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Radiolabeling with Technetium 99m for the Diagnosis of Coronary Heart Disease in Senegal

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Abstract: Coronary heart disease is the leading cause of death in industrialized countries. In Africa, its prevalence is increasing in line with the westernization of lifestyles, the improvement of socio-economic conditions and the increase in life expectancy. Therefore, myocardial perfusion scintigraphy presents itself as an effective imaging technique allowing improved prevention, diagnosis and therapeutic management and monitoring of patients at risk. Our present work has exclusively focused on the early diagnosis of patients at risk in the nuclear medicine department of the Grand Yoff General Hospital (HOGIP). Our work consisted of administering a radiopharmaceutical to a patient and monitoring its fate in the body by external detection of gamma radiation using a Mediso Nucline TM gamma camera. We used vectors like sestamibi and tetrofosmin. These vectors have the particularity of having an affinity and a tropism for the myocardial tissue. These two vectors were labeled with technetium 99m (radiotracer). Indeed, these radioactive tracers attach themselves to the organ to be studied from where they emit gamma radiation captured by a gamma camera which detects the signal from this organ and reconstructs a computerized static or dynamic image. This made it possible to make a diagnosis of ischemia or myocardial necrosis in 57% of cases in women and 82.5% of cases in men in a sample of 45 patients. Thanks to the qualitative visual interpretation of the distribution of the tracer, a diagnostic aid was provided by the semi-quantitative analysis provided by the study of the polar maps (bull's eyes). This myocardial perfusion scintigraphy can be a valuable diagnostic aid, especially in our countries where income is limited.

Keywords: Coronary Heart Disease, Diagnosis, Radiolabeling, Technetium 99m

1. Introduction

Cardiovascular disease is the leading cause of death in the world: more people die every year from cardiovascular disease than from any other cause. An estimated 17.7 million deaths are attributable to cardiovascular disease, or 31% of total global mortality. Of these deaths, an estimated 7.4 million are due to coronary heart disease and 6.7 million to stroke. More than three-quarters of cardiovascular disease deaths occur in low- and middle-income countries [1–3]. In Africa, its prevalence is increasing in line with the westernization of lifestyles, the improvement of socio-economic conditions and the increase in life expectancy [4, 5]. Coronary artery disease is a progressive disease, initiated by damage to the walls of the vessels that supply blood to the heart (the coronary arteries). These lesions trigger a complex process of remodeling and atherosclerosis that leads to the thickening of the arterial wall and therefore a decrease in blood flow to the heart.

Nevertheless, in recent years, following an improvement in prevention, diagnosis and therapeutic management and its follow-up, mortality rates from coronary heart disease have fallen, which suggests a glimmer of hope. One of the main methods that have led to this positive development is myocardial perfusion scintigraphy. "This method of nuclear medical imaging is a reliable means of early diagnosis of patients at risk". It is a nuclear medicine examination to explore the irrigation of the heart muscle using a product (radioisotope) injected intravenously, most often in addition to a stress test. It makes it possible to evaluate the circulation of blood at the level of the heart muscle (evaluation of the perfusion) and gives information on its function and its capacities of contraction [6–8]. In this manuscript, we focused on radiopharmaceuticals used in the diagnosis of myocardial perfusion pathologies. Indeed, these radioactive tracers attach themselves to the organ to be studied from where they emit gamma radiation captured by a gamma camera which detects the signal from this organ and reconstructs a computerized static or dynamic image. The main tracers that bind to the myocardium to perform myocardial scintigraphies are thallium 201, Methoxy isobutyl isonitrile (MIBI)-99mTc, tetrofosmine-99mTc and fatty acids. We will present a critical study of radiopharmaceutical practice in myocardial perfusion scintigraphy in the nuclear medicine department of Idrissa Pouye general hospital. We will also specify the place it occupies in the diagnostic assessment, based on the imaging it allows to obtain.

2. Materials and Methods

2.1. Materials

2.1.1. Radiopharmacy Laboratory Equipment

The radiopharmacy laboratory is equipped with an AMERCARE type shielded fume hood or glove box, a CAPINTEC CRC-25R type activity meter, an Ultratechnekow® FM (Mallinckrodt) type technetium generator, a water bath, sealed transport cases used to transfer syringes to the injection room or in imaging, a sealed bin, sealed covers suitable for elution bottles, syringes of variable volumes (5ml, 3ml), castles in lead for storing radiopharmaceuticals, management notebooks.

