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DOSIMETRY IN MYOCARDIAL PERFUSION IMAGING

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ABSTRACT

This paper conducts a dosimetric investigation on the myocardial perfusion image protocol, together with a literature reviewing, motivated by the significant statistic increasing on mortality, morbidity and disability associated with cardiovascular disease, surpassing infectious diseases. Nuclear Cardiology plays a role n the diagnostic functional evaluation of the heart and in the prognostic of patients with suspected or known cardiac ischemia. In the context of unstable myocardial ischemic syndrome, myocardial perfusion cintigraphy is a non-invasive procedure performed by administering a radiopharmaceutical targeted to the heart. As tool for this study are that the images obtained by thoracic angiotomography and abdominal aorta as a anatomic and functional information for model reproduction in SISCODES – System of Codes for Absorbed Dose Calculations based on Stochastic Methods. Data were manipulated in order to create a voxel computational model of the heart to be running in MCNP – Monte Carlo Neutron Particle Code. . It was assumed a homogeneous distribution of Tl-201 in cardiac muscle. Simulations of the transport of particles through the voxel and the interaction with the heart tissue were performed. As a result, the isodose curves in the heart model are displayed as well as the dose versus volume histogram of the heart muscle. We conclude that the present computational tools can generate doses distributed in myocardial perfusion.

1. INTRODUCTION

In the early twentieth century, cardiovascular disease (CVD) accounted for less than 10% of all deaths worldwide. In the end of the century, CVD was responsible for nearly half of all deaths in developed countries and 25% in developing countries. In 2020, CVD will be responsible for 25 million deaths annually, and coronary artery disease (CAD) will overtake infectious diseases as the world's number one cause of death and disability. [3]

In Brazil, cardiovascular diseases account for 26.6% of total recorded deaths, ranking the first place when considering only those over 50 years. In recent years, there is an increase in patient survival, because of the possibility of early and late recanalization by percutaneous coronary intervention and thrombolytic revascularization. The proper selection of patients with coronary artery disease (CAD) in acute and chronic diagnostic procedures is based in part on the perception of the extension of affected myocardium, but potentially viable, with the aim of reversing ventricular dysfunction. [8]

The overall increase in CVD is the result of the drastic change in health status of individuals during the twentieth century. Before 1900, infectious diseases and malnutrition were the most common causes of death. These have gradually been

supplanted, in some countries, for chronic diseases such as cardiovascular disease and cancer, thankful in large part to nutrition improvement and public health measures. These changes are called epidemiological transition, and it never occurs in isolation, but intertwined with changes in public and personal health (economic transition), social structures (social transition) and demography (the demographic transition). And, as the transitions are linked to the evolution of social and economic forces, this changes comes at different speeds around the world. During this era, the increased caloric intake (particularly saturated fats from animal and manipulated vegetable fats), the reduction of daily physical activity, the large smoking rates associated with diabetes and hyperlipidemia cause further increases of hypertensive disease and rapid increases in CVD and peripheral vascular disease. [3]

Despite improvements in health technology and better access to these decreases the likelihood of death among patients with acute manifestations of atherosclerotic disease, better survival means that more and more individuals are living for a longer period with CVD such as angina pectoris, congestive heart failure and cardiac arrhythmias. [3]

1.2. Myocardial Perfusion Scintigraphy

On this scintigraphy, a radiopharmaceutical is injected through a peripheral vein and was subsequently captured by myocytes - cells of the heart. This process is called myocardial perfusion. In many parts of the heart, the injected radioisotope emits radiation that is converted into a luminous image (flicker), observed through a cardiac CT. The images are obtained in two stages: rest and stress when there is increased blood flow to the heart. Radiopharmaceuticals, accumulate in proportion to regional myocardial blood flow, is analyzed for a decreasing in the intensity of radioisotope uptake in some part of the heart muscle. When this uptake is transient, coronary ischemia is point out; when it is persistent, fibrosis is the situation. Thus, myocardial perfusion imaging allows you to search the viable areas of the case, separating the viable areas from those involved on the treatment. In this case, the search is called myocardial viability. [1]

