Sudan University of Science and Technology

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Evaluation of ^{201}Thallium and ^{99m}Tc-Sestamibi Radiopharmaceuticals in detection of Ischemic Heart Disease

تقييم المواد الصيدلانية المشعة الثاليوم ^{201} والتكنيشيوم^{99م} المحضر بمادة السيستاميبي في الكشف عن مرض إفتقار الترويه الدموية للقلب

A thesis submitted for fulfillment of PhD degree in Nuclear Medicine

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بسم الله الرحمن الرحيم

{إِنَّ اللَّهَ وَمَلَائِكَتَهُ يُصَلُّونَ عَلَى النَّبِيِّ يَا أَيُّهَا الَّذِينَ آمَنُوا صَلُّوا عَلَيْهِ وَسَلِّمُوا تَسْلِيماً}

سورة الأحزاب الآية 65

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Dedication

To my dearest parents,Dr.Thuraya Mohammed Ahmed, Assoc.Prof.Dr.Adam Bakheet Mabrook, for my brother's soul Waddah, To my brothers Dr.Wael,Dr.Eng.Wafi, Dr.Waleed, and my lil sister Wafa,To our lovely family,To my friends and colleagues, To anyone who have taught me a word, I dedicate this humble work.

Abstract

Ischemic heart disease (IHD) recently have been consider as one of the major reasons of morbidity, it's defined as reduction of blood supply to the heart muscle, which is supplied by the coronary arteries in case of partial or complete occlusion in one or more of the coronary arteries the myocardial tissues begins to die, Nuclear Medicine plays an important role in detection of ischemic heart disease either reversible or irreversible (IHD), using a dedicated radiopharmaceuticals in detection clinically, the most commonly used radiopharmaceuticals are ^{99m}Tc-Sestamibi,^{99m}Tc-Tetrofosmin and ^{201}Tl .

This study focused on using counts/second /pixel(c/s/p),reversibility% among arteries i.e. LAD,LCX and RCA in evaluation of ^{99m}Tc-MIBI and ^{201}TL biodistribution in both conditions of stress and rest, and the factors affecting reversibility such as age, gender and obesity ,in addition to prevalence among genders, in the period from Feb.2014 until Jun.2016 a sample of one hundred and fifty patients with known ischemic heart disease (IHD) underwent Myocardial perfusion imaging (MPI) , using the slandered Bruce protocol of exercise and applying one day protocol, patients were classified into two groups Group(I): A sample of 73 patients (42 males) (31 Females)) were administrated with ^{99m}Tc-MIBI Group (II) :A sample of 77 (56 males) (21 females) injected with 74 to 111 MBq (2 to 3 mCi) of ^{201}TL,the obtained data was analyzed using QPS,Cedar , and Excel retrospectively.

The study results showed that the radiopharmaceuticals used in nuclear medicine have great capability to detect ischemic heart disease and Tl^{201} is the preferable radiopharmaceutical for detection of (IHD), Left anterior descending artery (LAD) is the most involved artery in ischemic heart disease, and the preferable radiopharmaceutical for detection of coronary artery disease is ^{99m}Tc-Sestamibi ,the study also revealed that the age of risk for this disease is 50-70 years , and the other factors such as obesity has a huge negative effect on development of IHD, the study also showed that the percentage of prevalence of IHD is higher among men in relevant to women and the reversibility among men is less in comparison to women and prevalence risk is relatively the same for both genders at the age after seventy years.

مستخلص

أعتبر مرض افتقار التروية الدموية للقلب مؤخرا أحد الأسباب الأكثر تسببا في الوفاة,حيث يؤدي نقص التروية الدموية للقلب والتي تتم عن طريق الشرايين التاجية إلى تلف النسيج القلبي في حال الإنسداد الجزئي او الكامل في أحد أوأكثر من الشرايين التاجية, يلعب الطب النووي دوراً هاما في الكشف عن مرض إفتقار التروية الدموية للقلب سواء كان النسيج القلبي قابلا للإسترجاع وظيفته اولا وذلك باستخدام المواد الصيدلانية المشعة المخصصة للكشف الإكلينيكي للقلب وتعتبر المواد ^{99م} تي-سي-سيستاميبي و^{99م} تي سي تيتروفوزمين والثاليوم ^{201} من اشهر المواد الصيدلانية المشعة المستخدمه لهذا الغرض, ركزت هذه الدراسة على حساب الكاونت\ثانية\بيكسل ونسبة الإسترجاع لوظيفة العضلة عبر الشرايين التاجية الثلاثة الرئيسية لتقييم انتشار المواد الصيدلانية المشعة ^{99م} تي-سي-سيستاميبي والثاليوم ^{201} في حالة الإجهاد العضلي القلبي والإسترخاء العضلي القلبي , ودراسة العوامل المؤثرة على نسبة الإسترجاع كالعمر والجنس والسمنه بالاضافة الى معدلات الإنتشار بين الجنسين في الفترة من فبراير2014 الى يوليو 2016 تم جمع عينة من 150 مريض يعانون من مرض افتقار التروية الدموية للقلب وباستخدام قياس بروس للإجهاد العضلي القلبي وبروتوكول اليوم الواحد, تم تقسيم المرضى الى مجموعتين ,مجموعة(أ) 73 مرييض منهم 42 رجال و 31 امراءة حقنت بمادة ^{99م} تي سي سيستاميبي ,محموعة(ب)77 مريض منهم 56 رجل و 21 امرأءة حقنت بمادة الثاليوم^{201} في حالتي الإجهاد والإسترخاء جمعت البيانات بأثر رجعي وحللت باستخدام برنامج سيدار و كيو بي اس ومن ثم اكسل ,وقد خلصت نتائج الدراسة إلى أن المادة الصيدلانية المشعه المستخدمة في الطب النووي لها مقدرة كبيرة في الكشف عن مرض افتقار التروية الدموية لعضلة القلب وأن الثاليوم ^{201} هي المادة المفضلة للإستخدام في الحالات المصابة بهذا المرض,كما أن الشريان الأكثر تسببا بهذا المرض هو الشريان التاجي الأيسر الأمامي,والمادة الصيدلانية المشعة المفضلة في حالات ماقبل تلف النسيج القلبي هي مادة ال تي سي سيستاميبي وخلصت النتائج أيضا إلى أن العمر الخطر لتطور المرض هو مابين 50-70 سنه, كما أن العوامل الأخرى كالسمنة لها أثر سلبي كبير في تطور الموضحت الدراسة أيضا ان نسبة المصابين بالمرض في الرجال أعلى بالمقارنة بالنساء وان نسبة عدم المقدرة على استعادة النسيج القلبي التالف أعلى في الرجال بالمقارنة منه في النساءمع تساوي خطر الإصابة تقريبا بين الجنسين في عمر مابعد السبعين.

List of Abbreviations

Abbreviation	Medical term
^{99m}Tc	Technetium pertechnitate
IHD	Ischemic Heart Disease
CAD	Coronary artery disease
MI	Myocardial Infarction.
WMA	Wall Motion Abnormalities
MIBI	Methoxy Isobutyl Isonitrile
^{201}TI	^{201}Thallium Chloride
MPI	myocardial perfusion imaging
RICK	Radiotherapy & isotope center Khartoum...
LAD	Left Anterior descending Artery
RCA	Right Coronary Artery
LCX	Left circumflex Artery
AHA	American Heart Association
RA	Right Atrium
LA	Left Atrium
SVC	Superior Vena Cava
IVC	Inferior Vena Cava
PT	Pulmonary Trunk
CA	Coronary Arteries
RCA	Right Coronary Artery
LCCA OR LCX	Left Circumflex Coronary Artery
AV	atrioventricular
EDV	End Diastolic Volume
LAD	Left Anterior Desending Artery
LV	Left Ventricle
ROI	Region Of Interest.
RV	Right Ventricle
ESV	End Systolic Volume
SV	Stroke Volume
Ca+	Calcium at first oxidation state
ATP	Adenosine Tri-Phosphate
VO2	Oxygen Volume.
T	Total time on the treadmill
QGS	Quantitative Gate SPECT
QPS	Quantitative Perfusion SPECT
CSMC	Cedars-Sinai Medical Center
MOCO	Motion Correction
QBS	Quantitative Blood Pool SPECT
QARG	Quantitative Automated Report Generator
CAT	Computed Angiography Tomography
MRI	Magnetic Resonance Imaging.
PET	Positron emission tomography
AC	Attenuation Corrected
TPD	Total Perfusion Deficit
QA	Quality Assurance
GFADS	Generalized factor analysis of dynamic sequences.
MUGA	Multi-Gated Acquisition
SPECT	Single Photon Emission Tomography

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CHAPTER ONE

1.1 Introduction:

Ischemic (or ischemic) heart disease is a disease characterized by reduced blood supply to the heart, Ischemia means a "reduced blood supply", The coronary arteries supply blood to the heart muscle and no alternative blood supply exists, so a blockage in the coronary arteries reduces the supply of blood to heart muscle, Most ischemic heart disease is caused by atherosclerosis, usually present even when the artery lumens appear normal by angiography, Initially there is sudden severe narrowing or closure of either the large coronary arteries and/or of coronary artery end branches by debris showering downstream in the flowing blood, Coronary artery disease (CAD) is presenting the start of many cardiomylopathies including reversible and irreversible ischemic diseases or myocardial infarction (MI), This disease is also affecting the myocardium wall motion causing wall motion abnormalities (WMA) due to lack of blood supply to different myocardium territories, ^{201}Thallium (*half-life ~72 hr emitting 70~80 Kev*) is considered as highly specific agent in detection of perfusion deficits of the myocardium in patients with severe coronary artery disease (CAD) compared to Methoxy Isobutyl Isonitrile (MIBI) which can be labeled with ^{99m}Tc (*Technetium half-life ~ 6 hrs emitting 141 Kev*) known as Sestamibi or Cardiotle, also proven high specificity and sensitivity in detection Ischemic

heart disease (IHD), Nevertheless, the prognostic values of both radiopharmaceuticals (^{201}Thallium-^{99m}Tc-Sestamibi) depending of their biodistribution over particular myocardium territories is a matter of debate (*Ayalew A et al, 2000*), investigations with the isonitrile complexes have shown them to undergo pattern of biologic distribution different from that of ^{201}TI *(*Raymond Taillefer *et,al.1997),* Another study revealed that patients could be shown to have significantly higher heart-to-lung ratios as compared to those in both other groups, both heart-to lung- and heart-to-whole body ratios tended to decrease with a higher degree of CAD *(Agnieszka Manka-Waluch et,al 2007)* . Ischemic Heart diseases are appearing as hypo intense areas throughout the heart segments acquired in nuclear medicine procedure of myocardial perfusion imaging (MPI)according to their specific territories within the myocardium, including Left Anterior descending Artery (LAD), Right anterior descending Artery (RCA) (*Figure 1.1*), and Left circumflex Artery (LCx) *(Figure 1.2),* which are divided into 17 segments as per the American Heart Association (AHA), are excellent tools to evaluate the performance of both agents within resulted perfusion deficits or ischemic portions throughout the myocardium for the patients with CAD in correspondence to their respective territories.