2.1.2. Patients

Our study involved 45 patients (17 men and 28 women) referred to the nuclear medicine department of HOGIP by the cardiology department of said hospital. The age of the patients varied between 36 and 77 years in the men and between 43 and 69 years in the women. The average age was 57 for men and 58 for women. The selection of patients for myocardial perfusion scintigraphy respected the following criteria:

(i). Inclusion Criteria

1) patients with signs or symptoms suggestive of coronary insufficiency,
2) asymptomatic patients but at high risk of coronary insufficiency,
3) patients with one or more known coronary stenoses referred for a functional assessment or evaluation of the efficacy of treatments.

(ii). Non-Inclusion Criteria

We did not include pregnant or breastfeeding women in this work.

2.2. Methods

2.2.1. Preparation and Dispensing of the Radiopharmaceuticals

Sestamibi and tetrofosmine are the only vectors used in the nuclear medicine department of HOGIP for myocardial perfusion scintigraphy. Of the 45 patients, 82% had received sestamibi-99mTc complex and 18% the tetrofosmine-99mTc complex.

(i). Labeling of Sestamibi with 99mTc

One vial with 24.675 mg of lyophilizate contains 1 mg of sestamibi. The labeling is done by a complexation reaction. It is produced by directly dissolving the lyophilisate of methoxy iso-butyl iso-nitrile (vector) in its bottle with a determined volume of sodium pertechnetate (marker) freshly eluted from a generator, containing the activity necessary for the number of examinations desired. The boiling protocol was used following the steps below:

1) Using a sterile syringe, aseptically withdraw approximately 1 to 3 ml of sterile, pyrogen-free solution of sodium pertechnetate (99mTc) (200 MBq to 11.1 GBq).
2) Aseptically inject the sodium pertechnetate solution into the vial placed in its lead container. Without removing the needle, subtract an equivalent volume of air to restore atmospheric pressure in the vial.
3) Shake the flask vigorously by inverting, 5 to 10 times.
4) Remove the flask from its lead protection and place it vertically so that the flask does not directly touch the bottom of a suitable boiling water bath for approximately 10 minutes.
5) Remove the bottle from the water bath and let it cool for about 15 minutes.

After labeling with pertechnetate (99mTc), the active ingredient, sestamibi, comes in the form of a complex in a clear sterile aqueous solution, without preservatives. It is possible to dilute the preparation after labeling, at the rate of 1 ml of solution in 4 ml of 0.9% NaCl. Storage will be between 2°C and 8°C. The undiluted preparation is stable for 10 hours. Labeling requires very specific temperature and pH conditions (which determine the type of bond and the degree of oxidation). After labeling, a volume containing the necessary activity is taken to be injected into the patient [5, 9–14].

(ii). Labeling of Tetrofosmin with 99mTc

Labeling is also done by a complexation reaction.

1) Dissolve the lyophilizate directly in its bottle with a determined volume of sodium pertechnetate solution, containing the activity necessary for the number of examinations desired.
2) Use a venting needle for correct marking.
3) Shake the product by inversion then leave to stand for 15 minutes at room temperature.

The 99mTc-tetrofosmine solution must not be mixed or diluted with a substance other than that intended for its preparation (Na Cl 0.9%). The kit and the labeled preparation should be stored between 2°C and 8°C. Undiluted preparation is stable for 12 hours [11, 14, 15].

2.2.2. Scintigraphic Examination

(i). Stress Test

The injection of the tracer is carried out with maximum effort. At the HOGIP, physiological stress is used as a stimulation test and is performed on a treadmill with different levels of increasing intensity. This test is followed by a recovery phase (Bruce Protocol).

(ii). Rest Test

The injection is performed in the absence of stress.

(iii). Administered Activities

The activities administered in the department for a myocardial perfusion scan vary, depending on the protocol chosen, between 371 and 839 MBq.

(iv). Protocols and Image Acquisition

Protocols

Several protocols were used

1) Stress-rest on the same day
2) Stress-rest over 2 days
3) In some patients (known, extensive infarction), only a scintigraphy at rest was performed.