The first scintigraphic myocardial perfusion was acquired in 1944 by Carr et al. based on cesium-131. Potassium-43 was used in 1973 by Zaret et al. It was possible to visualize the myocardial ischemia on induced stress. Analogue of potassium, thallium-201 (^{201}Tl) became available in 1974 and has been used successfully for over 25 years. In the early 90s, new compounds labeled with technetium-99m (^{99m}Tc) with new biological properties were introduced to assess myocardial perfusion. Any of these perfusion agents can be used to visualize the relative distribution of myocardial blood flow. The absolute quantification of myocardial blood flow is not possible with CT images and single photon emission tomography (SPECT), but can be performed with positron emission tomography (positron emission tomography - PET). [3]

The most important clinical application of myocardial perfusion imaging on stress is the assessment of ischemic heart disease. Studies show diagnostic use with exercise applying 201-Tl or 99m-Tc labeled agents. Generally, the correlation between the results of stress myocardial scintigraphy and angiography findings of coronary artery with contrast is good. There is sufficient evidence that the finding in perfusion scintigraphy with stress reflects the hemodynamic and functional stenosis of the coronary artery, providing important prognostic information. [2]

In 1999, close to five million myocardial perfusion imaging with stress were conducted in USA. On these studies, 65% were performed in conjunction with exercise and 35% after pharmacological vasodilatation. Regarding the stress images, 75% were acquired with ^{99m}Tc labeled compounds and 25% with ^{201}Tl. Tomography with single photon emission imaging technique was predominantly used in more than 90% of the studies. [2] Figure 1 illustrate the SPECT imaging following heart representation.

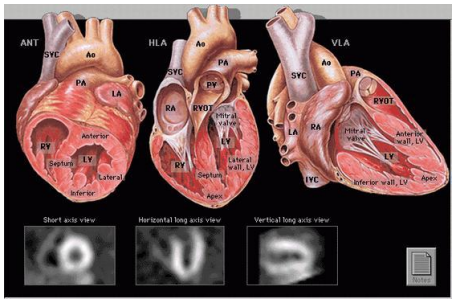

Figure 1. The SPECT imaging. Source: www.coracaosaudavel.com

1.3. Indications to myocardial perfusion

There are several indications for myocardial perfusion scintigraphy. The main ones are for the diagnosis of myocardial ischemia due to coronary disease in patients with intermediate pretest probability. Examples are asymptomatic patients with positive exercise test, symptomatic patients with normal stress test, and women with atypical angina, among others. [10]

In patients with known coronary disease, scintigraphy is important in assessing the impact of ischemic lesion boundary (30 to 60% obstruction by coronary angiography). Coronary artery disease is important in risk stratification and prognostic evaluation of patients with stable angina, and consequently aid in the treatment decision (surgery versus clinic). [10]

It is also important in risk stratification after AMI (Acute Myocardial Infarction) and unstable angina and risk stratification for patients who will undergo non-cardiac surgery (especially vascular). It also includes the evaluation of ischemia after myocardial revascularization or angioplasty - detection of restenosis or complications. [10] Myocardial viability can be investigated in patients with ischemic cardiomyopathy with ventricular dysfunction. Early diagnosis of ischemia can be performed in chest pain units. The evaluation of ischemia can be taken in the pediatric population in cases of congenital coronary anomaly and Kawasaki disease [10]. Also, it can be indicated to evaluate left ventricular function in heart failure, to identify viable areas of the heart muscle and monitoring of patients receiving chemotherapy with doxorubicin, to evaluate cardiac function after heart transplantation and heart valve disease. [10]

Within the ischemic syndrome - ACS, myocardial perfusion scintigraphy is emerging as an important tool in estimating the functional significance of angiographic coronary stenoses, to evaluate the effectiveness of therapeutic interventions, and risk stratification after myocardial infarction. However, the ability of nuclear cardiology in predicting the

occurrence of acute phenomena (fissure / plaque rupture with thrombosis), is still limited, although it has been the subject of intense research and new. [9] Studies have shown that individuals with a resting myocardial scintigraphy considered low risk, held in emergency, determines a risk of subsequent cardiac events reduced. On the other hand, patients with a high risk of scintigraphy are likely to develop acute, being revascularization (surgery or angioplasty) or coronary artery disease presenting to coronary angiography. [9]

1.4. Radiopharmaceuticals

Radiopharmaceuticals are radioactive chemical compounds used for diagnose and therapy. In nuclear medicine, about 95% of the radiopharmaceuticals is used for diagnosis and 5% for treatment. Since they are administered to humans, they must be sterile, pyrogen free agents and subject to all necessary measures for quality control like a conventional drug. [6]

