMA (asymmetric dimethylarginine), VCAM-1 (vascular cell adhesion molecule-1), ICAM-1 (intercellular adhesion molecule-1), P-selectin, E-selectin, fibrinogen, adiponectin, leptin, etc. [5-8].

Pathological changes during the onset of myocardial ischemia can occur in three anatomical components, which are epicardial vessels, small coronary vessels and coronary microcirculation. Coronary arteries are not finite, they are interconnected by two groups of intercoronary anastomoses. Coronary microcirculation is significantly influenced by the rheological properties of blood [13-15].

2. Examination Methods

Several methods are used in the diagnosis of IHD (ischemic heart disease) (*electrocardiography, exercise electrocardiography examination, echocardiography, electrocardiography and blood pressure monitoring, biochemical and haematological examinations*, etc.). Important methods include MSCT (multislide computer tomogpraphy) and classic SCA (selective coronary angiography), which is also a treatment method. Diagnostic methods include perfusion scintigraphy of the myocardium, which is important for early diagnosis of coronary artery disease [16, 17].

Scintigraphic examination of the myocardium allows to evaluate:

1. regional myocardial perfusion,
2. metabolism of the myocardium and its viability,
3. the presence of myocardial necrosis,
4. function of heart chambers,

It allows determining the extent and severity of the disorder, provides information on the state of the macrocirculation, as well as the state of the microcirculation. Selective coronary angiography primarily shows changes in the main coronary vessels and their branches. It can also indirectly indicate a disease of small vessels (*for example, atherosclerotic changes on the coronary arteries may not be visible, but a slow flow of contrast material is present*). Selective coronary angiography and perfusion scintigraphy are complementary examinations.

In MPS (myocardial perfusion scintigraphy), most often used radiopharmaceuticals are ^{99m}Tc sestamibi *(MIBI-methoxy-isobutyl-isonitril)* and ^{99m}Tc tetrofosmin *(Myoview-ethoxyethylfosfino-ethan).* With normal blood flow through the coronary vessels, the deposition of radioactivity in the myocardium is homogeneous. When the blood flow in the myocardium changes, defects in the deposition of radioactivity appear in the affected area. We usually use a two-day protocol with ^{99m}Tc tetrofosmin, starting with a stress examination, if necessary, we will do a rest examination with the application of ^{99m}Tc tetrofosmin on another day (Figure 4) [18, 22].

A perfusion defect appears in the basin of the narrowed vessel on scintigrams. A defect present only after exercise, regressing at rest, indicates the reversibility of perfusion in ischemia [19]. After an myocardial infarct, a permanent perfusion defect may be present. The effect of coronary stenosis on the blood supply to the myocardium, especially during exercise and at rest, is evaluated as a coronary flow reserve (Figures 1, 2).

In the patient in the 1st figure with the occurrence of angina pectoris during exercise, electrocardiography ascending depressions of ST I and aVL are displayed after exercise. A scintigraphic examination shows ischemia on the front and lower wall, with signs of reversibility of perfusion on the lower wall at rest. In SCA, a significant 95% stenosis was shown on RIA, PCI on RIA with stent implantation.

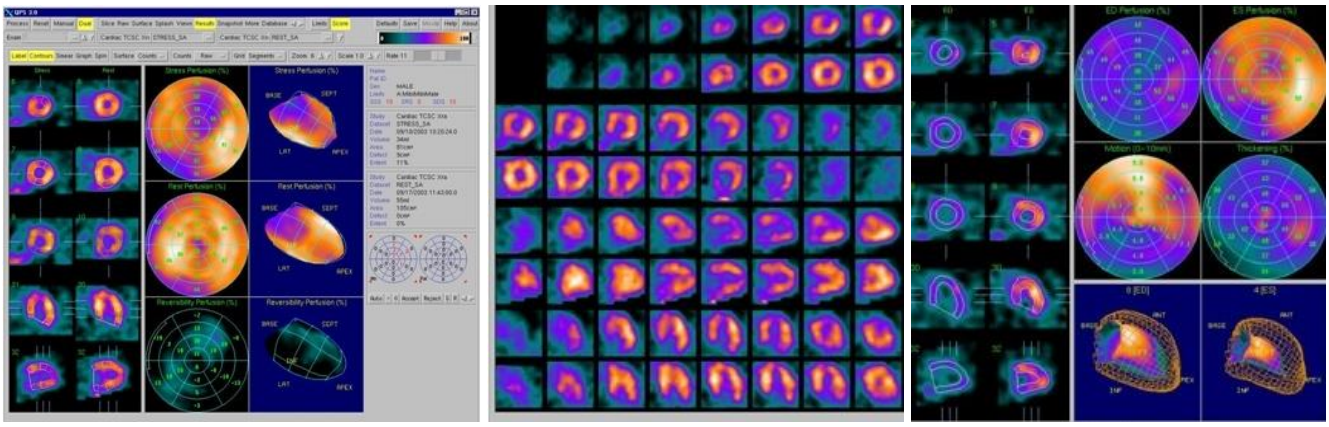

Figure 1. *SPECT-SCA patient (1947) after non-ST-elevation myocardial infarction, exertional angina pectoris, poor physical load tolerance (own source).*