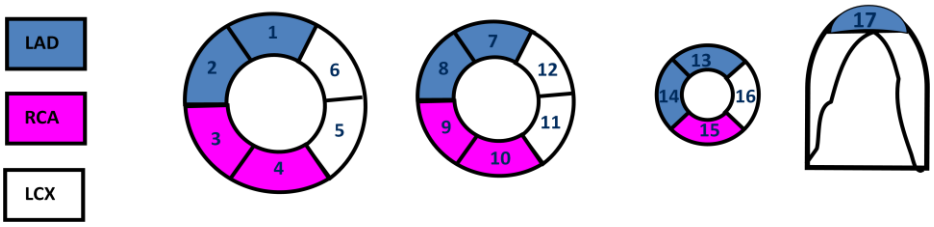


Figure 1.1. Shows different myocardium territories as per AHA classification

1.1.1 Reversible Myocardial ischemia and Myocardial infarction (MI):

Reversible myocardial ischemia is a term used to indicate that a person's heart can be saved with intervention before an event like a heart attack. Typical intervention is a stent or bypass, in nuclear medicine interpretations, If the amount of tracer in a particular segment is observed to be relatively low on the stress image and then increases at rest, known as a reversible defect, this is taken as showing ischemia. If there is a fixed defect in both stress and rest this is considered as irreversible myocardial ischemia or (MI).

1.2 Problem of the study:

Ischemic heart disease is considered as the highest mortality and morbidity disease among both genders, However, the capability to detect such disease using different imaging modalities are increasing , Specifically , Myocardial perfusion imaging (MPI) using Nuclear Medicine and Magnetic resonance imaging in order to evaluate the extend of ischemic portion of the heart, However, using radiopharmaceutical of choice in detection of such disease remains a matter of debate, due to several factors that may affect the reversibility and bio distribution of radionuclides, or labeled tracers during the process of detection, The specific impact of ischemia on the myocardial kinetics of ^{201}Thallium and ^{99m}Tc-MIBI remains a matter of debate(*Ayalew A et al, 2000*),those factors are including Age, Obesity, and prevalence among different genders, Although several ^{99m}Tc-Labled agents have been developed , However, Recent published researches have shown variable results of tracers kinetics when applied on patients suffering from CAD, One of the interesting studies in this regards compared ^{99m}Tc-Labled agents with ^{201}Thallium, However, the studies revealed that patients could be shown to have significantly higher heart-to-lung ratios using ^{99m}Tc-Labled agents as compared to ^{201}Thallium,But, also pointed that both heart-to lung- and heart-to-whole body ratios tended to decrease with a higher degree of CAD *(Agnieszka Manka-Waluch et,al 2007)* ,

1.3 Objectives of the study:

1.3.1General Objective:

To evaluate ^{201}Thallium and ^{99m}Tc-Sestamibi Radiopharmaceuticals effectiveness in detection of Ischemic Heart Disease (IHD**)**

1.3.2 Specific Objectives:

- To evaluate Coronary arteries reversibility % i.e. (LAD) (RCA) and (LCX) using ^{99m}Tc-Sesatmibi in patients suffering from (IHD)
- To evaluate Coronary arteries reversibility % i.e. (LAD) (RCA) and (LCX) using ^{201} TL in patients suffering from (IHD).
- To evaluate GIT to heart ratio -Lung to heart ratio % and affected territory within myocardium – to heart ratio using ^{99m}Tc-Sesatmibi in patients with (IHD).
- To evaluate GIT to heart ratio -Lung to heart ratio % and affected territory within myocardium – to heart ratio using ^{201}TL in patients with(IHD) .
- To determine Age of risk in patients suffering from (IHD) in both genders using (MPI) with ^{99m}Tc-Sestamibi and ^{201}TLin both conditions of stress and rest.
- To evaluate Obesity as risk factor related to reversibility of ^{201} Thallium and ^{99m}Tc-MIBI post injection in stress and rest.
- To evaluate gender as risk factor related to reversibility of ^{201} Thallium and ^{99m}Tc-MIBI post injection in stress and rest.
- To determine the radiopharmaceutical of the choice in IHD patients
- To determine the frequency % of IHD in gender.

1.4 Scope of the study:

The specific impact of ischemia on the myocardial kinetics of ^{201}Thallium and ^{99m}Tc-MIBI remains a matter of debate, So the following study will focus on several factors might affect the radiopharmaceutical bio-distribution in both conditions stress and rest.

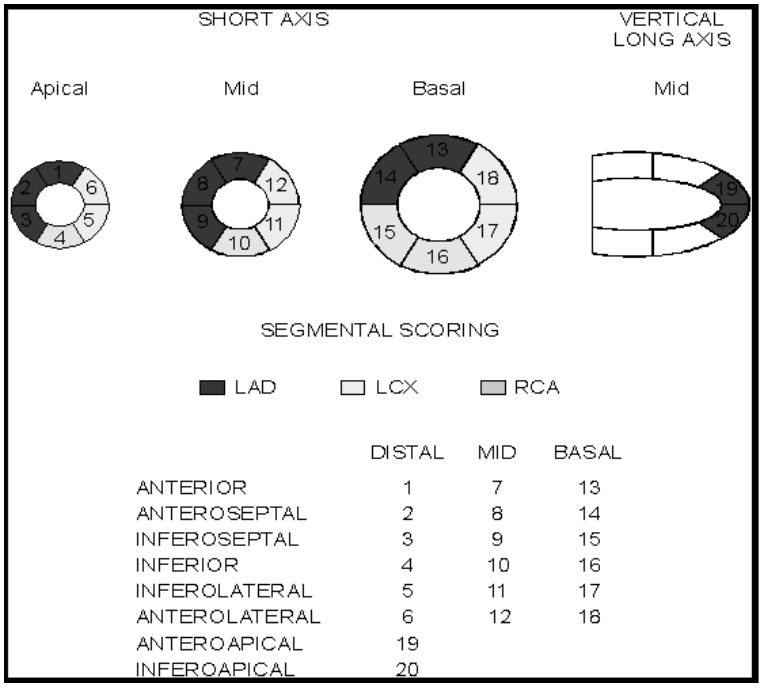


Figure 1.2 shows different heart territories to be evaluated by ROI's.

1.5 Thesis outline:

The study is designed into five chapters, chapter one deals with the research problem and the main objectives of the study , Chapter Two highlights the theoretical background of the study in (Section one), while discussing literature reviews at Section two, chapter three elaborates the followed methodology by researcher along with the selective used tools to obtain the results, chapter four is highlighting the estimated results and outcomes of the study, chapter five contains a detailed discussion of the estimated results, conclusion and researcher's recommendations.

1.6 Significance of the study:

In This study is going more specific as the researcher focused on measuring the counts/second/pixel (c/s/p) for the affected myocardium territory, This study helps the interpretators to further understand the mechanism of biodistribution of different radiopharmaceutical agents of the heart scintigraphy, and to justify the relevant factors affecting the distribution of the tracer in areas other than hear i.e. GIT, Lungs (Right and Left) along with the affected coronary artery, this study will help also the technologists in the field in the process of preparation of the radiopharmaceutical of the choice for IHD, as well as the interested local active community medicine committees by showing the prevalence of (IHD) and the factors related to this disease in order to take an effective approach preventing those factors, Through media and other tools of

combinations, this study will also help colleagues in the field of research to develop new prospective utilizing (counts/second/pixel) as a new interpretation tool for diagnose in nuclear medicine.

Chapter Two

Chapter two-Section one

2. Theoretical Background

The heart is a muscular organ about the size of a closed fist that functions as the body's circulatory pump. It takes in deoxygenated blood through the veins and delivers it to the lungs for oxygenation before pumping it into the various arteries (which provide oxygen and nutrients to body tissues by transporting the blood throughout the body). The heart is located in the thoracic cavity medial to the lungs and posterior to the sternum.

2.1 Anatomy of cardiovascular system:

The heart is a powerful muscle that pumps blood throughout the body by means of a coordinated contraction. The contraction is generated by an electrical activation, which is spread by a wave of bioelectricity that propagates in a coordinated manner throughout the heart. Under normal conditions, the sino-atrial node initiates an electrical impulse that propagates through the atria to the atrioventricular node, where a delay permits ventricular filling before the electrical impulse proceeds through the specialized His-Purkinje conduction system that spreads the electrical signal at speeds of meters per second throughout the ventricles. This electrical impulse propagates diffusively through the heart and elevates the voltage at each cell, producing an action

potential, during which a surge in intracellular calcium initiates the mechanical contraction. The normal rhythm is altered when one or more spiral (reentrant) waves of electrical activity appear. These waves are life-threatening because they act as high-frequency sources and underlie complex cardiac electrical dynamics such as tachycardia and fibrillation.(*www.ajronline.org*)

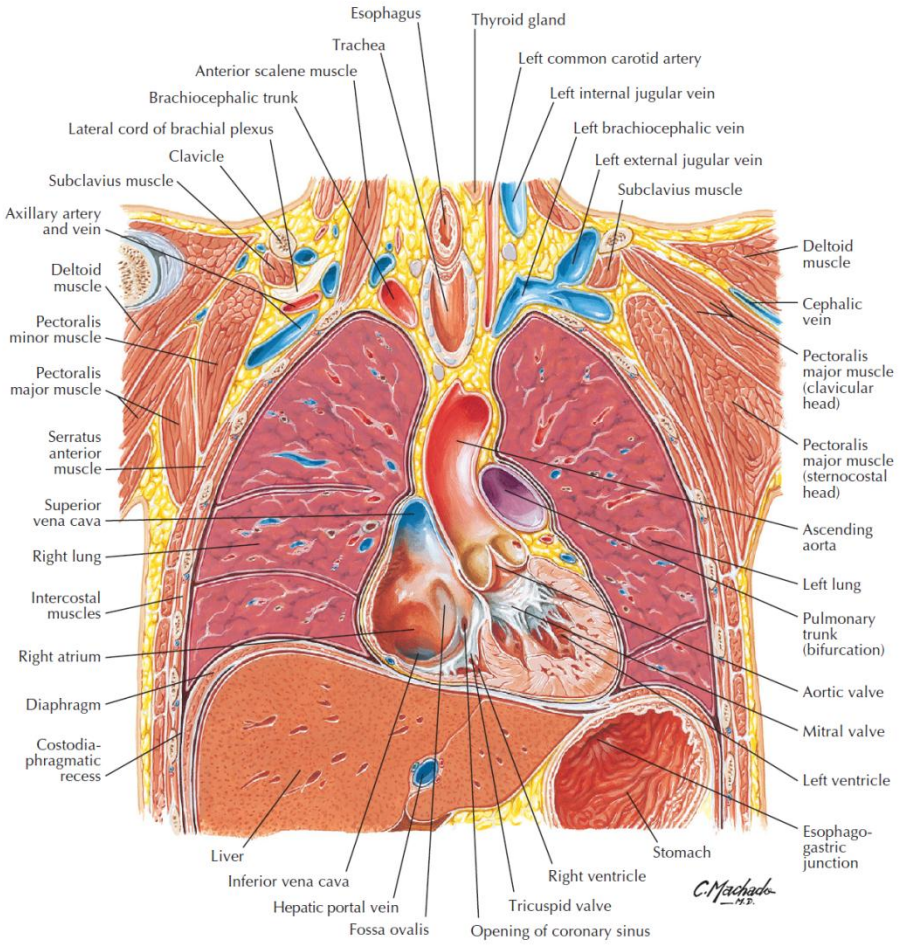


Figure 2.1 (A) shows the anatomical general position and structure of the heart muscle. (*Netter's Atlas of Human Anatomy, 6th Edition,2014***)**

2.1.1 Right Ventricle (RV):

The lower right chamber of the heart. During the normal cardiac cycle, the right ventricle receives deoxygenated blood as the right atrium contracts. During this process the pulmonary valve is closed, allowing the right ventricle to fill. Once both ventricles are full, they contract. As the right ventricle contracts, the tricuspid valve closes and the pulmonary valve opens. The closure of the tricuspid valve prevents blood from returning to the right atrium, and the opening of the pulmonary valve allows the blood to flow into the pulmonary artery toward the lungs for oxygenation of the blood The right and left ventricles contract simultaneously; however, because the right ventricle is thinner than the left, it produces a lower pressure than the left when contracting. This lower pressure is sufficient to pump the deoxygenated blood the short distance to the lungs.