The radiopharmaceutical can be a radioactive element such as Xe-133, or an I-131-iodine labeled compound, or Tc-99m labeled protein It consists of two components, a radionuclide and a pharmaceutical. Its usefulness is dictated by the characteristics of its components. The pharmaceutical is chosen based on their localization in organ and its involvement in the physiological function of the organ. [6]

1.5. Thallium – Tl-201

Provided by cyclotron, thallium-201 has a half life of 74 hours, generating, in their process of decay, predominantly the X-ray radiation of 69 to 83 keV, plus a gamma radiation of 166 keV and 135 keV. As a flow tracer, once injected intravenously, the thallium-201 chloride is distributed to almost all body tissues (except brain, due to their failure to transpose the blood-brain barrier) in proportion to the regional blood flow and accumulates mainly in the myocardium, kidneys, liver, intestines and skeletal muscles.

When administered to an individual at rest, the myocardial uptake of thallium-201 is rapid, with about 90% of the uptake occurring in the first pass. This chemical collecting uses active transport mechanisms by the sodium-potassium pump and passive diffusion dependent on the transmembrane electrical potential gradient. When compared to the agents labeled with technetium-99m, the extraction of thallium-201 myocardial correlate more linearly with the increase in coronary flow and remained so until this stream reach two times the background.

A hallmark of thallium-201 is its ability to redistribute, also called the phenomenon of redistribution. This property makes it possible to evaluate the flow changes induced by stress (physical or pharmacological), with images obtained immediately after administration of the agent in this step, and compare them to images taken several hours later (on average 4 hours). As a result of the redistribution that occurred during that period of repose, the hypoperfused areas during the stage of stress tend to standardization in relation to areas normoperfused, once at rest the changes of coronary flow tend to be smaller than under stress.

This transience of the perfusion defect in stress observed in relation to the rest is usually interpreted as indicative of ischemia, whereas the persistence of low uptake in a given

segment can translate fibrosis or hibernating or stunned myocardium. Given these possibilities, often it is necessary an additional dose of the radiotracer or reinjection, usually at the reallocation of images for the characterization of viable myocardium.

Traditionally used in myocardial perfusion imaging thallium-201 has recently been employed less as a result of its energy profile less favorable and long physical half-life that limits the dose used, with advantages for agents labeled with technetium-99m. However, it is still used in ischemic heart disease due to the long experience, some centers, this agent is of choice. [11]

After injection at peak exercise, Tl-201 accumulates rapidly in the myocardium irrigated by normal coronary arteries and subsequently suffers a slow bleaching. In normal patients, 2 h after injection, there is a clearance of approximately 30% and after 4 h, 35%. The rate of clearance of Tl-201 is related to heart rate at peak exercise, exercise duration and serum (or concentration in the blood) of Tl-201. The kinetics in the ischemic myocardium is variable. In case of significant coronary artery stenosis, the initial uptake of Tl-201 during the year is lower when compared with the normal myocardium. Soon after, bleaching in ischemic tissues is lower than normal, may occur in their accumulation over time. Thus, ischemic perfusion defects normalizes or “fill up" after some time. The initial uptake of Tl-201 or fibrosis in the infarcted myocardium is significantly lower than in normal myocardium [3].

1.6. SPECT - Single Photon Emission Computed Tomography

The SPECT uses a gamma camera to acquire images. To capture the image of the SPECT gamma camera is rotated around the patient. Multi-dimensional images are captured 2D - the patient's body. The radiation is collected at defined points during the rotation, typically every 3-6 degrees. In most cases it is given a rotating gamma camera with 360 degrees to achieve optimization in the reconstruction. The time of capture, at each point varies but is usually 15 to 20 seconds. This gives a total time of examination between 15 and 20 minutes. Since most modern machines have more than one head (part of the machine that contains all the detection system). The more heads you have the machine; it will capture a larger area radiation simultaneously.

Images can be black and white or color, depending on the exam. The color images are more common in surveys that show the brain and heart. The resolution is 64x64 or 128x128 pixels, each pixel representing a portion of 3-6 mm of the patient's body. The image resolution depends on energy, if energy is too low, are more likely to happen the other events of detection than the ideal (Detection of Scattering, Scattering Object and Septal Penetration); the thickness of the crystal not may be too thick. You must have an ideal thickness, for if there is a higher probability of happening, especially the scattering event detection. Efficiency of collection, if collection is not very efficient, there will be harm to the image. Consequently, the physician who will review the examination could not see a cancer, for example, that the patient may have, but due to low collection efficiency, the image was not optimal. The distance is directly related to collection efficiency.