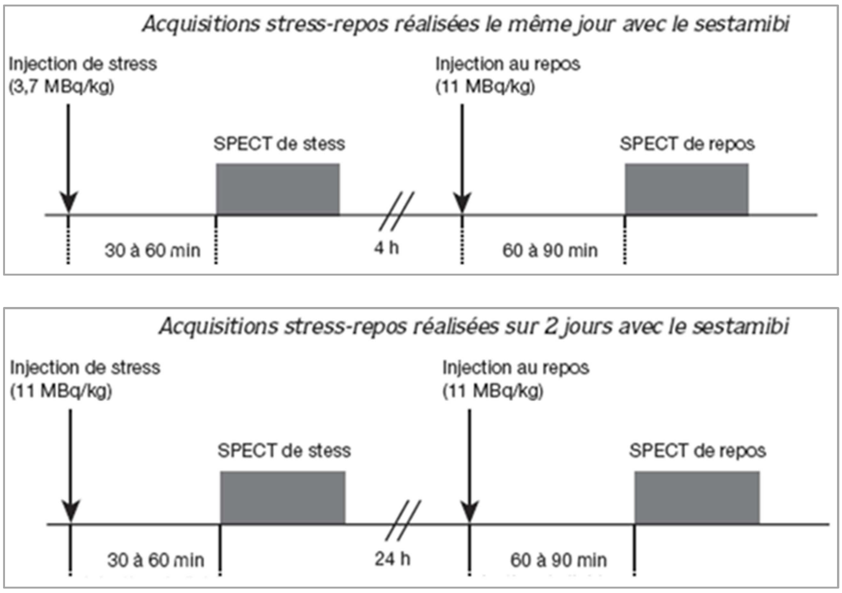


Figure 1. *Protocols and image acquisition [11].*

Sestamibi-99mTc and 99mTc-tetrofosmine are tracers of coronary flow. The absence of redistribution of these two products requires the performance of two different injections for the study at exercise and at rest [11].

Image acquisition

The acquisition is done in two distinct sequences. The first acquisition is made about 30 to 60 minutes after the stress and the second acquisition is made at rest 60 to 90 minutes later. Acquisition during stress and acquisition at rest take place in the same way. The patient is most often supine on the examination table.

3. Results

The scintigraphic diagnosis is based on the comparison of radiopharmaceutical uptake during exercise and at rest:

1) Healthy myocardium: normal fixation during stress and at rest.
2) Myocardial ischemia: hypofixation during stress reversible at rest.
3) Myocardial necrosis (myocardial infarction): hypofixation during stress not reversible at rest.

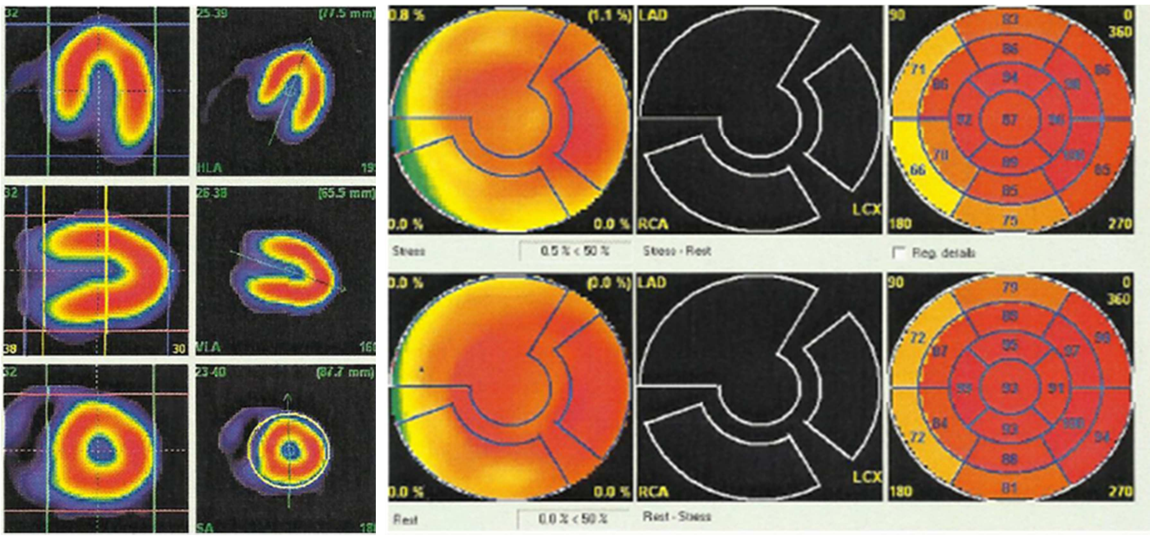
We will therefore present examples of normal and abnormal examinations (ischemia and necrosis) then we will give the different proportions obtained according to the patients.