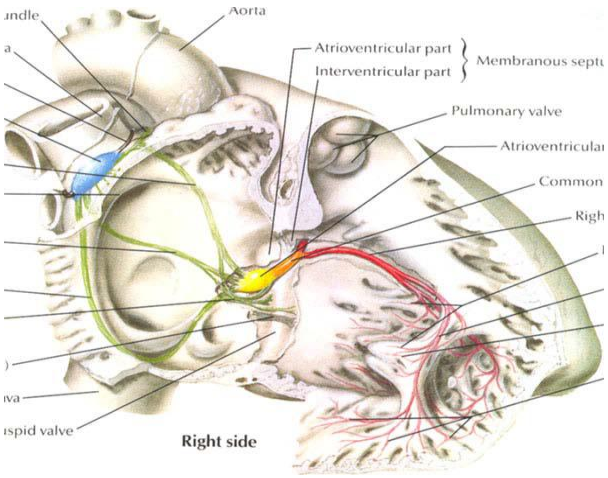


Figure 2.2 shows the anatomical structure of the conducting system of the heart i.e AV node ,SA node and Branches . (*Netter's Atlas of Human Anatomy, 6th Edition***,***2014***)**

2.1.2 Left Ventricle (LV):

The lower left chamber of the heart. During the normal cardiac cycle, the left ventricle receives oxygenated blood through the mitral valve from the left atrium as it contracts. At the same time, the aortic valve leading to the aorta is closed, allowing the ventricle to fill with blood. Once both ventricles are full, they contract. As the left ventricle contracts, the mitral valve closes and the aortic valve opens. The closure of the mitral valve prevents blood from returning to the left atrium, and the opening of the aortic valve allows the blood to flow into the aorta and from there throughout the body. The left and right ventricles contract simultaneously; however, because the left ventricle is thicker than the right, it produces a higher pressure than the right when contracting. This higher pressure is necessary to pump the oxygenated blood throughout the body.

2.1.3 Right Atrium (RA):

The upper right chamber of the heart. During the normal cardiac cycle, the right atrium receives deoxygenated blood from the body (blood from the head and upper body arrives through the superior vena cava, while blood from the legs and lower torso arrives through the inferior vena cava). Once both atria are full, they contract, and the deoxygenated blood from the right atrium flows into the right ventricle through the open tricuspid valve.

2.1.4 Left Atrium(LA):

The upper left chamber of the heart. During the normal ardiac cycle, the left atrium receives oxygenated blood from the lungs through the pulmonary veins. Once both atria are full, they contract, and the oxygenated blood from the left atrium flows into the left ventricle through the open mitral valve.

2.1.5 Superior Vena Cava (SVC):

One of the two main veins bringing deoxygenated blood from the body to the heart. Veins from the head and upper body feed into the superior vena cava, which empties into the right atrium of the heart.

2.1.6 Inferior Vena Cava(IVC):

One of the two main veins bringing deoxygenated blood from the body to the heart. Veins from the legs and lower torso feed into the inferior vena cava, which empties into the right atrium of the heart.

2.1.7 Aorta:

The central conduit from the heart to the body, the aorta carries oxygenated blood from the left ventricle to the various parts of the body as the left ventricle contracts. Because of the large pressure produced by the left ventricle, the aorta is the largest single blood vessel in the body and is approximately the diameter of the thumb. The aorta proceeds from the left ventricle of the heart through the chest and

through the abdomen and ends by dividing into the two common iliac arteries, which continue to the legs.

2.1.8 Pulmonary trunk (PT):

A vessel that conveys deoxygenated blood from the right ventricle of the heart to the right and left pulmonary arteries, which proceed to the lungs. When the right ventricle contacts, the blood inside it is put under pressure and the tricuspid valve between the right atrium and right ventricle closes. The only exit for blood from the right ventricle is then through the pulmonary trunk. The arterial structure stemming from the pulmonary trunk is the only place in the body where arteries transport deoxygenated blood. .(*www.innerbody.com)*

2.1.9 Pulmonary veins:

The vessels that transport oxygenated blood from the lungs to the left atrium. The pulmonary veins are the only veins to carry oxygenated blood.

2.1.10 Pulmonary Valve:

One of the four one-way valves that keep blood moving properly through the various chambers of the heart. The pulmonary valve separates the right ventricle from the pulmonary artery. As the ventricles contract, it opens to allow the deoxygenated blood collected

in the right ventricle to flow to the lungs. It closes as the ventricles relax, preventing blood from returning to the heart.

2.1.11 Aortic Valve:

One of the four one-way valves that keep blood moving properly through the various chambers of the heart. The aortic valve, also called a semi-lunar valve, separates the left ventricle from the aorta. As the ventricles contract, it opens to allow the oxygenated blood collected in the left ventricle to flow throughout the body (Figure 2.4). It closes as the ventricles relax, preventing blood from returning to the heart. Valves on the heart's left side need to withstand much higher pressures than those on the right side. Sometimes they can wear out and leak or become thick and stiff.(*www.innerbody.com)*

2.1.12 Mitral Value:

One of the four one-way valves that keep blood moving properly through the various chambers of the heart. The mitral valve separates the left atrium from the left ventricle. (Figure 2.3) It opens to allow the oxygenated blood collected in the left atrium to flow into the left ventricle. It closes as the left ventricle contracts, preventing blood from flowing backwards to the left atrium and thereby forcing it to exit through the aortic valve into the aorta. The mitral valve has tiny cords attached to the walls of the ventricles. This helps support the valve's small flaps or leaflets.

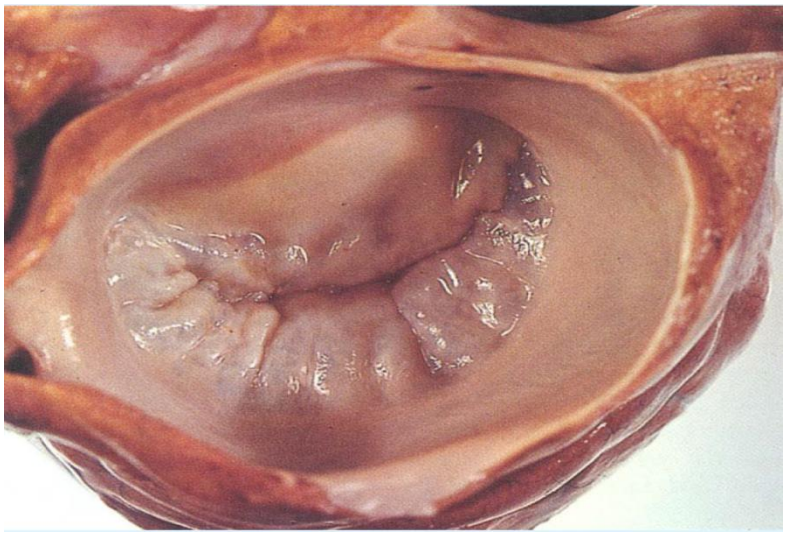


Figure 2.3 Shows the anatomical structure of the mitral valve . (*Netter's Atlas of Human Anatomy, 6th Edition,2014*)

2.1.13 Tricuspid Valve:

One of the four one-way valves that keep blood moving properly through the various chambers of the heart. Located between the right atrium and the right ventricle, the tricuspid valve is the first valve that blood encounters as it enters the heart. When open, it allows the deoxygenated blood collected in the right atrium to flow into the right ventricle. It closes as the right ventricle contracts, preventing blood from flowing backwards to the right atrium, thereby forcing it to exit through the pulmonary valve into the pulmonary artery.

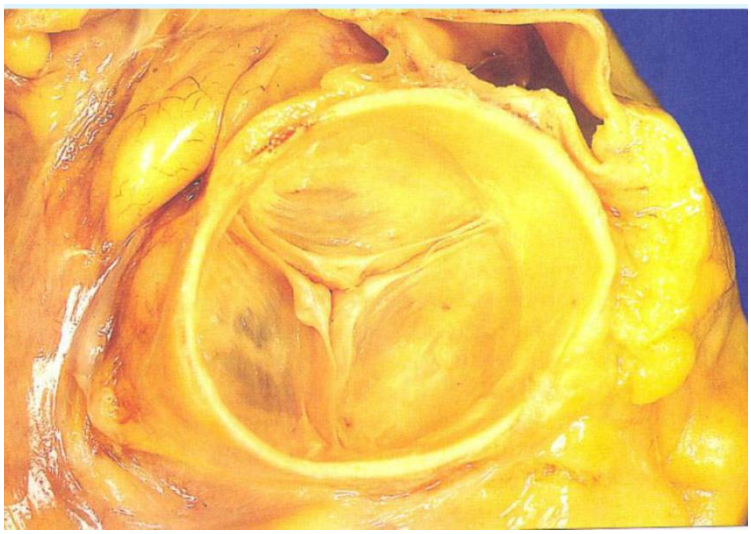


Figure 2.4 Shows the anatomical structure of the Aortic valve . (*Netter's Atlas of Human Anatomy, 6th Edition,2014)*

2.1.14 Atria:

The two upper cardiac chambers that collect blood entering the heart and send it to the ventricles. The right atrium receives blood from the superior vena cava and inferior vena cava. The left atrium receives blood from the pulmonary veins. Unlike the ventricles, the atria serve as collection chambers rather than as primary pumps, so they are thinner and do not have valves at their inlets.(*www.innerbody.com)*

2.1.15 Ventricles:

The two lower cardiac chambers that collect blood from the upper chambers (atria) and pump it out of the heart. Because the ventricles pump blood away from the heart, they have thicker walls than the atria so that they can withstand the associated higher blood pressures. The right ventricle pumps oxygen-poor blood through the pulmonary artery and to the lungs. The left ventricle pumps oxygen-rich blood through the aorta and to the rest of the body

2.2 Blood Supply:

2.2.1 Normal Cardiac Blood flow:

The blood flow through the heart usually keeps up with the body's demand. The demand is increased by exercise and strong emotions, both of which make the heart pump more quickly and more forcefully, causing the heart to use more oxygen. As a rough rule, when the heart beats twice as fast, it needs twice as much oxygen (Depre et al., 2011). Normally, the extra oxygen needed during exercise is supplied by a faster and a more voluminous blood flow through the coronary arteries (Michael Jay Katz,et al 2015) .

2.2.2 Coronary Arteries (CA):

Just beyond the aortic valve—the outflow valve of the left ventricle of the heart—the right and left coronary arteries are the first branches of the aorta. The two coronary arteries and their main branches run in grooves along the outside of the heart; these grooves separate the left and right ventricles and they also separate the atria from the ventricles. The coronary arteries and their main branches are called epicardial arteries because they run on the outer surface of the heart. Each major coronary artery is 2 mm to 4 mm wide, about half the diameter of a pencil. From the coronary arteries and their major branches, many small arteries run into the muscular walls (see Figure 2.5). of the heart, and these small arteries give rise to rich capillary networks that bathe the cardiac muscle cells with blood. All arteries inside the heart walls are fed by branches of either the right or left coronary arteries. In most people, the left coronary artery supplies most of the blood used by the left ventricle and the interventricular septum, while the right coronary artery supplies most of the blood used by the walls of the right ventricle. However, people vary in the way the blood supply to the heart is divided between the right and left coronary arteries.