The shorter the distance, the higher is the collection efficiency. That is why, upon examination, the machine heads are brought closer to the patient. Each type of hole has its field of capture. The parallel-hole collimator captures radiation from an area just

their size. The converging-hole collimator captures radiation in an area smaller than him, and he has a funnel shape. And the divergent collimator captures radiation from an area larger than him; he has the shape of a fan.

Myocardial perfusion images are interpreted qualitatively by visual analysis, often with computer quantification. By submitting normal, a diffuse homogeneous uptake, a defect is a localized myocardial area with fewer uptakes than normal; the defects can vary in intensity from mildly reduced to almost complete absence of uptake. It is considered reversible defects if present in the initial phase of stress disappears or decreases in intensity in the resting phase, or in the delayed images. This pattern indicates myocardial ischemia. Improvement over time in images with Tl-201, then it is called redistribution, except for compounds marked with Tc-99m. [3]

When a defect is present in the stages of exercise and rest or delayed images, and that does not change, then its fixed defect. This pattern usually indicates infarction and fibrotic tissue. However, in some patients, fixed defects in the images with Tl-201, 2h to 4h after the injection, have better capture images in 24 hours or redistribution after reinjection at rest. Likewise, a fixed defect with agents labeled with Tc-99m (which involves injection at home) may underestimate myocardial viability. [3]

The image pattern called redistribution reversal occurs mainly in images with Tl-201. However, a "reverse defect is occasionally observed with agents labeled with Tc-99m. The image shows the initial stress of a defect or a normal pattern, while the rest or delayed images show a new defect or a defect still more serious. This pattern is often occurs in patients with myocardial infarction undergoing thrombolytic therapy or percutaneous coronary artery angioplasty. The phenomenon is possibly caused by an excess of the initial uptake of tracer in a reperfused area with a mixture of necrotic and viable myocytes. The initial accumulation is followed by a rapid clearance of necrotic tissue. Although the role of this finding is controversial, it represents no evidence of stress-induced ischemia. With PET using fluorine-18-fluorodeoxyglucose (FDG), the presence of viable myocardium has been demonstrated in the areas of reverse redistribution. [3]

Regarding the pulmonary uptake usually no or very little activity is seen in the lung fields in post-exercise images. Increased pulmonary uptake can be quantified correctly lung / heart, which presents normal values lower than 0.5 for Tl-201 and less than 0.45 for Tc-99m-sestamibi. This image pattern indicates abnormal left ventricular dysfunction and severe stress-induced coronary artery disease, and indicates a poor prognosis. When the left ventricle appear larger in images from exercise to rest in pictures or late, may indicate transient left ventricular dilation, and this pattern of expansion also indicates left ventricular dysfunction-induced stress, it has been suggested that, instead of a real increase in left ventricular volume, the cause of this pattern would subendocardial uptake of the radiotracer and thus apparent thinning of the myocardium in stress images. [3]

Usually, the right ventricle is only slightly seen in the home or in stress myocardial perfusion SPECT images. The myocardial mass and blood flow of the right ventricle are approximately 50% lower than the left ventricle. The increased visualization of the right ventricle at rest is abnormal and in most cases indicates hypertrophy of it. When this pattern occurs in images on exercise, is associated with severe coronary artery disease

[3]. The diagnosis of silent ischemia is established in the change detection objective and characteristics of myocardial injury. Among the methods are configured primarily to stress electrocardiography, ambulatory electrocardiographic monitoring, and treadmill test with thallium-201 perfusion and stress echocardiogram.

1.7 MCNP - Monte Carlo N-Particle Transport Code

The Monte Carlo method can be used to simulate theoretically a statistical process, as the interaction of particles with nuclear materials, and is particularly interesting for solving problems of nuclear transport complexes that cannot be modeled by codes based on deterministic methods. In particle transport, the Monte Carlo technique is to follow each of many particles throughout his career until some terminal event such as absorption, escape, among others. The three-dimensional simulation of the transport of nuclear particles is an important tool for improving procedures radiotherapy in oncology. [10]

1.8 SISCODES

The SISCODES – System Codes for Absorbed Dose Calculations for Method Stochastic is a computer program recently developed by the group NRI – Research Center for Radiological – UFMG, registered in the CNPq, the purpose of creating computational voxel models for use in simulations computational protocol of irradiation in the code MCNP. [11]