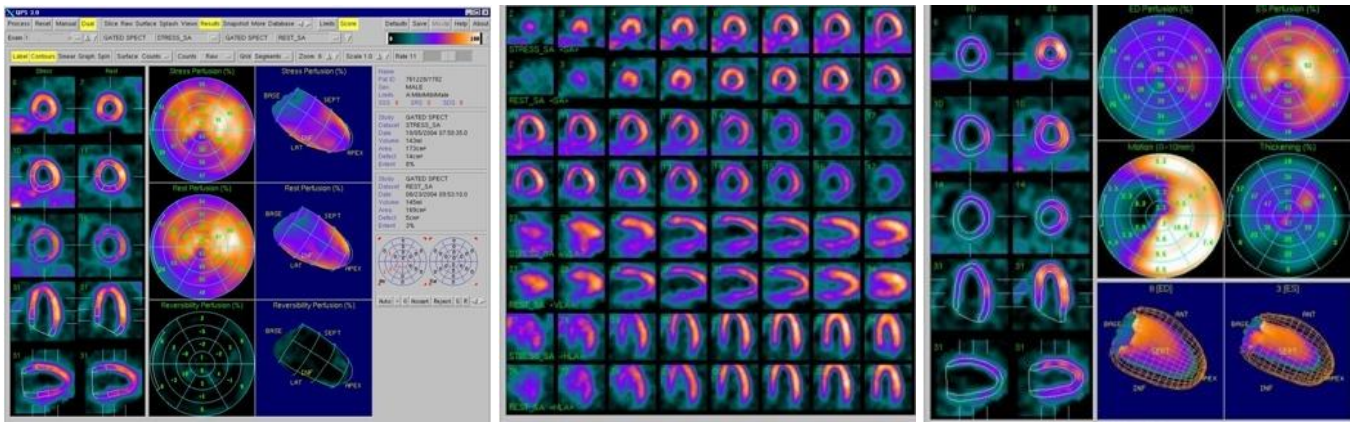

Figure 2. *Healthy sportsman (1976) with sudden rest chestpain (own source).*

The patient in the 2nd figure is an active sportsman who suddenly developed angina at rest with typical changes on the ECG (elevation of ST II, III, aVF). An acute coronary angiography was performed with no detected changes in the coronary vessels.

Myocardial perfusion scintigraphy taken 14 days after the performed coronary angiography, which showed ischemia on the lower wall with a kinetic disorder in the septal area. Q wave II, III, aVF was formed on the ECG.

Accumulation of the radionuclide in the cell is an active process for which preserved perfusion, integrity of the cardiomyocyte membrane, and metabolic viability of the cell are necessary. The principle of the identification of myocardial viability is the assessment of the integrity of the myocyte sarcolemma and myocardial perfusion [15, 20, 21]. Coronary reserve can be changed even with intact epicardial vessels, precisely by changing the function of intramyocardial vessels [3, 19].

Dysfunctional segments with a fixed defect accumulating < 50% of maximum radioactivity are considered to be a post-MI scar, with accumulation of radioactivity > 50% of maximum, it may be a chronically hypoperfused "hibernating" myocardium. The finding of normal perfusion in a dysfunctional hypokinetic or even akinetic segment usually indicates a "stunning" myocardium.

Figure 3 shows a 22-year-old female diabetic patient, with diabetes lasting 20 years, on dialysis with the appearance of sudden weakness, without angina (possible cardiac autonomic neuropathy). At the beginning, the ECG curve was normal, gradually developing negative T waves II, III, aVF, V3-V6, on echocardiography without local kinetics disorders, diastolic function changed. Cardiospecific markers were positive (Troponin hs-I-900ng/l – with a gradual decrease to the norm, NT-proBNP 25.OOOng/l – with a decrease to the norm, CRP, D-Dimers, minerals in the norm).

Resting perfusion scintigraphy of the myocardium showed light perfusion disturbances in end diastole on the front wall, in the area of the septum and lower wall, disturbances in the kinetics and contractility of the LV (left ventricle) on the front and lower wall, in the area of the septum, reduced systolic function of the left ventricle, EF (ejection fraction) 37%. The myocardium is viable. This is stunned myocardium, our evaluation of nonSTEMI (non-ST elevation myocardial infarction) at the level of small vessels.