3.1. Normal Examination

The different sections after reorientation give normal scintigraphic images that can be observed with some patients. Here we show the example of a 68-year-old patient sent to the service for scintigraphic examination. This patient presented the following clinical picture: obesity (body mass index 31.25 kg/m^2), increased blood pressure (15/8), increased HDL cholesterol and angina pain. On the ECG, she presents a repolarization disorder, hypertrophy of the left ventricle with increased filling pressure and dilation of the left atrium on the DOPPLER echo.

The scintigraphy is performed on the same day with a stress test with sestamibi at 699 MBq (stress test stopped at 80% of the MTF for muscle fatigue) and a rest examination at 444 MBq.

The scintigraphic images show homogeneous and normal fixation of the radiopharmaceutical according to the sections along the sagittal and frontal axes.



(a) (b)

Figure 2. *(a) reoriented images, (b) normal (Stress-rest) polar maps (bull's eyes) of the normal subject.*

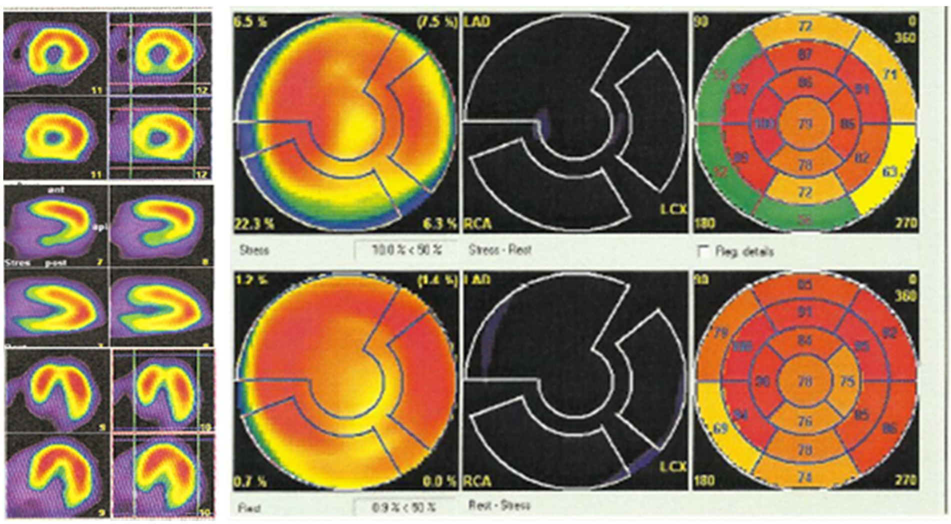
3.2. Abnormal Examination

3.2.1. Myocardial Ischemia

Here we show the example of a 53-year-old patient sent to the service for scintigraphic examination. This patient presented the following clinical picture: pain with tingling, onset of discomfort for minor physical activity without loss of consciousness and pain in the left scapula. During exercise, sestamibi-99mTc at 814 MBq is injected and at rest sestamibi-99m Tc at 402 MBq.

1) Short axis: the images show hypofixation of the radiotracer at the level after exercise and an improvement in hypofixation at rest.
2) Long vertical axis: we have a hypofixation of Sestamibi-99mTc at the posterior level and lower with the stress and an almost normal fixation at rest.
3) Long horizontal axis: we obtain a septal hypofixation with the stress which disappears during the acquisition at rest.

The patient has posterior, inferior, and septal ischemia.