There is not much overlap between the territories of the major branches of the coronary arteries, therefore, if one of the major branches suddenly becomes blocked, there is no other blood supply to the

territory served by that branch, and muscle in that territory will be deprived of oxygen (Warnica, 2013).

a common finding in coronary artery disease is collateral circulation, the development of additional arteries that form a natural bypass from one side of a blocked artery to the other, Research suggests that coronary collateral circulation may help to reduce ischemia, preserve ventricular function, and improve prognosis in patients with coronary artery disease (Seiler et al., 2013).

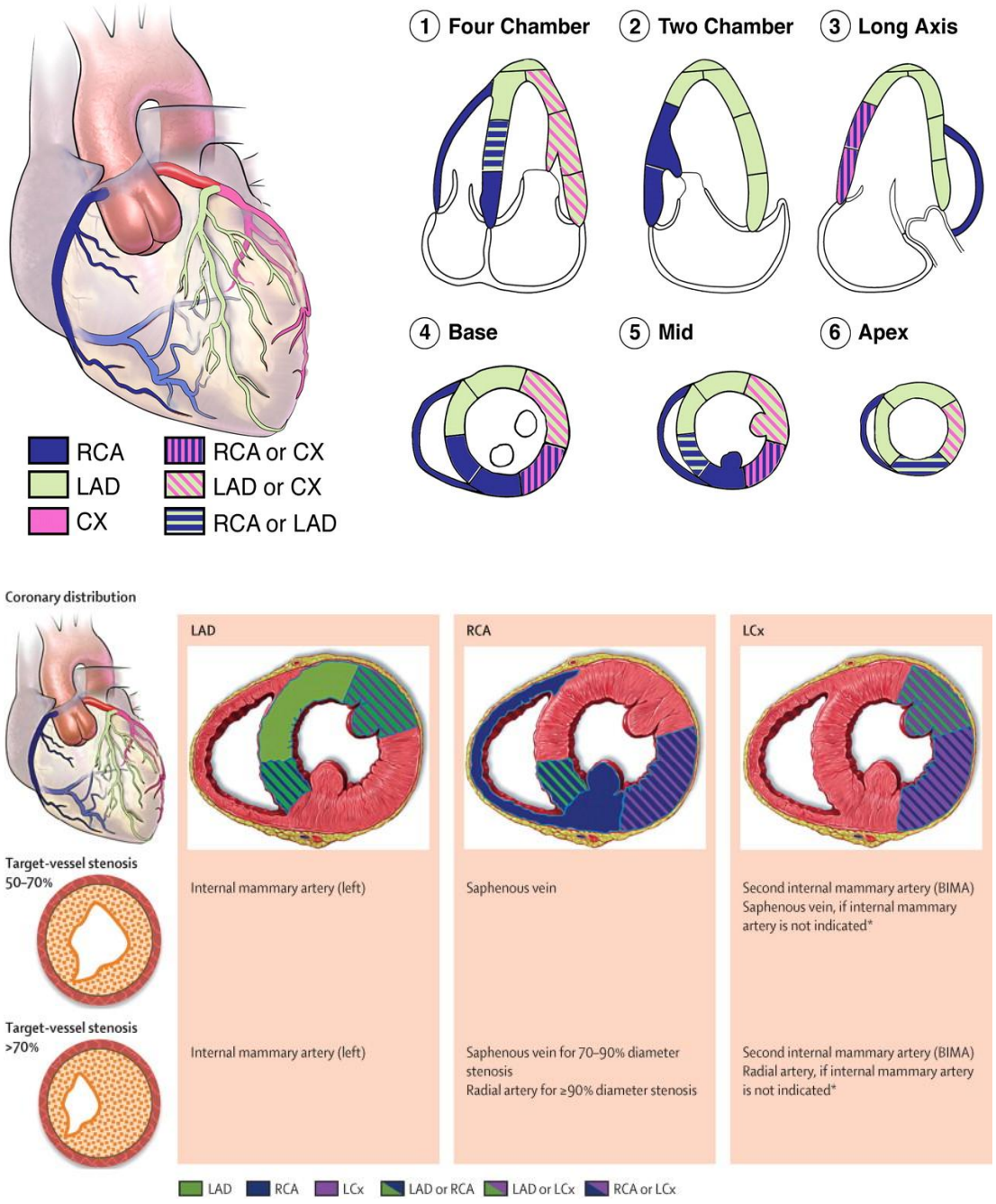


Figure 2.5 Shows blood supply to different territories within the myocardium segments *(www.thelancet.com)*.

2.2.2.1 Left Anterior descending Coronary Artery (LAD):

The left coronary artery splits into two main branches, the left anterior descending (LAD) coronary artery and the left circumflex coronary artery. The LAD coronary artery runs down the front of the heart along the groove between the left and right ventricles. In most people, the LAD supplies blood to the front wall of the left ventricle and to the interventricular septum. Forty to fifty percent of heart attacks are caused by an obstruction of the left anterior descending coronary artery; the left circumflex coronary artery runs to the left (at a right angle to the LAD) along the groove between the left atrium and the left ventricle. The left circumflex coronary artery supplies blood to the side or lateral wall of the left ventricle. Fifteen to twenty percent of heart attacks are caused by an obstruction of the left circumflex coronary artery.

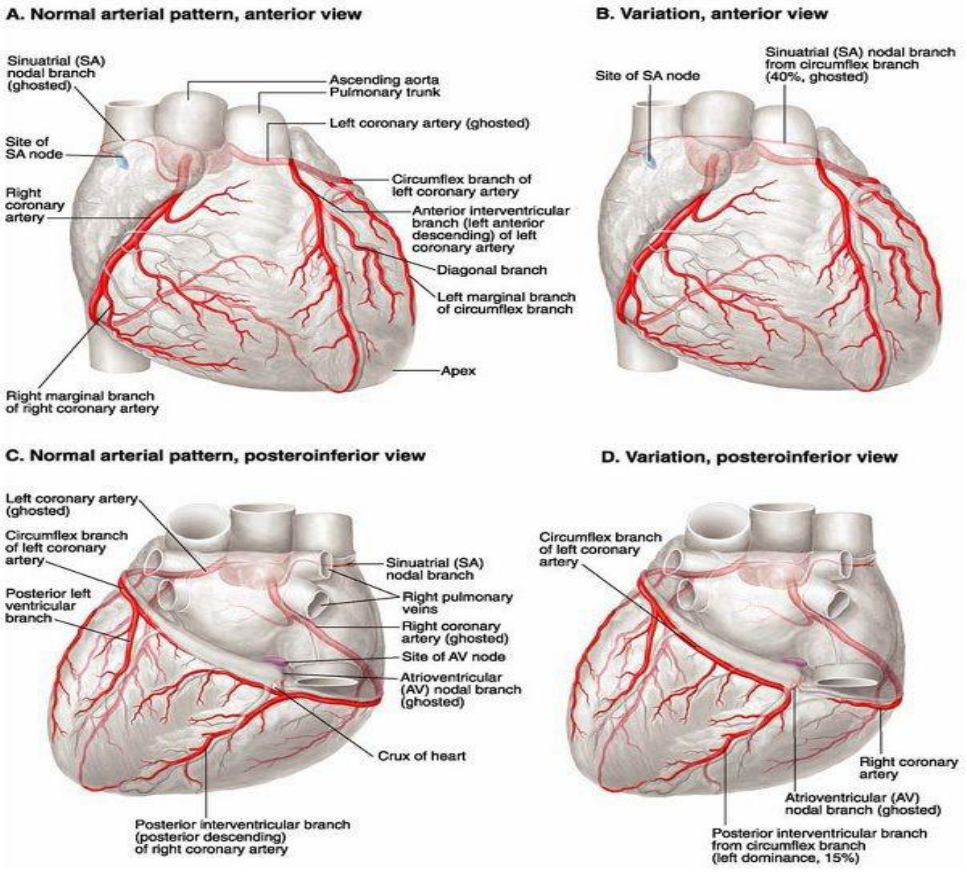


Plate 4-23 Coronary Arteries, Normal Patterns and Variations

Figure 2.6: Shows anatomical positions of Left anterior descending (LAD), right coronary artery (RCA) and Left Circumflex Coronary (LCx) Arteries in different orientation (*mynotes4usmle.tumblr.com*).

2.2.2.2 Right Coronary Artery (RCA):

The right coronary artery runs to the right, along the groove between the right atrium and the right ventricle. The right coronary artery branches behind the heart and gives rise to the posterior descending coronary artery, which parallels the LAD in front. The right coronary artery supplies the bottom and backside of the heart, and in most people, it supplies blood to the right ventricle and to the sinus and AV nodes of the heart's electrical conduction system. Thirty to forty percent of heart attacks are caused by an obstruction of the right coronary artery (Figure 2.6).

2.2.2.3 Left Circumflex Coronary Artery (LCCA) OR (LCX):

The other branch of the LCA. It brings blood to the lateral wall of the LV (i.e. the left-most side of the heart). Occlusion can lead to MI in this location. The LCCA also supplies the papillary muscles. These are the small muscles within the left ventricle to which the leaflets of the mitral valve are attached. If these muscles infarct, the mitral valve becomes incompetent, i.e. you develop mitral insufficiency (Figure 2.7).

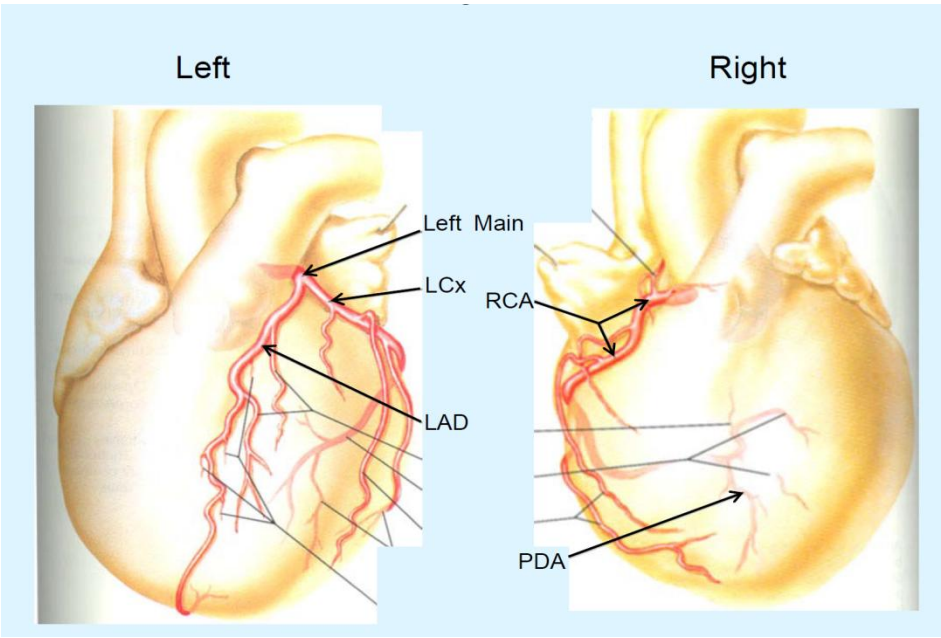


Figure 2.7 Shows anatomical positions of Left anterior descending, right coronary artery and Left Circumflex Coronary Arteries 2.*(mynotes4usmle.tumblr.com)*.