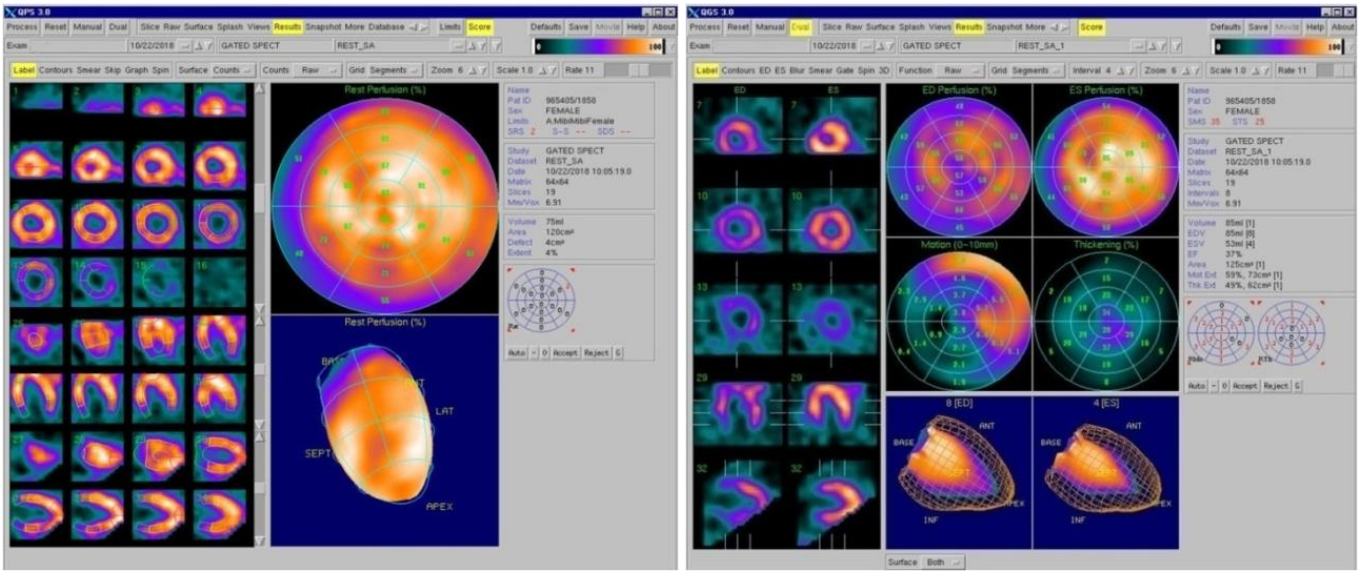

Figure 3. *22 years old woman with long lasting diabetes mellitus (20 years) and chronic kidney disease. Sudden faintness, no chest pain (own source).*

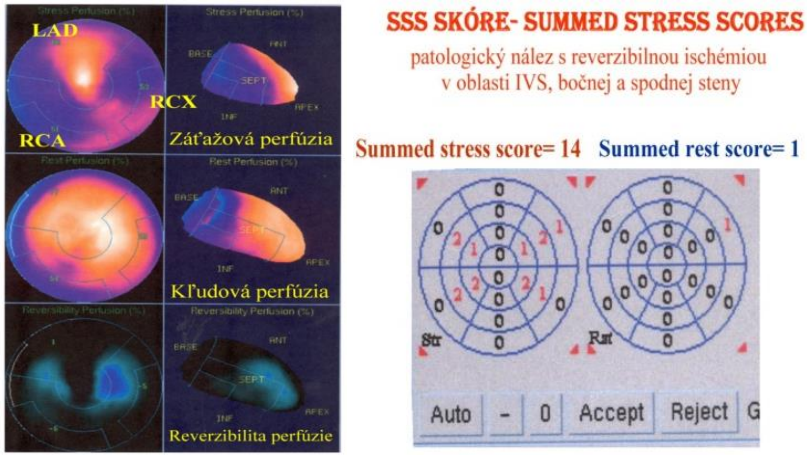

Figure 4. *Myocardial scintigraphy- hypoperfusion of septum and lateral wall, very suspect multivessel disease, quantification on the left side (own source).*

In Figure 4, a patient with poor exercise tolerance with a burning sensation in the chest on exertion shows ischemia on the lateral and inferior wall and in the septal area on myocardial perfusion scintigraphy. Specific changes are not displayed on the ECG curve. The patient was sent for coronary angiography, where RIA stenosis was detected proximally and in the middle 75%), RMI stenosis 75%, RCA 75-80%. Patient indicated for cardiac surgery CABG to RIA, RMI, RCA-RIP.

Patients with diabetes are a specific group for the diagnosis of cardiac complications. Cardiac complications of diabetes include:

1. Coronary heart disease based on atherosclerosis of the coronary arteries.
2. Small vessels disease.
3. Diabetic cardiomyopathy.
4. Cardiac autonomic neuropathy (CAN) [11, 22].

The prevalence of coronary heart disease in patients with diabetes is approximately 45%, in non-diabetics approximately 25%. The occurrence of silent ischemia is more frequent in approximately 10-20% of diabetic patients, compared to 1-4% of non-diabetics [23, 24]. Coronary heart disease in patients with diabetes is more severe than in non-diabetics. The occurrence of inflammation in vulnerable atherosclerotic plaques is more common. In diabetes, the collateral circulation is formed more slowly. In diabetes, the protective effect of estrogens on the vascular wall decreases in women, atherosclerotic changes are more pronounced in women with diabetes and occur at a younger age [25, 26, 27]. The development of new medicaments (e.g. *SGLT2 inhibitors, GLP-1 receptor agonists*), improving the morbidity and mortality of patients with diabetes, shows that an ill diabetic must be detected as soon as possible (Figure 5).