(a) (b)

Figure 3. *(a) contiguous sections (stress-rest) along the 3 axes, (b) polar maps (stress-rest) of posterior, inferior and septal ischemia.*

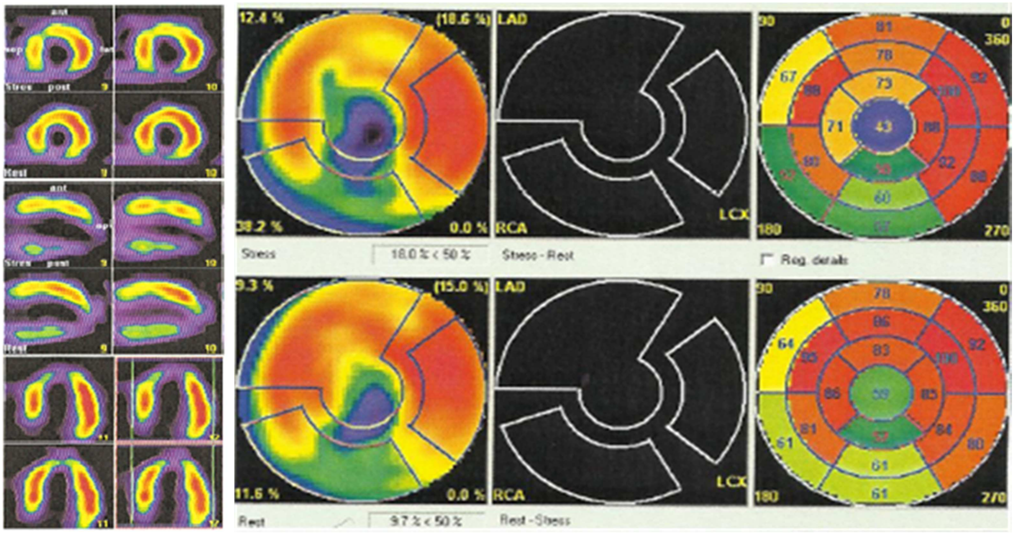
3.2.2. Myocardial Infarction

Images of myocardial infarction are observed with some patients:

Here we show the example of a 77-year-old patient sent to the service for scintigraphic examination. This patient presented the following clinical picture: acute coronary syndrome and chest pain on exertion. During exercise, Sestamibi-99mTc is injected at 22 mCi and at rest Sestamibi-99mTc at 12.5 mCi. After processing the images, the interpretation can be made along the cutting axes of the heart:

1) Short axis: the scintigraphic images show hypofixation at the posterior and anterior level to the stress. At rest, the hypofixation of the radiotracer persists at the posterior level and improves at the anterior level.
2) Long vertical axis: there is hypofixation at the apical level, lower and posterior to the stress. This hypofixation is irreversible at rest.
3) Major horizontal axis: there is hypofixation at the septal and apical level during stress. At rest, this hypofixation of the radiotracer persists at the apical level and improves at the septal level.

This patient presents with anteroseptal ischemia and posterior, inferior and apical infarction.

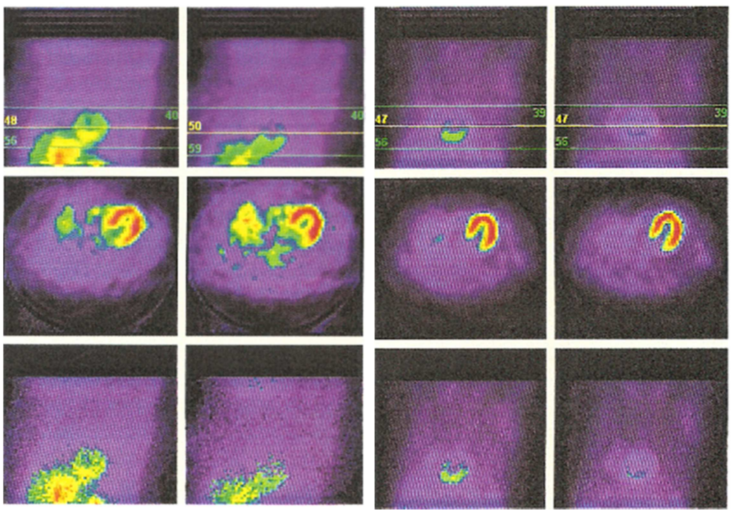


(a) (b)

Figure 4. *(a) coupes jointives (stress-repos) suivant les 3 axes, (b) cartes polaires (stress-repos) d'un infarctus postérieur, inférieur et apical.*

3.2.3. Extra-Myocardial Fixations

Here we show the example of a 68-year-old patient sent to the service for scintigraphic examination. This patient presented the following clinical picture: atypical coronary syndrome, sensation of pain under the left breast. On the DOPPLER echo, there is mitral and pulmonary insufficiency. The maximal stress test is clinically and electrically negative.