2.3 Cardiovascular Physiology

The heart is a muscular organ that lies in the center (left) of the thoracic cavity. It is composed mostly of myocardium (cardiac muscle) and is enclosed in the pericardial sac. The heart has four chambers, divided into left and right halves. Each half contains an upper chamber, the **atrium** (for receiving blood) and a lower chamber, the **ventricle** (for pumping blood). One-way flow in the heart is ensured by 4 heart valves:

1) The *right* (*tricuspid*) *atrioventricular* (AV) *valve*.

2) The *left* (*bicuspid/mitral*) *atrioventricular* (AV) *valve*.

3) The *pulmonary semilunar valve* in between the right ventricle and the pulmonary trunk.

4) The *aortic semilunar valve* in between the left ventricle and the aorta. The pulmonary trunk leaves the right ventricle and aorta leaves the left ventricle. Blood between the two sides do not mix. Each of the sides contract together in a coordinated fashion, first both of the atria contract, this is then followed by both of the ventricles contracting.

Arteries - are vessels that carry blood away from the heart.

Veins - are vessels that carry blood toward the heart.

A ring of fibrous connective tissue (called the fibroskeleton) surrounds the openings between the top and bottom chambers. The fibroskeleton has several functions:

1. Provides a site of attachment for AV valves and helps keep theses openings patent during contraction.
2. Maintains integrity of the shape of the heart when ventricles contract, while allowing the apex and the base to be pulled together
3. It electrically separates (insulates) the atria from the ventricles, thus guarding against the spread of electrical signals that are not through the intrinsic electrical conduction system (discussed later).

Within the cardiovascular system there are two circuits or circulations - the *pulmonary* and *systemic*.

Pulmonary Circulation - Pumps blood to and from the Lungs. Often termed the "right side" of the heart. This circuit can also be thought of as starting at the R ventricle and ending at the L atrium.

Systemic Circulation - Pumps blood to and from the body. Often termed the "left side" of the heart. This circuit can also be thought of as starting at the L ventricle and ending at the R atrium.

Volumes and Pressures of the Dual Pump

The cardiovascular system is a *closed circulatory system*, and for that to exist, the volume of blood in both sides of the pump *must be equal*. The pressures of the fluid in either side of the heart, however, are very different. The proximity of the lungs to the heart (about 4 inches) means that the right pump (R ventricle) does not have to work very hard to move the blood to the lung tissue. The minimum pressure required from the pulmonary circuit is normally about 25 mmHg.

The systemic circuit, however, is much more involved and the left pump (L ventricle) needs to work very hard to move the blood to every part of the body. The minimum pressure required from the systemic circuit is normally about 80 mmHg. Therefore, the pressure generated by the left side of the heart is over three times greater than that generated by the right side. As a consequence, the muscular wall of the left ventricle is about three times thicker than the right ventricle.

The Cardiac Cycle

The cardiac cycle is the period of time from the beginning of one heartbeat to the beginning of the next. There are two main stages: Diastole - the time during which cardiac muscle relaxes and Systole - the time during which cardiac muscle is contracting. Atria and ventricles do not contract at same time, but each side of the heart

contracts at the same time. For convenience, the cardiac cycle can be divided into 5 stages.

Atrial and Ventricular Diastole: The Heart at Rest

The heart is at rest and the atria and ventricles are relaxing. The atria are filling with venous blood. The AV valves open as ventricles relax and blood flows by gravity from atria to ventricles. During this phase, the ventricles are about 80% of filled with blood, this is termed *passive filling*.

Atrial Systole: Completion of Ventricular Filling

When the atria contract (systole), the remaining 20% of blood fills the ventricles, this is like a "topping off" of the ventricles. Atrial systole begins following depolarization of the SA node, as a wave of depolarization (electrical signal) across the atria is followed by a wave of contraction that pushes blood into the ventricles to complete ventricular filling. Some blood is forced back into veins, creating a small retrograde blood movement, measured as a pulse in the jugular vein.

At this time, just prior to ventricular systole (the next stage), the ventricles are full of blood, this is termed End Diastolic Volume (EDV) and represents the maximum ventricular volume. At rest in a 70 Kg male, this value is typically 135ml in each ventricle.

Early Ventricular Systole (part one) and the First Heart Sound

Ventricular systole begins at the apex of the heart as spiral bands of muscle squeeze blood upward toward the base. The increasing pressure of the blood in the ventricles forces the AV valves closed - creating the first heart sound, the "lub" of "lub dub".

Both ventricles are now 'sealed' compartments in that the AV and semilunar valves are closed. The ventricles are continuing to contract, but if all valves are closed, the blood goes nowhere. The heart is in Isovolumic Ventricular Contraction. This occurs when the blood volume inside the ventricles remains the same (prefix iso- means 'same'), but pressure is increasing. During this phase, the atria repolarize and relax as the ventricles continue to contract.

Ventricular Systole (part two): Ventricular Ejection

When ventricular contraction generates enough pressure it opens the semilunar valves, and blood enters arteries (RV => pulmonary trunk/artery, LV => aorta). The high-pressure blood is forced into the arteries (ejection of blood from ventricles), which displaces lower-pressure blood, creating blood movement. Remember that each ventricle has equivalent blood volumes but different pressures. The RV requires a min of 25 mmHg and the LV requires a min of 80 mmHg to open the semilunar valves. At these respective pressures, the pressure gradient which drives blood flow is established.

At this time, just after ventricular systole, the ventricles have just ejected blood but the ventricles do not empty. In fact, at rest they only eject about half of the blood volume in the ventricle. The blood volume remaining in the ventricles after ejection is termed End Systolic Volume (ESV). A typical value for a 70 Kg male at rest is about 65ml per ventricle that remains in the heart after ejection. We can calculate how much blood left the heart (called Stroke Volume) if we know the maximum volume, EDV, and subtract the volume remaining after contraction, ESV. This means that about 70ml of blood is ejected per beat. (www.encyclopedia.com)

Stroke Volume (SV) = EDV - ESV

2.4 Pathology of the Heart

Coronary artery disease is the umbrella term for various syndromes of heart ischemia that are caused by atherosclerotic obstruction of the coronary arteries. The atherosclerotic damage ranges from gradual narrowing of the coronary arteries (due to bulging patches of plaque) to the sudden obstruction of a coronary artery by a blood clot that has been dislodged from the surface of a ruptured plaque. Wild Iris Medical Education, Inc. (2015).

2.4.1 Ischemic Heart Disease (IHD):

Myocardial ischemia occurs when blood flow and blood volume are insufficient to supply all the oxygen needed by the heart muscle, As soon as the blood flow to an area of heart muscle is stopped, the cells begin to lose their energy stores, and within a few minutes the muscle cells are no longer able to contract. Any region of the heart that loses all its blood flow will stop working almost immediately. Although muscle cells stop working, they do not begin to die until 20 to 40 minutes after losing their blood supply. If blood flow is restored within a half hour, most muscle cells will eventually recover; however, the recovery can take from 10 minutes to several days. During that time, the heart acts “stunned” and may not contract well unless stimulated by ionotropic drugs (Schoen,2010).

Ischemic Heart Disease (IHD) is synonymous with coronary heart disease or arteriosclerotic heart disease, is the most reliable indicator of atherosclerosis available today. Practically all patients with myocardial infarction, as defined by electrocardiographic and enzymatic changes, have coronary atherosclerosis. Rare exceptions are due to congenital anomalies of the coronary vessels, emboli, or ostial occlusion due to the other types of cardiac or vascular disease. Cerebrovascular disease (stroke) is a less reliable criterion for the presence of atherosclerosis. It includes cerebral thrombosis and cerebral hemorrhage. Cerebral thrombosis, including infarction or softening without evidence of embolus, is usually due to atherosclerosis. On the other hand, cerebral hemorrhage is most often the result of congenital aneurysms or of vascular defects peculiar to hypertension and diabetes. Dissections of the aorta, peripheral vascular disease, thrombosis of other major vessels, and ischemic renal disease likewise are not used to determine the prevalence of atherosclerosis in a population or as an index of atherosclerosis elsewhere. Therefore, from an epidemiologic standpoint, consideration of atherosclerosis focuses on IHD.*(Prof. Jiří Horák,2015)*

2.4.1.1 Reversible Ischemic Heart Disease

Reversible ischemia refers to a condition which results in a lack of blood flow to a particular organ which can be reversed through use of medications or surgery. It most often refers to hindered blood flow to the heart muscle, but it can refer to an obstruction blocking any organ in the body, including the brain. Whether or not a case of ischemia can be reversed will depend on the underlying cause. Plaque buildup in the arteries, weakened arteries, low blood pressure, blood clots, and unusual heart rhythms can all be causes of reversible ischemia.

The most common types of reversible ischemia affect the heart muscle. Some causes may affect anyone, but there are habits which make this condition more likely. These can include eating a diet high in fat and bad cholesterol and low in good cholesterol. Smoking, being overweight or obese, and a sedentary lifestyle are also risk factors. When the arteries become clogged due to plaque, (*Figure 2.8*) blood flow may become heavily restricted. Plaque buildup is one of the most common causes of reversible ischemia, especially in the Western world where fatty foods are consumed in excess.

When ischemia is reversible, this means that doctors are able to correct the underlying causes of restricted blood flow. Treatment can include medications to reduce plaque or break down clots, as well as surgery in some instances when an artery is damaged and needs to be repaired

directly. Not all cases of ischemia can be reversed. Sometimes it takes the occurrence of a serious medical problem, such as heart attack or stroke, before ischemia is discovered.

In some cases reversible ischemia can cause long-term damage and side effects even if the condition itself is properly treated. For instance, if a heart attack occurs due to lack of blood flow, a permanent weakening of the heart muscle may result. Those who suffer from ischemic stroke may suffer from permanent brain damage. For these reasons, avoiding habits and behaviors which increase the risk of ischemia is important for maintaining long-term health and vitality. It is also important to recognize the symptoms of heart attack and stroke, as well as other health problems, so that swift action can be taken if they occur.