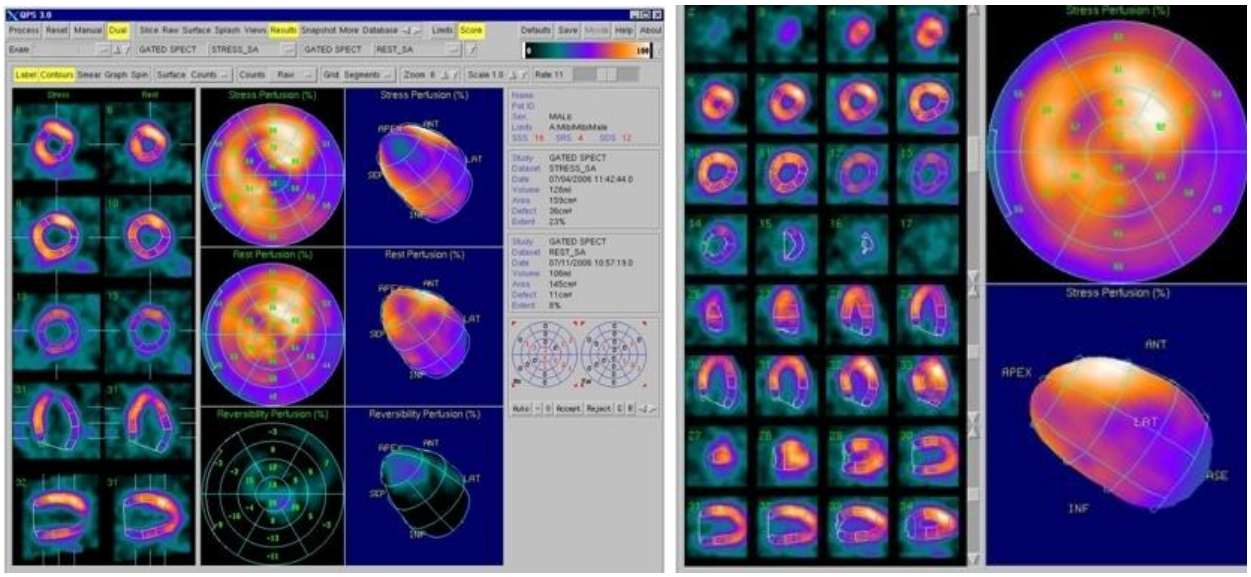

Figure 5. *Positive perfusion scintigraphy in patient with diabetes mellitus- silent ischaemia. Left upper image- after exercise test, left lower image- rest examination, lateral wall ischaemia. On the left before treatment, on the right after treatment. (own source).*

Figure 5 shows a patient being treated for diabetes mellitus, stress perfusion scintigraphy shows ischemia on the side wall. Patient without subjective problems, ECG and echocardiography examination without current changes. Signs of silent ischemia, cardiac autonomic neuropathy. The coronary angiographic examination showed a stenosis of RCX 70%, PCI-implanted stent. Microvascular angina can also be accompanied by classic anginal complaints, changes on the ECG, coronary angiography is negative. The pathophysiological substrate of microvascular angina is a reduced ability to vasodilate, with a reduced level of nitric oxide (NO) and a preponderance of vasoconstrictor factors such as endothelin, local angiotensin II, natriuretic peptide, etc. [11, 12].

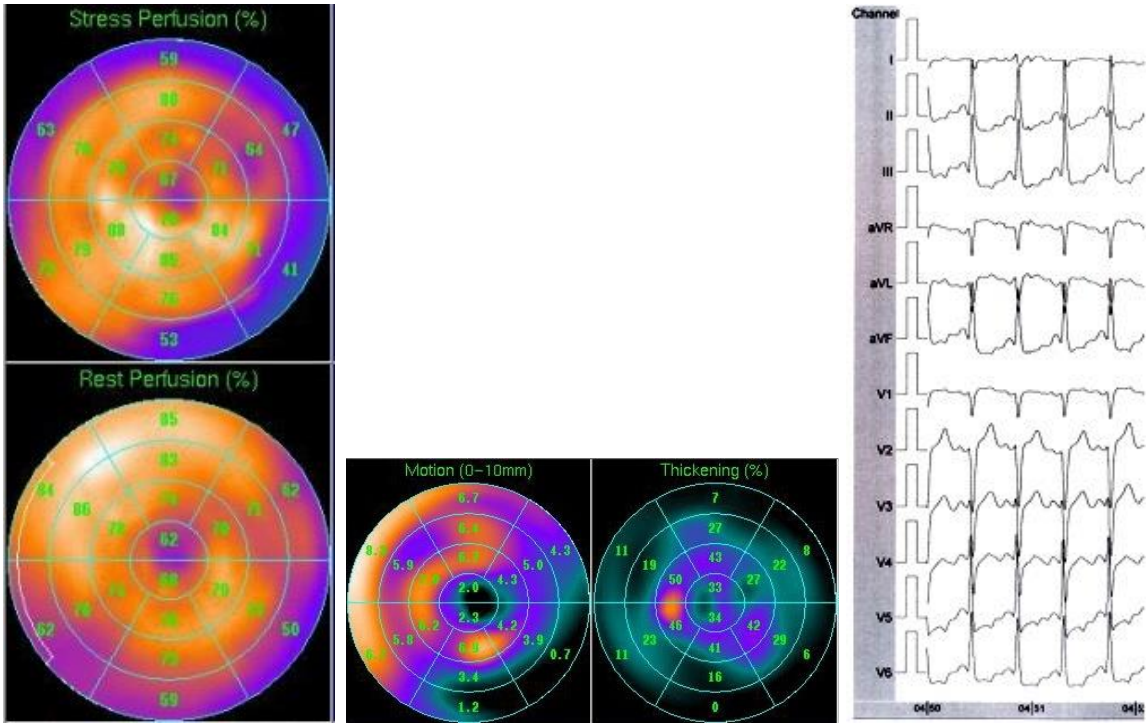

Figure 6. *Selective coronarography: small vessel disease. Perfusion scintigraphy: Left image- lateral wall ischaemia after exercise on the upper image, normal finding in rest examination. Middle image- lateral wall thickening and motion disorders. Right image- ECG with pathological findings (own source).*

Small vessel disease is a functional and structural abnormality of the coronary microcirculation. The structural abnormality is caused by a change in the basement membrane, mainly by its thickening and endothelial proliferation of arterioles, which limits the vasodilation reserve of the coronary blood flow (Figure 6). Clinically, they can be manifested by angina pectoris, ischemic changes on the ECG at rest or during exertion. Non-invasive and invasive diagnostic methods help in differential diagnosis [28-30].

Changes in the area of microcirculation can be manifested as:

1. Syndrome X (clinical picture of coronary heart disease, positive stress test, negative SCA).
2. Small vessel disease.
3. Endothelial dysfunction, increase in vascu lar resistance, reduced ability to vasodilate, hyperinsulinemia, insulin resistance.
4. Microvascular stunning.
5. Presence of inflammation.
6. More frequent occurrence of nonSTEMI.
7. Positive biochemical markers (hs-CRP, microalbuminuria, increased level of Lp-PLA2).