After completing the construction of the voxel model, the SISCODES converts the model into a format understood by the MCNP, and then working as an interface to this code. Thus, the simulation of the treatment is done in the MCNP code, where the transports of particles through the interaction of the voxels and with the tissue are evaluated. The MCNP returns to the data obtained after the simulation, the number of incident particles per unit area (fluency) or the absorbed dose in each voxel. With this data and the voxel model built, the SISCODES is able to generate isodose curves in the model presented in colors that represent the percentage of fluency or absorbed dose, depending on what was requested in the MCNP simulation. [11]

2. MATERIALS AND METHODOS

2.1 Voxel model construction and adjustments.

A set of contrasted CT images of a heart with normal morphology are selected. The contrast is important in order to allow separation among the various cardiac structures. The images are taken from a set of CT sections of an adult chest. Sixty images, each one representing a 2mm layer, were selected from 355 axial slices of the CT, including the region of interest (heart and part of the mediastinum) [10]. The CT images were obtained in DICOM (Digital Imaging and Communications in Medicine) which is the standard for medical images storage and transmission [11]. The select image set was trimmed limiting the heart region. Those were converted to a voxel model of tissues by SISCODES (Computational system for dosimetry in neutron and photon based on stochastic methods).

At first, the tomographic images are converted into a three dimensional model based on the grayscale of each image region. This model is then "filled" by the tissues identifying each structure with the aid of the gray tone of the image. The available tissues had its chemical composition and mass density previously entered into a database, as well as nuclear information, based on data from ICRU-46. Each tissue has also an associated color, which allows the identification of the distinct tissues used in the model. After identifying each tissue and organ in the model, the myocardial perfusion protocol can be simulated.

The images were converted from DICOM to JPEG format since the original format was not compatible with the SISCODES. After images conversion, the grayscale model was prepared and the model was “filled” with tissues corresponding to the various structures of the heart. Knowledge of the heart anatomy was required. The tissues used in the model were previously stored in the SISCODES database.

2.2 SPECT - Single Photon Emission Computed Tomography

A set of images from a SPECT myocardium image was used to guide the radio source distribution in the cardiac muscle. A maximum uptake time was used to get the source distribution.

2.3 Source Distribution

A set of voxels from myocardic muscle is selected to receive a distributed source of Tl-201. For each selected voxel a source was defined. The gamma source from Tl-201 was specified from literature (ENSDF Decay Data in the MIRD - Medical Internal Radiation Dose).

3. RESULTS

It was assumed a homogeneous distribution of Tl-201 in the heart muscle. As a result, the isodose curves in the voxel model of the heart are presented, as well as the histogram versus dose volume of the heart muscle.

Figure 1 shows respectively the cardiac tomography imaging, heart in voxel model and colored in isodose curves. Highlighted in red to the heart muscle and green water to the coronary artery. Table 1 represents percentage absorbed dose of value maximum of dose in isodose curves.

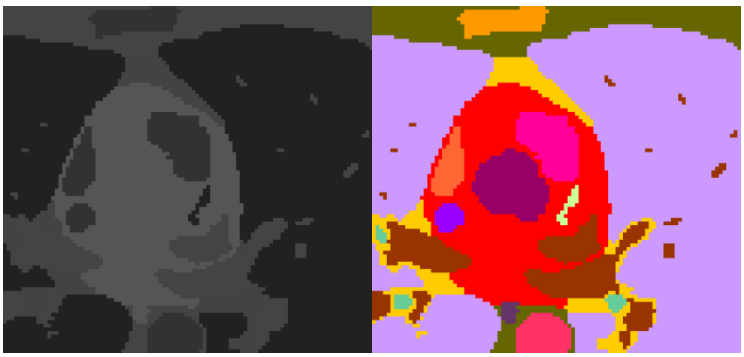

Figure 1. Images of the heart respectively in computed tomography, voxel SISCODES. Read areas on model represents the heart muscle and white is the coronary artery.