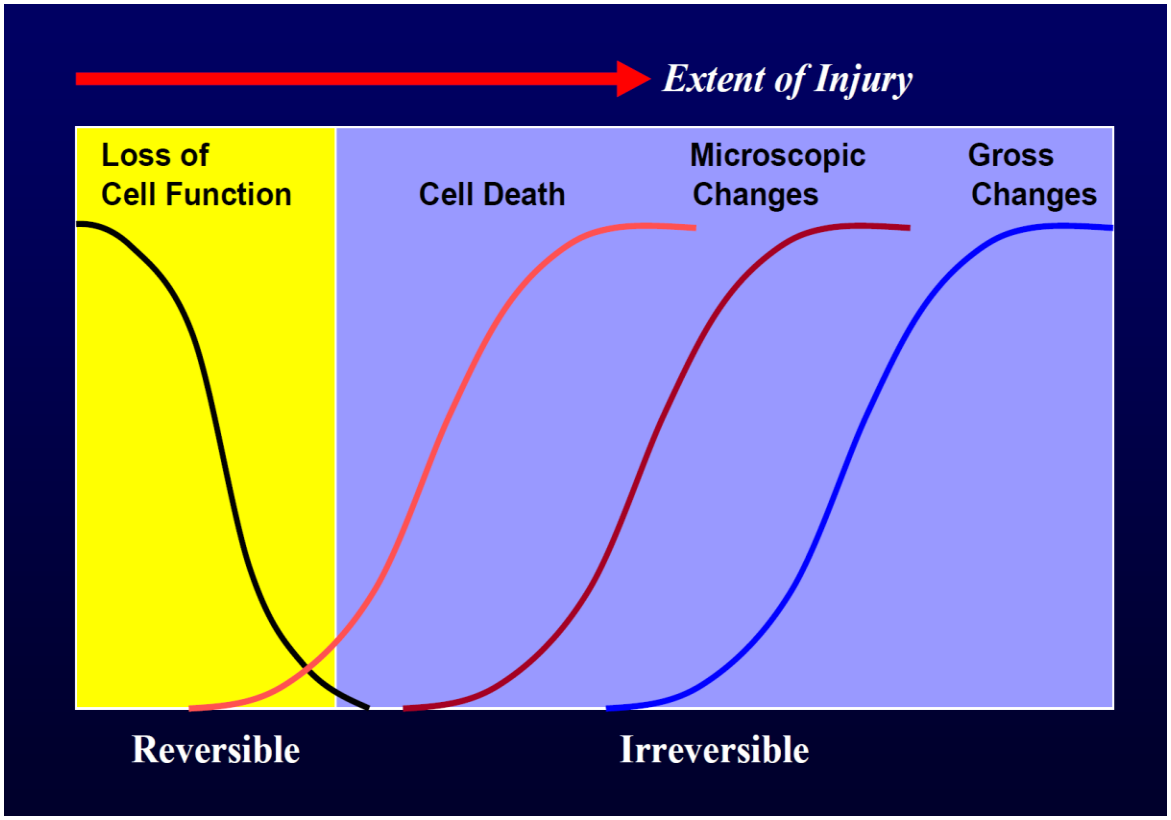


Figure 2.8 Elaborates the mechanism of reversibility within the myocardium throughout time and progress of cell injury *(Source: Robbins Basic Pathology, WB Saunders, 2003)* **.**

2.4.1.2 Irreversible Ischemic Heart Disease

When the period of ischemia extends beyond 30 min, certain ischemic lesions become irreversible. The shift from reversibility to irreversibility is related to a critical decrease in concentrations of high-energy phosphate compounds and/or in free energy change of ATP hydrolysis. The decrease in high-energy phosphate levels inhibits the Na pump, which results in Ca+ + overload. In this situation not only does reperfusion not result in recovery, but it may aggravate the situation by activating positive feedback mechanisms. With respect to this problem the following should be mentioned (1) the no-reflow phenomenon and changes in osmotic pressure, (2) the waste of oxidative energy on Ca absorption instead of ATP synthesis in mitochondria, and (3) the peroxidation of lipids and the formation of radicals, which causes membrane breakdown. Upon reperfusion, cells often swell due to increased osmotic pressure generated during ischemia by accumulation of lactic acid and phosphate. The resulting increase in extravascular resistance eventually occludes the nutritive vessels. The importance of this phenomenon has recently been demonstrated by the finding that much better recovery of electrical and biochemical functions occurs when the osmotic pressure of the reperfusing solution is increased to levels above normal to avoid cell swelling. Dangers secondary to reperfusion of ischemic tissue may also result from altered Ca+ + homeostasis. During ischemia the

concentration of free Ca+ may increase secondary to release of Ca+ from the sarcoplasmic reticulum and mitochondria. Upon reoxygenation, the reenergization of the mitochondria in the presence of high concentrations of Ca++ and adenosine diphosphate will not restore ATP formation; instead, all energy provided will be spent by the mitochondria for the absorption of Ca. This process results in severe depletion of ATP and formation of rigor mortis (stone heart). The third factor that plays an important role in the irreversible phase of myocardial infarction is excessive membrane leakage. During ischemia membrane permeability increases, in part because of the rise in intracellular Ca+ + and interaction of phosphatides and fatty acids with the membrane constituents. Upon reperfusion the reavailability of oxygen together with large amounts of xanthine, a degradation product of ATP, results in the formation of superoxide and hydroxyl radicals.2 ` Thus, the peroxidation of membrane lipids and fatty acids would further enhance membrane leakage. (Figure 2.9) Fairly good and reliable information is now available on the processes that occur during the different phases of myocardial ischemia. The underlying mechanisms for ischemia-induced changes especially those of the irreversible phase, are less well understood. This kind of information is important in predicting whether recovery of normal contractile and electrical activity may be expected after removal of an obstructing

thrombus. Future research should therefore be aimed at delineating and solving problems related to reperfusion (*E Carmeliet,1984*).

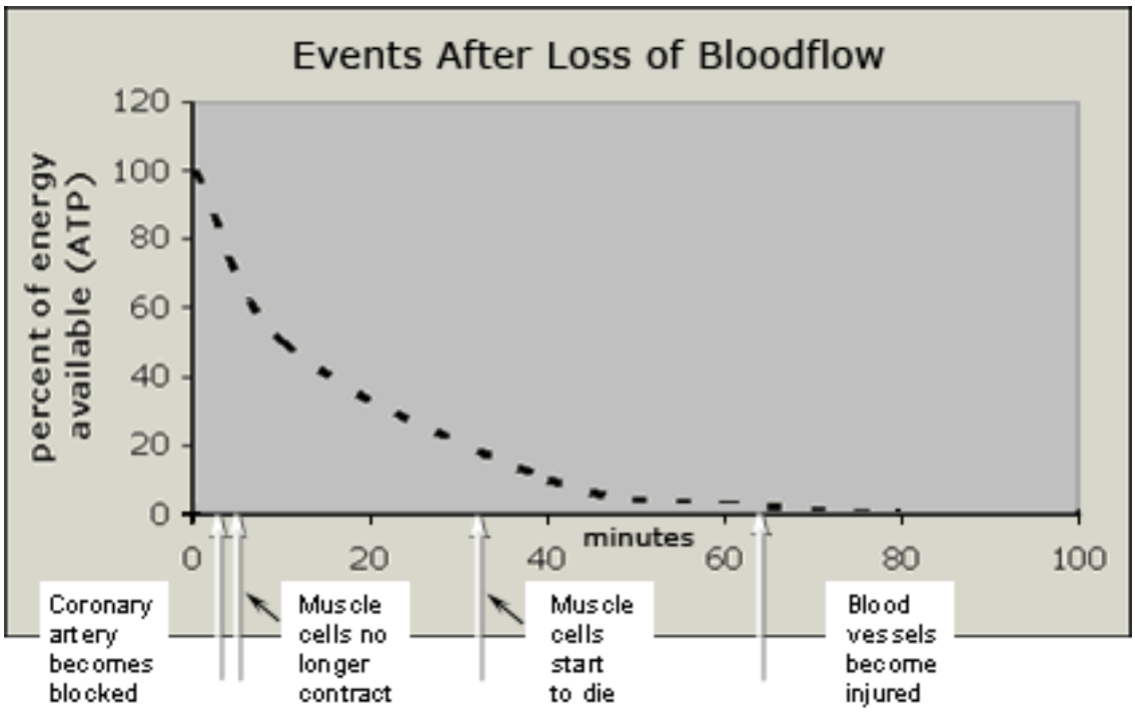


Figure 2.9 Elaborates the mechanism of scar formation throughout the time leading to partial or total blockage of coronary arteries *(Adapted from Schoen, 2010.)* .

2.4.2 Symptoms Of Ischemia:

Heart ischemia usually produces symptoms, and the classic symptom of reduced oxygen supply to the heart is a particular type of chest pain called angina pectoris, or simply angina. Angina arises many seconds or even minutes after a sudden arterial blockage. Typically, angina pain feels like crushing or squeezing, although sometimes it is described as burning. The sensation is usually felt inside the chest behind the sternum, and the feeling can radiate to the lower part of the neck, jaw, shoulder, back, or down the ulnar side (inside) of the left arm; in some cases the feeling can radiate to either or both arms. In some people, the discomfort of angina is mild, but other people get diffuse unbearable pain. Although women tend to visit their physicians more often than men and therefore report more symptoms, including chest pain, their angina symptoms usually present in the form of upper abdominal discomfort, neck or jaw pain, or shortness of breath as opposed to crushing or squeezing chest pain. Women are also more likely than men to associate their angina with emotional or mental stress (Charney, 2011).

Angina is a classic symptom of myocardial ischemia. However, angina is not a perfect indicator of heart problems. Myocardial ischemia can occur without angina; moreover, some people get angina although they have no detectable ischemia.

2.4.3 *Pathophysiology of Ischemic Heart Disease (IHD)*

Discomfort due to myocardial ischemia occurs when the oxygen supply to the heart is deficient in relation to the oxygen need. Oxygen consumption is closely related to the physiologic effort made during contraction, and coronary venous blood is normally much more desaturated than that draining other areas of the body. As a consequence, the removal of more oxygen from each unit of blood, which is one of the adjustments commonly utilized by exercising skeletal muscle, is already employed in the heart in the basal state. Therefore, the heart must rely primarily on an increase in the coronary blood flow for obtaining additional oxygen.

The blood flow through the coronary arteries is directly proportional to the pressure gradient between the aorta and the ventricular myocardium during systole and the ventricular cavity during diastole but is also proportional to the fourth power of the radius of the coronary arteries. A relatively slight alteration in coronary luminal diameter below a critical level can produce a large decrement in coronary flow, provided that other factors remain constant. Coronary blood flow occurs primarily during diastole, when it is unopposed by systolic myocardial compression of the coronary vessels.

When the epicardial coronary arteries are narrowed critically (>70 percent stenosis of the luminal diameter), the intramyocardial coronary arterioles dilate in an effort to maintain total flow at a level that will avert myocardial ischemia at rest. Further dilatation, which normally occurs during exercise, is therefore not possible. Hence any condition in which increased heart rate, arterial pressure, or myocardial contractility occurs in the presence of coronary obstruction tends to precipitate anginal attacks by increasing myocardial oxygen needs in the face of a fixed oxygen supply.

By far the most frequent underlying cause of myocardial ischemia is organic narrowing of the coronary arteries secondary to coronary atherosclerosis. A *dynamic* component of increased coronary vascular resistance, secondary to spasm of the major epicardial vessels (often near an atherosclerotic plaque) or more frequently to constriction of smaller coronary arterioles, is present in many, perhaps the majority, of patients with chronic angina pectoris. There is no evidence that systemic arterial constriction or increased cardiac contractile activity (rise in heart rate or blood pressure or increase in contractility from liberation of catecholamines or adrenergic activity) due to emotion can precipitate angina unless there is also organic or dynamic narrowing of the coronary vessels. Acute thrombosis superimposed on an atherosclerotic plaque is frequently the cause of unstable angina and acute myocardial infarction.

Aside from conditions that narrow the lumen of the coronary arteries, the only other frequent causes of myocardial ischemia are disorders such as valvular aortic stenosis or hypertrophic cardiomyopathy, which cause a marked disproportion between the coronary perfusion pressure and the heart's oxygen requirements.

An increase in heart rate is especially harmful in patients with coronary atherosclerosis or with aortic stenosis, because it both increases myocardial oxygen needs and shortens diastole relatively more than systole, thereby decreasing the total available perfusion time per minute. Tachycardia, a decline in arterial pressure, thyrotoxicosis, and diminution in arterial oxygen content (such as occurs in anemia or arterial hypoxia) are precipitating and aggravating factors rather than underlying causes of angina. .(Prof. Jiří Horák,2015)

Dr. O'Connor made 4 points about coronary artery atherosclerosis:

1. The disease is worst in the proximal portions of the arteries (which run along the outer, i.e. epicardial, (surface of the heart). The distal, smaller branches of the arteries (that lie within the heart muscle) are far less affected.
2. If atherosclerotic narrowing involves one branch of a coronary artery, you can bet that another branch(es) will also be narrowed.
3. The heart muscle can receive enough blood flow if the atherosclerotic narrowing of a coronary artery is no greater than 75%. Beyond 75%, the muscle becomes significantly ischemic/hypoxic (e.g. patient may experience ischemic chest pain).