In Figure 6, it is a patient with pressure pains in the chest independent of physical exertion. The ECG curve shows ischemic changes electrocardiography in II, III, and VF, V4-V6. A scintigraphic examination shows ischemia on the side wall, with reversibility of perfusion at rest, with altered kinetics and partly also contractility of the side wall. During selective coronary angiography, changes in small vessels are displayed (slowed contrast material flow).

3. Semiconductor Ionizing Radiation Detector

An ionizing radiation detector (gamma camera) is a device capable of detecting ionizing radiation.

According to the principle, there are two main types of detectors that form the basic unit for imaging devices (gamma camera):

1. Scintillation detector of ionizing radiation on a conventional SPECT gamma camera (scintillation in the crystal).
2. Semiconductor detector of ionizing radiation (ionization in a solid substance in a semiconductor).

Compared to scintillation detectors, semiconductor detectors have significantly more accurate energy resolution and significantly higher sensitivity [31, 32]. In digital semiconductor gamma cameras with direct conversion of gamma radiation, one hole on the collimator (pinhole) corresponds to one detection unit of the semiconductor and also to one resulting image point (pixel). The spatial resolution of new semiconductor cameras (given by one pixel) is 2.5 mm, which is 2x better than scintillation cameras of classic design. At the Nuclear medicine clinic at Central Military Hospital Ruzomberok, Slovakia we have been working with a CZT 530c cardio camera with semiconductor detectors since September 2019 (Figure 7).

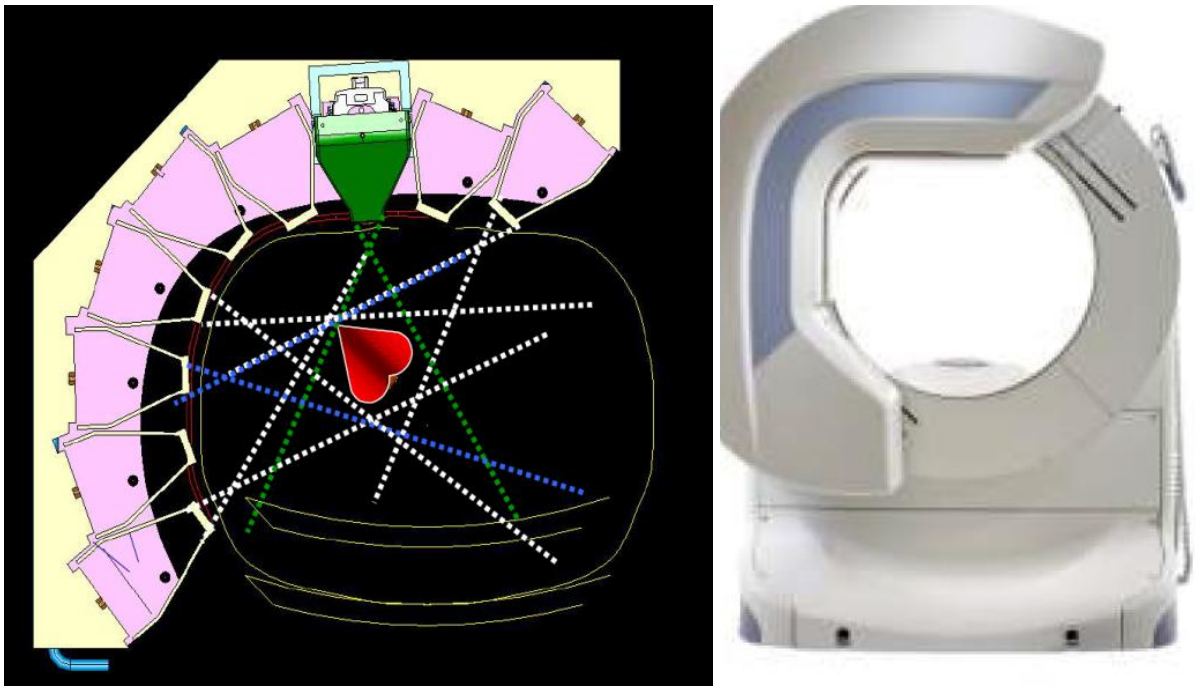

Figure 7. *Semiconductor Cadmium-Zinc –Telllurid detector on CZT gamma camera (Vitola, 2004) (33).*

4. A Set of Examined Patients

During the years 2003-2016, we performed myocardial perfusion scintigraphy on the Millenium gamma camera, VG Hawkeye f. GE in about 25 thousand patients. We analysed a set of 4270 respondents examined in the years 2014-2016, in whom the myocardial perfusion scintigraphy was performed.

In this set, there were 61% negative findings and 39% positive findings in the sense of positivity for ischemic heart disease. Of the number of positive findings, conservative medical treatment was recommended in 19%, MSCT coronary angiography in 7% and SCA in 13%. The sensitivity was around 95% and the specificity around 90% (Figure 8).