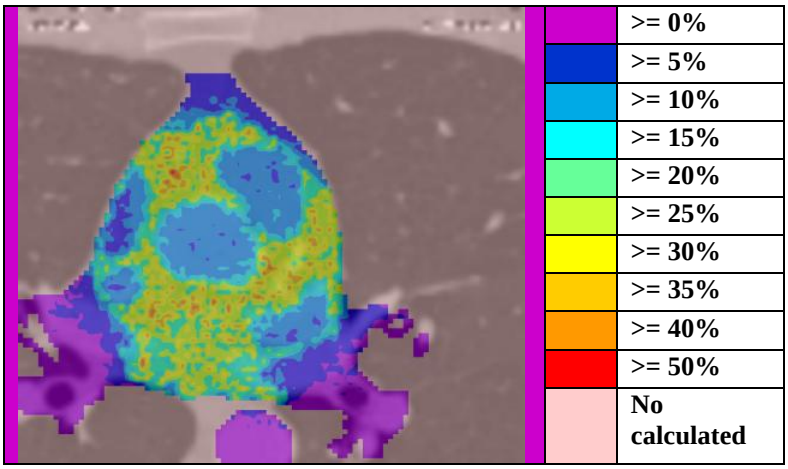

Figure 2. Isodose areas on a heart section, following by the percentage absorbed dose of maximum value.

The percentage of absorbed dose represented by isodose curves is based on a maximum value which in this case was $2.11\text{-}10^{-11}$Gy/transition. All values are normalized to the maximum value. This value can be multiplied to the patient´s injected activity, in Bq, and the percentage of heart uptake of that same patient, in %, in order to have values in unit of absorbed dose rate in Gy/s. The dose rate can be converted to dose multiplying by 1.44 and the effective half-live of the nuclide on the heart, in seconds. The effective half-life of the nuclide on the heart depends on the patient´s physiologic stage.

One can see that the dose deposition occurred evenly in the regions that represent heart muscle and coronary colored areas in red and green in the voxel model and warmer areas considered in the model of isodose curve. Indeed, the isodose are so disperse on the heart muscle that it cannot be easily interpreted. Therefore, a histogram dose versus volume may be applied.

Figure 2 represents the histogram that shows the relationship between the percentages of absorbed dose to the volume percentage.

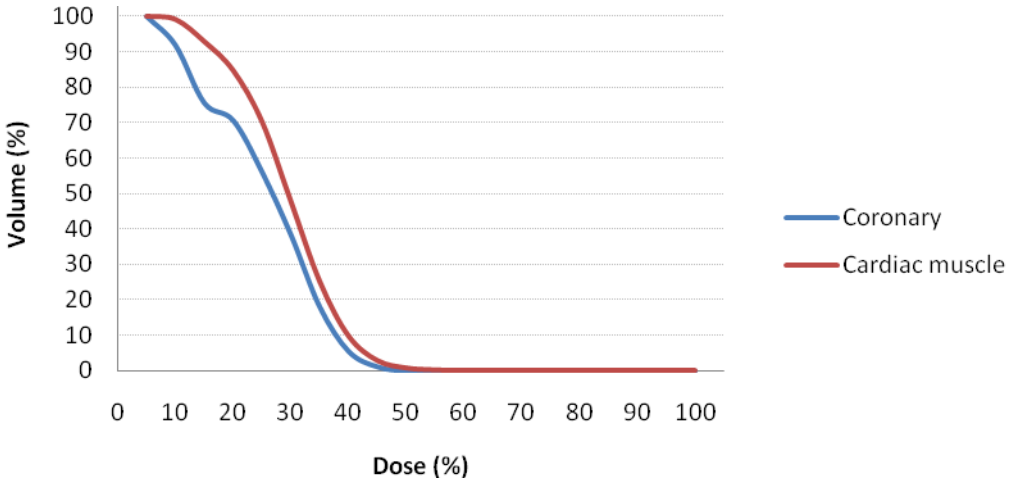

Figure 2. Histogram versus dose volume

A value of 100% of volume received 5% of the maximum dose. For the following occurs coronary 80% of volume received 15% of dose maximum, 70% of the volume received 20% of dose maximum, 60% of volume received 25% of dose maximum, 40% of volume received 30% of dose maximum. While for the heart muscle is 80% of volume received 20% of dose maximum, 70% of volume received 25% of dose maximum, 60% of volume received 30% of dose maximum, 40% of volume received little more than 30% of dose maximum.

The heart muscle received a greater percentage of the maximum dose when compared to percentage of dose received by the coronary artery.

4. CONCLUSIONS

As conclusion, the present computational tools are capable of generating doses distributed in myocardial perfusion image protocol. Further studies involving real patient´s images shall be done to obtain dosimetric data for each case. Specially, effective half-live of the radiopharmaceutical on the heart is need to measure in order to accomplish this methodology.

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