(a) (b)

Figure 5. *Extra myocardial fixations obtained before image processing with the use of sestamibi-99m Tc (a) and Myoview (b).*

3.3. Distribution of Patients According to the Pathology Observed After the Examination

Our study allowed us to obtain normal, ischemic or necrotic images. The distribution of these images can be done according to gender.

1) In men Out of 17 patients, 17.5% had a normal examination, 59% had ischemia and 23.5% had necrosis.
2) In women Out of 28 patients, 43% had a normal examination, 46.5% had ischemia and 10.5% had necrosis.

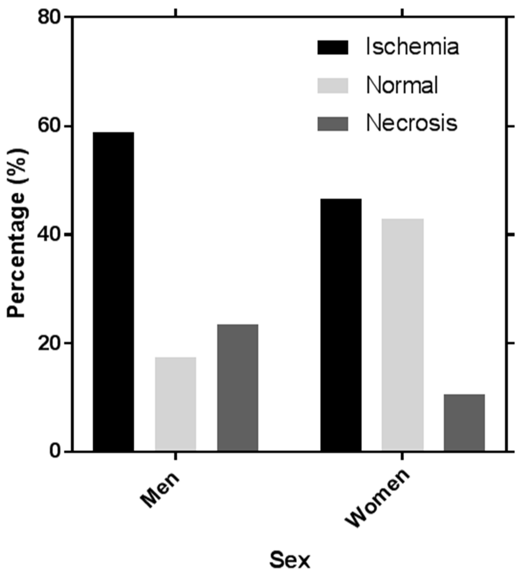


Figure 6. *Distribution of patients according to the pathology observed after the examination.*

4. Discussion

4.1. Choice of Radiopharmaceuticals

Several radiopharmaceuticals are available for the study of myocardial perfusion, the technetium derivatives used in our study and thallium 201 (^{201}Tl). Thallium 201 is a good tracer of myocardial flow and viability. It is said to be a mixed tracer of perfusion and metabolism. However, the physical properties of 99mTc are more advantageous than those of ^{201}Tl because 99mTc has a half-life of approximately 6 hours decreasing the dose delivered to the patient with injected activities ranging from 10 to 20 mci (irradiation of 15mSv) against 2 at 3 mci for thallium (irradiation of 35 mSv), in addition its energy of 140 keV is suitable for scintillation cameras. Finally, its more affordable cost makes it more available in our health structures with very limited financial means. In practice, 2 technical products are available. Sestamibi-99mTc (Cardiolite®) and tetrofosmin labeled with 99mTc (Myoview). They are tracers of coronary flow. The absence of redistribution of these 2 products requires the performance of 2 different injections for the study at exercise and at rest [16, 17].

4.2. Pharmacokinetic Properties of the Radiopharmaceutical and Cardiac Scintigraphic Imaging

The important properties of technetium 99mTc-sestamibi for diagnostic examinations rely exclusively on its binding to certain tissues. The cationic complex 99mTc $[MIBI]^{6+}$ (technetium [99mTc]-sestamibi) accumulates in the healthy myocardium in proportion to the circulation. In the case of a normal myocardial perfusion, the arrival of the radiopharmaceutical at the level of these myocardial cells is ensured by a coronary flow which is not subjected to any constraint during its course at the level of the coronary arteries which ensure the vascularization of the myocardium. A narrowing of the coronary lumen prevents coronary flow from adapting to needs (coronary stenosis). This results in an imbalance between the needs and the oxygen supply of the myocardium. During exercise, the radiopharmaceutical supply in the myocardial cells becomes insufficient (reduction in coronary flow) thus resulting in hypofixation in the mitochondria, and consequently hypofixation visible on the scintigraphic image. At rest, the needs are not enormous. There is a quasi-normalization of the hypo perfusion and consequently, of the fixation of the radiotracer in the event of ischemia. Myocardial infarction is caused by total obstruction of the lumen of the coronary arteries. This results in the death of the myocardial territory due to the absence of blood supply depending on the obstructed coronary artery. Pharmaceutical radios can no longer reach the level of the myocardial cells and therefore there will be no more fixation in the mitochondria. This results in irreversible hypofixation at rest. The elimination of technetium [99mTc]-sestamibi, mainly hepatobiliary, can be the cause of reconstruction artifacts: when these activities are very close and inseparable from the activity coming from a cardiac wall (decreased activity relative to the other walls, masking of a hypoperfused zone) or when these foci are more distant but induce a “shadow effect” during reconstruction, with an artefactual gap on a myocardial segment. For sestamibi, it is desirable to promote the biliary clearance of this tracer by offering a snack rich in lipids (milk, fresh cream, butter, cheese, etc.), approximately 30 min before the start of the acquisitions carried out at rest. The ingestion of 100 to 300 ml of cold water, 5 to 10 min before the acquisition, can also make it possible to reduce the sub-diaphragmatic activity. Although the hepatic clearance of tetrofosmin is faster than that of sestamibi, it has also been shown that the combined ingestion of lipids and a cold drink improves the quality of acquisitions made with tetrofosmin [11, 18–21].