4. Collateral circulation refers to branches of other, nonoccluded coronary arteries that may be able to supply blood to an ischemic area. Can help prevent, or limit the size of, an MI. (Figure 2.10)

In the United States, atherosclerosis usually begins in childhood or adolescence and then gradually worsens over many decades. Any medium or large artery in the body can be affected; most atherosclerosis causes no clinical problems. Many people have atherosclerosis throughout their bodies but develop no serious medical symptoms, and the disease is only discovered at autopsy (Lam, 2012).

When atherosclerosis causes the coronary arteries to become very narrow or when plaques rupture and send clots into the arteries of the heart, a person is said to have coronary artery disease. *(www.uky.edu, 2015*).

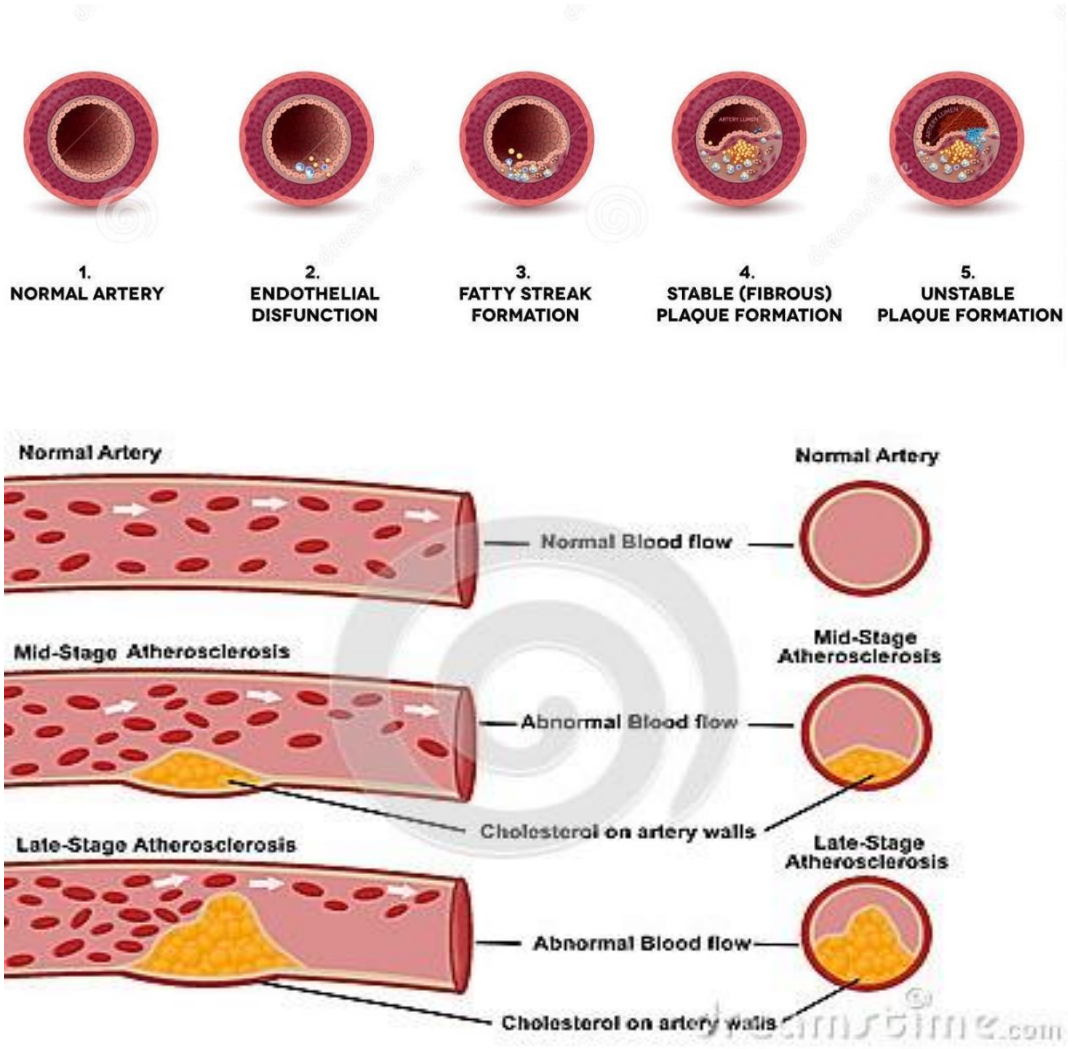


Figure 2.10 Elaborates the progress of atherosclerosis leading to partial or complete occlusion of one or more of the coronary arteries (*www.dreamstime.com)* .

2.4.4 Atherosclerosis:

Atherosclerosis is the disorder that underlies coronary artery disease. Atherosclerosis thickens the walls of medium and large arteries. The atherosclerotic thickenings occur as bulges, called plaques, in the arterial walls. Plaques contain lipids, white cells, smooth muscle cells, and connective tissue in a poorly organized mass that lies just under the endothelial lining of the artery wall.

2.4.5 Atherosclerosis of the Coronary Arteries:

Rather than uniformly thickening arterial walls, atherosclerosis is patchy and unevenly distributed. The specific coronary arteries affected by atherosclerosis vary from person to person, but there is a common feature: within a coronary artery, plaques are found most often at branch points, places where the blood flow naturally becomes turbulent. The narrowing of coronary arteries usually occurs slowly, and in response, new small collateral arteries have time to grow into the fields of the atherosclerotic arteries to help bolster the local oxygen supply. These collateral arteries will sometimes provide enough extra blood flow to keep the heart muscle working comfortably at a resting rate. The collateral arteries are small, however, and they do not have the capacity to keep up with the oxygen demands of heart muscle during exercise. Even with the growth of small collateral arteries, the continual narrowing of the coronary arteries by atherosclerosis can eventually produce ischemia and anginal pain. Initially, these

symptoms occur only when the patient is exercising; later, the symptoms begin to occur even when the patient is at rest. Besides slowly narrowing the coronary arteries, atherosclerosis can cause a sudden medical crisis. The degeneration of a plaque can seed clots into the bloodstream and can also trigger local vasospasm. These lead to a marked reduction of blood flow, and the resulting damage can range from temporary to permanent and from mild to fatal.

2.4.6 Stable Angina:

When one or more coronary arteries have become narrowed and cannot meet the demands of a hard-working heart, the patient has chronic stable angina. This syndrome is characterized by ischemic heart pain that shows up when patients exercise and that goes away in a few minutes after they rest. Blood flow to the heart must be reduced by two thirds to three fourths before a patient develops the symptoms of chronic stable angina. The chest pain of chronic stable angina is short-lived and occurs predictably. Particular amounts of exercise, trauma, weather changes, or strong emotions may trigger angina. In chronic stable angina, resting or nitroglycerin tablets will relieve the chest pain in a few minutes. The occurrence of angina is influenced by the general tone of the sympathetic nervous system (which tends to be, for example, higher in the mornings) and by the demands of blood flow by the gastrointestinal tract after a meal. Therefore, although the symptoms of chronic stable angina are fairly predictable, the amount of

exercise or stress that will produce these symptoms varies during the course of a day. The chest pain of chronic stable angina can also be brought on by any medical condition that increases the work of the heart, such as hypertension, aortic stenosis, systemic infections, or thyrotoxicosis. Likewise, conditions that reduce the oxygenation of the blood, such as COPD, anemia, or high altitudes, can also cause angina.

2.4.7 Stable Ischemic Heart Disease

A second chronic syndrome is stable ischemic heart disease, or ischemic cardiomyopathy, in which years of damage from ischemia have weakened the heart sufficiently that it gradually fails. Stable ischemic heart disease is a major cause of congestive heart failure in older adults. Most patients with this condition have had acute myocardial infarctions in the past, although not all infarctions may have been symptomatic. In people who have had “silent” myocardial infarctions, heart failure from stable ischemic heart disease can be the first evidence of their coronary artery disease.

2.4.8 Prognosis:

A patient with any form of coronary artery disease has a higher chance of dying when the left ventricle of the heart has been weakened. Signs of a failing left ventricle include an enlarged heart, pulmonary edema, leg and ankle edema, jugular venous distension, or a third heart sound (S3). Previous myocardial infarctions weaken the heart, so a history of past heart attacks also worsens a patient's prognosis (Warnica, 2011).

2.4.6 Risk Factors

2.4.6.1 Introduction

Coronary artery disease creeps up quietly. In most patients, atherosclerosis builds over decades. Although it probably begins before most people are out of their teenage years, the coronary effects of atherosclerosis usually do not show up until middle age. The most common symptom of coronary artery disease is chest pain, which can be accompanied by shortness of breath and tiredness, and these are the symptoms that often bring the patient with CAD to the doctor. However, CAD can be symptomless and "silent" for years. Even those patients who have been diagnosed with coronary artery disease because of occasional temporary chest discomfort can at the same time be suffering acute myocardial infarctions without apparent symptoms. More than half of the patients who die suddenly from CAD have had no previous symptoms. Frequently, those patients who suffer from silent myocardial infarctions also have type 2 diabetes. In spite of the

variation in the overt signs and symptoms of coronary artery disease, there are some characteristics and risk factors present in most patients with the disease (Boudi, 2014b).

A) ***Non- preventable Risk Factors***

1. AGE

Age is the strongest risk factor for coronary artery disease; most cases occur in patients aged 40 years or older, although mortality and morbidity are higher in the elderly. More than 80% of people who die of CAD are aged 65 years or older (Boudi, 2014b). Elderly women who have heart attacks are more likely than men are to die from them within a few weeks (AHA, 2014a).

2. GENDER

Overall, CAD is slightly more common in men than in women; in the United States, 9.1% of men and 7.0% of women have the disease. Women tend to develop symptomatic coronary artery disease about 10 years later than men. In the United States, men over 40 years of age have a 49% chance of developing the disease in their lifetime, while the chance for women over the age of 40 years is 32% (Boudi, 2014b). It is thought that the higher estrogen levels in premenopausal women protect them from some of the heart damage done by atherosclerosis, but this protection disappears after menopause.

3. RACE/HEREDITY

African Americans have a higher prevalence of, and a higher death rate from, CAD than European Americans. In part, the difference results from the higher incidence of hypertension, obesity, and metabolic syndrome among African Americans. This racial disparity is also thought to result from the fact that African Americans, on average, tend to seek treatment later than European Americans and are less likely to receive invasive treatment (Boudi, 2014b). Americans of Asian Indian origin are 2 to 3 times as likely as European Americans to develop coronary artery disease (Boudi, 2014b). Heart disease risk is also higher among Mexican Americans, American Indians, native Hawaiians, and some Asian Americans. This may be due in part to higher rates of obesity and diabetes in these populations (AHA, 2014a). Children of parents with heart disease are more likely to develop it themselves. African Americans tend to have more severe high blood pressure than Caucasians and a higher risk of heart disease. Most people with a strong family history of heart disease have one or more other contributing risk factors (AHA, 2014a). Individuals with familial hypercholesterolemia, an inherited metabolic disorder affecting the LDL receptors, carry a genetic mutation that makes it difficult for their cells to remove LDL from their blood (McLaughlin, 2014). Recent studies have shown that genetic predisposition is responsible for around 50% of the risks associated with CAD. Several genes may contribute to

the predisposition, with each having only a mild to moderate influence on whether a person will get CAD purely from a genetic perspective. Over 50 genetic variants related to coronary artery disease have been identified and are currently being studied. Ongoing clinical trials are continuing to investigate how genes influence a person's risk for CAD (Roberts, 2014).