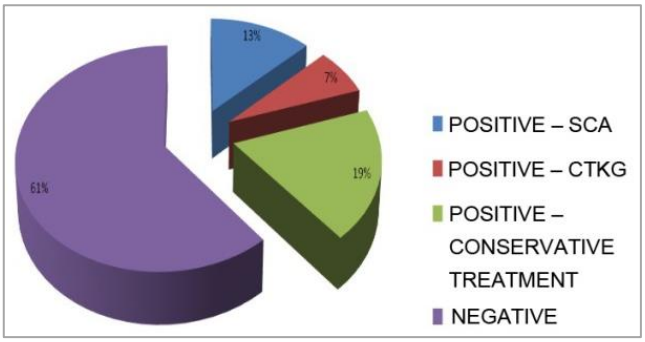

Figure 8. *Analysis of a set of 4270 patients with negative and positive findings.*

In the analysed set of 4270 examined there were 950 patients with diabetes. In this group, when examined by perfusion scintigraphy of the myocardium, we found a negative finding in 28% and a positive finding, indicative of ischemia, in 72% of diabetics.

With a positive finding, we recommended coronary angiography in 42% of diabetics, MSCT in 12% and SCA in 30%. In 30% of the pathological findings, the detected changes indicated a change in microcirculation (there were changes in kinetics, increased LV volume, perfusion changes only in end diastole, changed LV diastolic function, reduced LV systolic function (Figure 9).

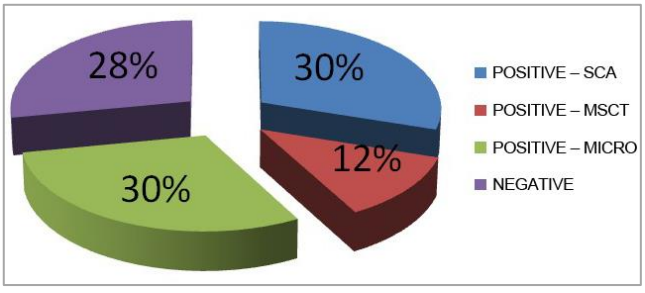

Figure 9. *Analysis of the set of 950 patients with diabetes mellitus with negative and positive findings.*

In the set with a positive finding in terms of ischemia, approximately 25% of patients with diabetes had perfusion changes without accompanying clinical manifestations (silent ischemia) (Figure 10).

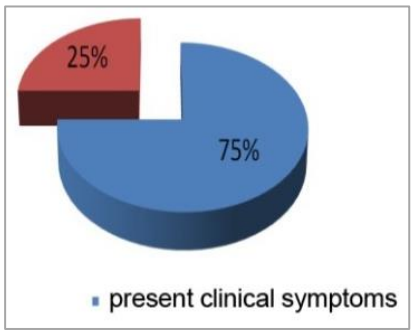

Figure 10. *Silent ischaemia presence in the set of 950 patients with diabetes mellitus.*

On the cardiology gamma camera CZT 530c f. GE over a period of two years, 2019-21, we performed myocardial perfusion scintigraphy in 2900 individuals. In this group, we found a negative finding in 49% of individuals and a positive finding in 51% of individuals. From the set of positive findings indicative of coronary heart disease, we recommended coronary angiography in 24% of those examined, MSCT in 13%, and SCA in 11%. Medical treatment was recommended to the remaining 27% of the examined patients (Figure 11).

In the group of 2900 individuals, there were 880 patients with type 1 and type 2 diabetes. In the patients with diabetes, during perfusion scintigraphy of the myocardium, we found a negative finding in 26% and a positive finding indicating ischemia in 74%. With a positive finding in 36% of patients with diabetes, we recommended coronary angiography, namely MSCT in 15% and SCA in 21%. For other pathological findings, i.e. in 38% of diabetics, scintigraphic changes indicated the presence of microcirculatory changes (Figure 12).

The standard for quantification of coronary flow reserve (CFR) is dynamic positron emission tomography (PET). Blood flow and CFR quantification programs were originally developed for PET scanners, later converted for use on CZT cameras in dynamic SPECT. The sensing system enables rapid data collection, application of lower radiopharmaceutical activity, thereby reducing radiation exposure.

Coronary flow reserve can be determined by comparing blood flow after pharmacological stress and blood flow at rest. A value of CRF > 2 is considered to be a normal coronary reserve [30-32].

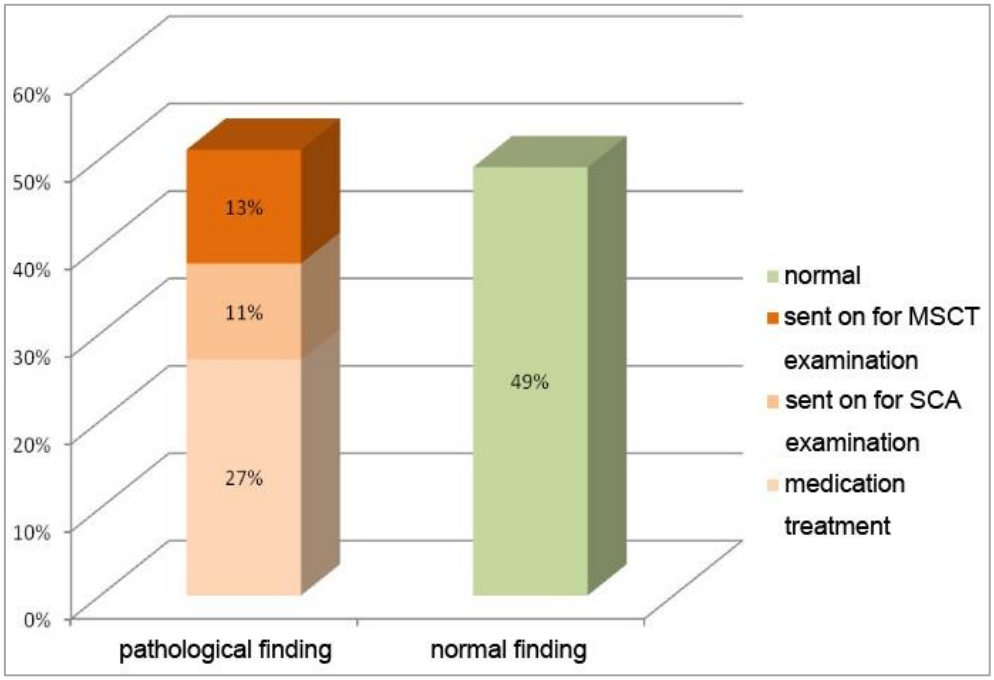

Figure 11. *Analysis of a set of 2900 patients with negative and positive findings.*