4.3. Evaluation of the Distribution of the Radiotracer in the Myocardium

SPECT gives a 3D view of the myocardium and allows, after reconstruction, an improvement in the contrast of the lesions and the elimination of superpositions of the ventricular cavities. The usual approach is to visually interpret the images to detect hypofixations pointing to ischemia or infarction [22].

An objective characterization of uptake abnormalities based on a measure of relative tracer uptake (ratio of uptake in the suspect region and uptake in the normal region) is likely to improve diagnosis and patient follow-up. The severity of the abnormalities can be assessed qualitatively, but it is preferable to use a semi-quantitative visual method, with a technique of segmentation of the left ventricle. For visual semi-quantitative analysis, it is advisable to take into account only frank and obvious abnormalities of perfusion, and it is then necessary to exclude moderate and suspicious anomalies (uptake greater than 75%) and certain physiological decreases in uptake. which can be observed in the proximal portion of the inter-ventricular septum (region of the membranous septum). It is also advisable to use a segmentation method of the left ventricle. In our study, the 17-segment model, recommended by the American College of Cardiology and the American Heart Association, was used to standardize the interpretation methods for all cardiac imaging techniques. tomography (echocardiography, MRI, tomoscintigraphy, etc.). This model is very easy to use routinely and provides a more accurate estimate of the segmental distribution of left ventricular mass. Above all, its use should allow prescribing cardiologists to better understand the results (this model is also recommended for the interpretation of echocardiograms and MRIs) [23, 24].

The extent of an anomaly can be considered small if it does not exceed 10% of the left ventricle, medium when it affects 11 to 20% of the left ventricle and large when it exceeds 20% of the left ventricle. The use of bull's eyes does not make it possible to dispense with the analysis of sections according to the three standard planes; however, this mode of presentation may better correlate the perfusion images to the anatomy of the coronary network. Several factors can interfere with the quantification of images such as attenuation, diffusion, movement, partial volume effect. It should be noted that the supine position adopted during image acquisition, if it is more comfortable for the patient, is at the origin of attenuation artefacts. The latter are most often present on both stress and rest acquisitions. These are, in particular, lower diaphragmatic attenuations (acquisitions in the supine position, most often in men) and anterior and/or apical breast attenuations (especially in young women) [11, 25, 26].

4.4. Exam Limitations

In general, the patients received in the service do not reach the maximum of stress. In other words, they do not do all the bearings either for reasons of fatigue or feelings of pain. The diagnostic and prognostic performance of myocardial scintigraphy is highly dependent on the quality of the ischemia provocation test to which it is coupled. The stress test is undoubtedly the reference provocation test, but it is necessary to know how to substitute another test, most often pharmacological, when the stress appears contraindicated, impossible or risks being sub-maximal and then leading to false negatives.

5. Conclusion

Our work consisted of labeling a radiopharmaceutical compound and administering it to a patient and monitoring its fate in the body by external detection of gamma radiation. This made it possible to make a diagnosis of ischemia or myocardial necrosis in 57% of cases in women and 82.5% of cases in men. Thanks to the qualitative visual interpretation of the distribution of the tracer, a diagnostic aid was provided by the semi-quantitative analysis provided by the study of the polar maps (bull's eyes). The performance of these scintigraphic techniques are often decision-making tools in cardiology and generally guide the cardiologist's diagnosis. The quality of imaging is highly dependent on compliance with the preparation and administration protocol. Changes in tracer elimination kinetics by reducing extracardiac fixations also contribute to improving the quality of imaging. Proper management of radiopharmaceuticals encompassing its supply, transport and storage is essential for the sustainability of activities to meet the needs of populations.

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