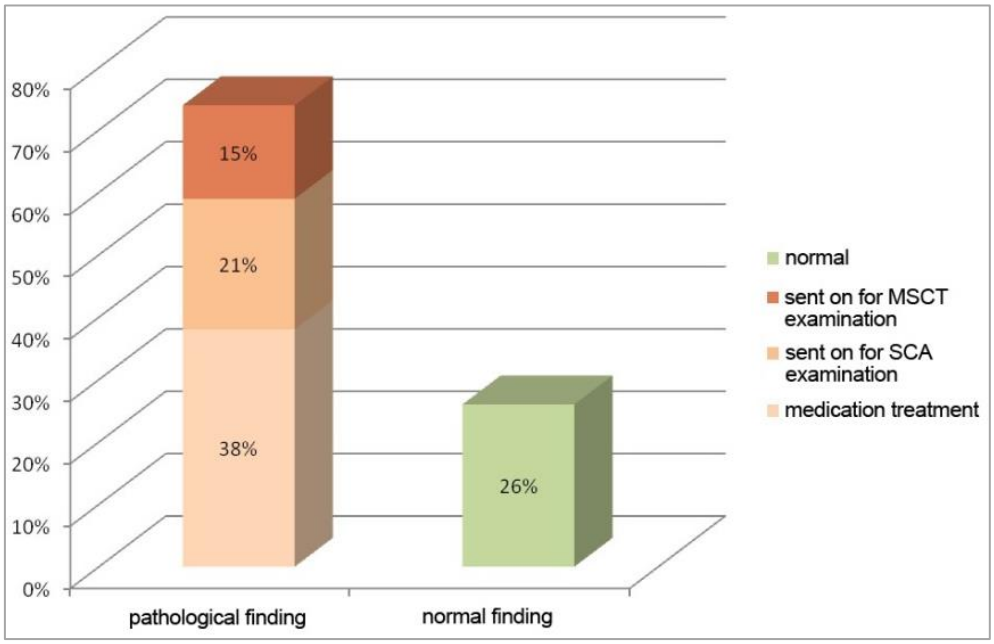

Figure 12. *Analysis of the group of 880 patients with diabetes mellitus with negative and positive findings with further recommendations.*

In our Nuclear medicine department, we perform dynamic SPECT on a 530c CZT camera from the second half of 2019. The workplace owns a license for the CFR SPECT program 4DM CFR. Perfused ^{99m}Tc radiopharmaceutical is administered as a bolus. The speed of application should be the same during stress and resting examinations *(1 ml/min.)*. Vasodilatation hyperemia is induced during pharmacological stress. We followed the two-day "Ottawa protocol" with a bolus application of the radiopharmaceutical at rest, the second day with a bolus application after a pharmacological load *(Regadenoson 400ug) (activity 3MBq/kg)*. Obtained indices > 2.0 indicate a normal coronary reserve.

Before the examination, the myocardium should be focused by applying a small dose of the radiopharmaceutical (*approx 35-40 MBq)*. This is followed by a dynamic SPECT recorded in list mode (*the study itself is recorded as non-gated, then a routine gated SPECT study follows*). The results allow a more accurate assessment of myocardial perfusion abnormalities compared to results obtained by conventional methods (Figure 13).

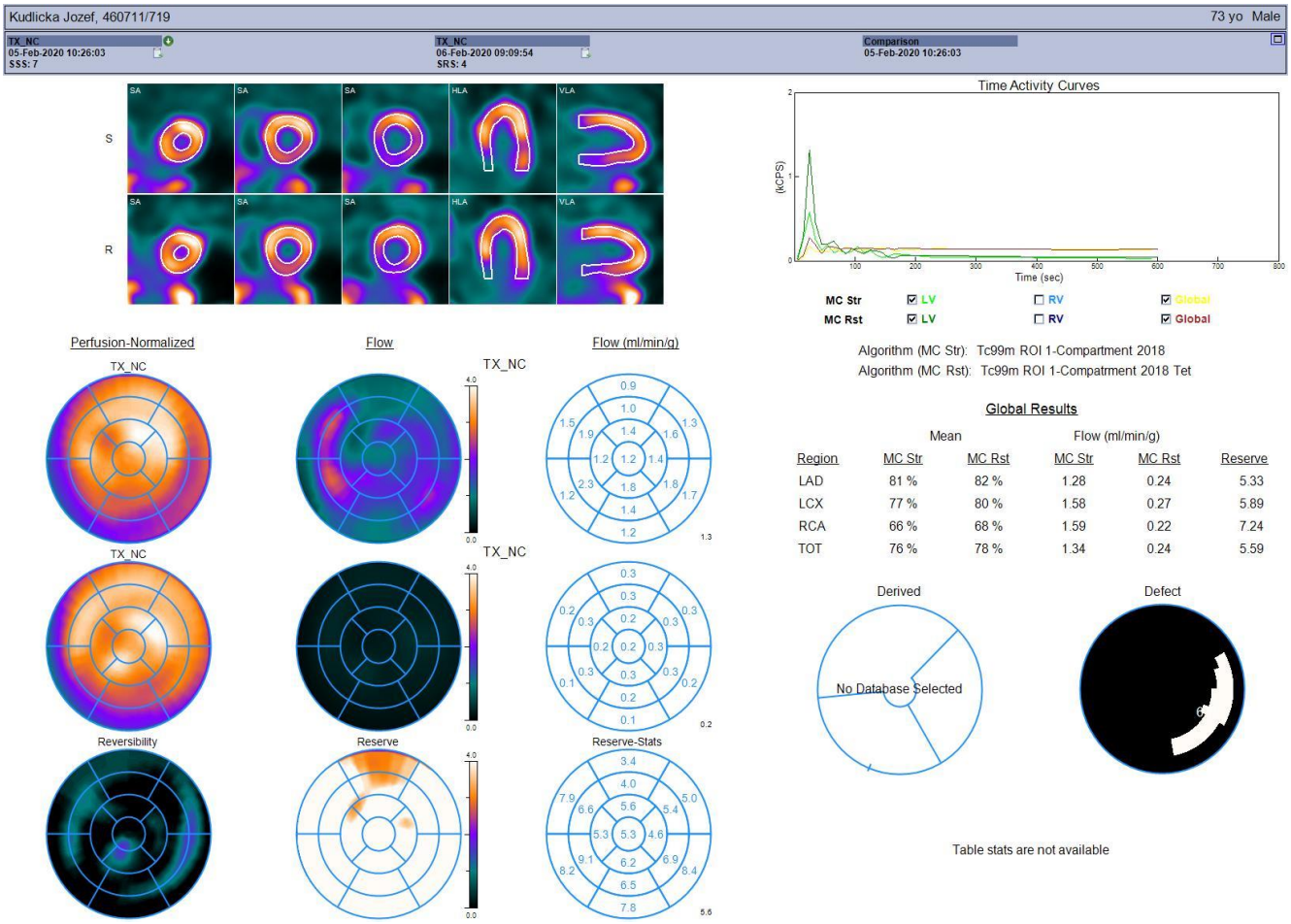

Figure 13. *Normal findings in scintigraphy and selective coronarography, normal findings during coronary angiography, normal indexes of coronary flow reserve (own source).*

We statistically evaluated the significance of positive findings between the Hawkeye gamma camera and the CZT 530c cardio camera using a relative value test, a so-called z-test. The test showed a statistically significant difference in the capture of positive findings between the HawkEye gamma camera (39%) and the CZT 530c cardio camera (51%) at the level of significance $p > 0.00001$.

Also, a statistical significance of the difference of positive findings in patients with diabetes compared to positive findings in all non-diabetic subjects was found $p > 0.00001$.

5. Conclusion

The importance of perfusion scintigraphy of the myocardium in the diagnosis of functional changes of the myocardium is of great benefit in the detection of early changes in coronary heart disease and also in the diagnosis of microvascular angina pectoris. The new type of cardio-gamma camera "Discovery CZT 530c" based on the principle of semiconductor detectors gives a possibility to significantly increase their resolution, enabling more accurate assessment of myocardial perfusion abnormalities. Reducing the dose of the radiopharmaceutical reduces the radiation burden for a patient by 50%.

Abbreviations

CZT	Cadmium-Zinc-Tellur
Lp-PLA2	Lipoprotein-Associated Phospholipase A2
PAI-1	Plasminogen Activator Inhibitor-1
HDL	High Density Lipoprotein
oxLDL	Oxidized Low-Density Lipoprotein
ADMA	Asymmetric Dimethyl Arginine
VCAM-1	Vascular Cell Adhesion Molecule-1
ICAM-1	Intercellular Adhesion Molecule-1
IHD	Ischemic Heart Disease
MSCT	Multislide Computer Tomography
SCA	Selective Coronary Angiography
MPS	Myocardial Perfusion Scintigraphy
^{99m}Tc	Technetium
MIBI	Methoxy-Isobutyl-Isonitril
MYOVIEW	Ethoxyethyl-Fosfino-Ethan
RIA	Ramus Interventricularis Anterior
PCI	Percutaneous Coronary Intervention
SPECT	Single Photon Emission Computed

MSA	Tomography
ECG	Electrocardiography
NT-proBNP	N-Terminal Fragment of the Natriuretic Peptide Prohormone Molecule Type B
CRP	C Reactive Protein
LV	Left Ventricle
EF	Ejection Fraction
nonSTEMI	Non-St Elevation Myocardial Infarction
RMI	Ramus Marginalis Sinistra 1
RCA	Ramus Coronaria Dextra
CABG	Coronary Artery Bypass Graft
RIP	Ramus Interventricularis Posterior
CAN	Cardiac Autonomic Neuropathy
SGLT2	Sodium-Glucose Cotransporter 2 Inhibitors
GLP-1	Glucagon Like Peptid 1
RCX	Ramus Circumflexus
NO	Nitric Oxide
hsCRP	High Sensitive CRP
CFR	Coronary Flow Reserve
PET	Positron Emission Tomography
MBq	Megabecquerel

Author Contributions

Anton Lacko: Formal Analysis, Methodology, Validation
Ján Straka: Methodology, Data curation
Anton Hruboň: Methodology, Validation
Jozef Babečka: Conceptualization, Visualization
Lukáš Lacko: Conceptualization, Software

Conflicts of Interest

The authors declare no conflicts of interest.

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