B) ***Preventable Risk Factors:***

1. SMOKING

People who smoke have a risk of developing CAD that is 2 to 4 times higher than that of nonsmokers. Nicotine causes the sympathetic nervous system to constrict arteries and raises blood pressure, causing arterial wall damage. The damage encourages the formation of atherosclerotic plaque. Cigarette smoking is also an important independent risk factor for sudden cardiac death in patients with CAD. Cigarette smoking adds a cumulative effect when other risk factors are present to greatly increase the risk for CAD. People who smoke cigars or pipes seem to have a higher risk of death from CAD as well. Exposure to second-hand smoke also increases the risk of heart disease for nonsmokers (AHA, 2014a). Patients who smoke should be strongly encouraged to quit smoking. An important factor is to educate patients on the risks of smoking and offer assistance in developing an action

plan to help the patient stop smoking. The best smoking cessation programs include a combination of the following components:

• Behavioral modification therapies

• Medications such as antidepressants

• Nicotine replacement strategies, such as patches or gum (McLaughlin, 2014)

2. HIGH CHOLESTEROL

As blood cholesterol rises, so does the risk of CAD. When other risk factors (e.g., hypertension and smoking) are present, this risk increases even more. Low HDL cholesterol is a risk factor for heart disease. Likewise, a high triglyceride level combined with low HDL cholesterol or high LDL cholesterol is associated with atherosclerosis, which increases a person's risk for CAD *(Figure 2.11).* Cholesterol level is affected by age, gender, heredity, and diet. Genetic factors, type 2 diabetes, and certain drugs, such as beta blockers and anabolic steroids, also lower HDL cholesterol levels. Smoking, being overweight, and being sedentary can all result in lower HDL cholesterol

3. HYPERTENSION

Hypertension causes inflammation, which can damage the lining of arteries and increases fatty deposits contributing to the development of atherosclerosis and CAD. For people at increased risk for CAD, blood pressure control is an important factor. A diagnosis of hypertension is confirmed when two or more elevated blood pressure readings are obtained on separate visits.

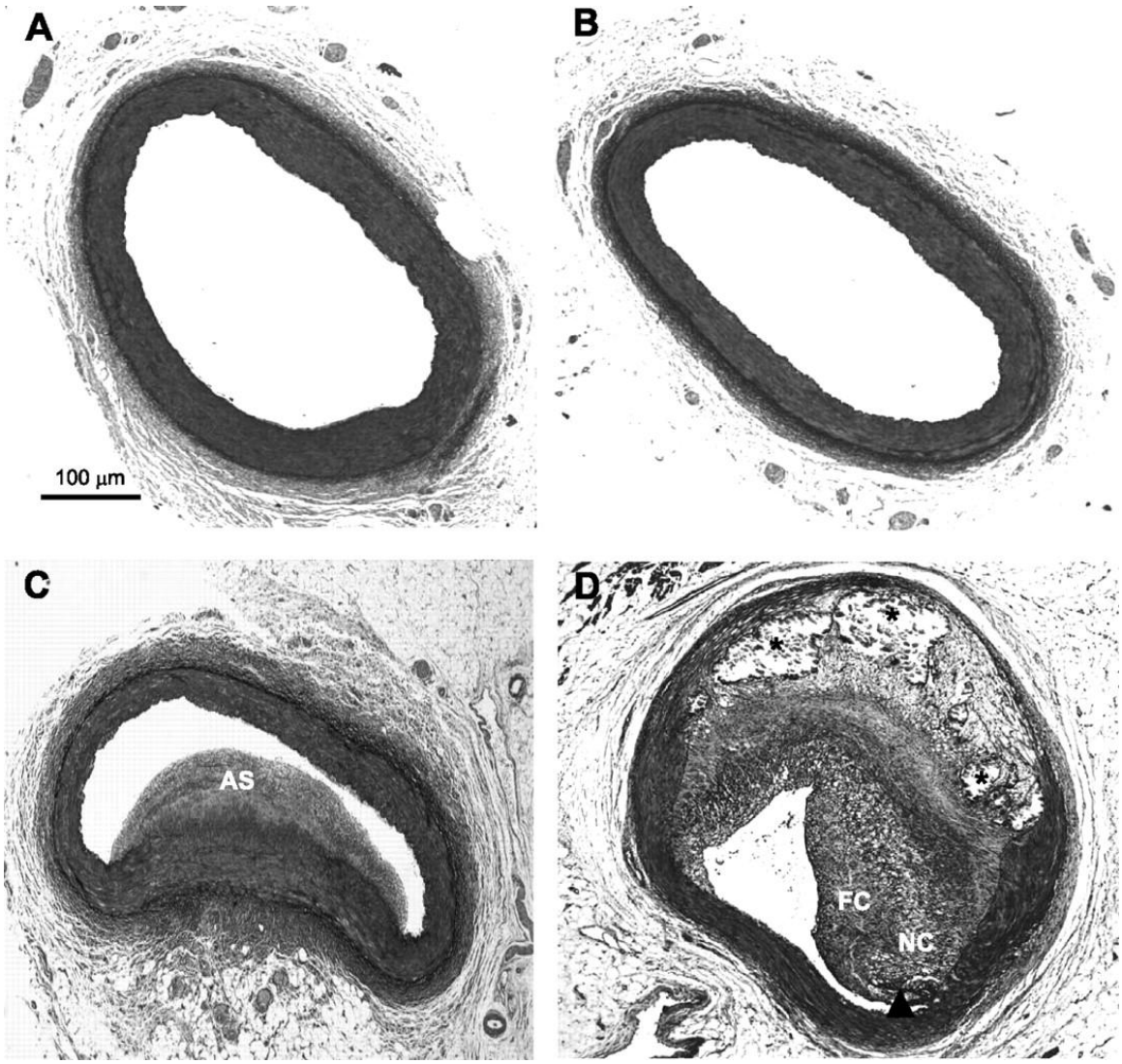


Figure 2.11 Shows Induction of both diabetes mellitus (DM) and hypercholesterolemia (HC) results in advanced atherosclerosis. Representative histological samples: control (*A*), DM only (*B*), HC only (*C*), and DM/HC (*D*). While HC only produces atherosclerosis (AS), only the DM/HC group developed complex lesions as evidenced by a large necrotic core (NC), calcifications (asterisks), and a thin fibrous cap (arrowhead). FC, fibrous cap. Movat pentachrome staining. *(Source: Damir Hamamdzic et, al ,2010)*

4. OBESITY

Obesity increases the risk for heart disease by causing the heart to work harder, which leads to hypertension. With obesity, high blood cholesterol and triglyceride levels also increase, while HDL levels decrease. Obesity is defined as a body mass index (BMI) of 30 or greater. Patients who have a larger waist measurement than hip measurement are at increased risk for CAD (McLaughlin, 2014). Obese patients are also at increased risk for developing metabolic syndrome and diabetes (AHA, 2014a). Exercise alone rarely leads to significant weight loss. A reduced-calorie diet is usually necessary as well. Overweight people with CAD may need to reduce the total number of calories that they eat each day. Referral to a dietitian may be indicated to assist patients with meal planning and monitoring. Even a modest weight loss makes a difference. Patients who are overweight should be encouraged to follow a comprehensive weight loss plan. A goal of achieving a 10% weight loss will lower a person's risk for CAD. A small but consistent weight loss of 1/2 to 2 pounds per week is the safest way to accomplish this (AHA, 2014a).

5. DIABETES

Diabetes is a strong risk factor for developing CAD. Even when glucose levels are under good control, diabetes increases the risk of heart disease and stroke. The risks are even greater if blood sugar is not well controlled. Around 65% of people with diabetes die of some form of heart or blood vessel disease (AHA, 2014a).

Patients with type 2 diabetes may have an increased risk of CAD because of disturbances in protein and fat metabolism, which may lead to weight problems. As a result, most patients with type 2 diabetes are overweight or obese. Maintaining a normal weight with diet and exercise as well as taking prescribed medications is important to maintain adequate blood sugar control (McLaughlin, 2014).

2.5 *Single Photon Emission Computed Tomography (SPECT):*

Single photon emission computed tomography produce images of gamma rays entitled by a radioactive tracer, Positron emission tomography (PET) images the two 511kev photon produced when a position comes into contact with an electron. *(Shackett, Pete,(2009).*

SPECT image are superior to planar images in contrast but at same cost to resolution because each image represent a slice through the patient. Much of the background activity is eliminated increasing the contrast resolution decreases with distance form a scintillation camera because the camera must view the patient from all angle.

2.5.1 Instrumentation

The main components of SPECT system are the scintillation camera the gantry and the computer systems (hardware and soft ware) these components work together to acquire and reconstruct the homographic images.

2.5.2 Scintillation camera:

The basic components of a scintillation camera are a collimator a sodium iodide (SPECT) crystal. Photomultiplier tubes pulse height analyzers and spatial positioning circuitry. Gamma rays (photon) pass through the collimator and cause a scintillation event in the crystal.

2.5.3Gantry:

The frame that supports the scintillation camera used for SPECT must be able to rotate and position the camera precisely. Making size and stability important factors size is practical issue because the gantry is largest part of the SPECT system.

2.5.4 Collimators:

The collimators is the focusing device of a SPECT camera gamma rays have too much energy to be focused by a lens in the same way that visible light photons are in film or digital camera. Instead collimators are made up of an array of long narrow. Collimators are rated by their sensitivity and resolution. In general the sensitivity and resolution of a collimator are inversely related a very high sensitivity collimator has low resolution and a very high resolution collimator has low sensitivity.

Parallel Hole collimators are most commonly used to SPECT but increased sensitivity can be obtained with converging collimators in which the hole converge on a line (fan beam) or appoint (cone beam) Converging collimators require more complex setup procedures than do parallel hole collimators if used for SPECT and once the images have been acquired they require special image reconstruction software that may result in much longer reconstruction times.

Converging collimators allow more of the crystal to be used which increases sensitivity; is realized with a decrease in the size of the field of view. Converging collimators pose a problem for cardiac SPECT because the field of view does not necessarily covers the entire Thorax.

2.5.5 SPECT Reconstruction:

Methods of reconstruction the radionuclide distribution from planar projections have been the subject of investigation sir ice the possibility was proven by radon in 1917 the advent of computers a accelerated research into different methods of image reconstruction and many have been proposed these reconstruction algorithms fall into two categories: interactive methods and analytic methods. Analytic methods are based on exact mathematical solution to the image reconstruction problem whereas interactive methods estimate the distribution through successive approximation.

2.5.6 Imaging and Clinical Applications:

Imaging of myocardial perfusion with radiopharmaceuticals is the most commonly performed cardiac examination in clinical nuclear medicine practice. Its primary goal is to determine the adequacy of blood flow to the myocardium, especially in conjunction with exercise or pharmacologic stress for the detection and evaluation of coronary artery disease (CAD). Although the basic principles are similar, protocols for imaging vary among the radiopharmaceuticals used. SPECT myocardial perfusion (Fred A. Mettler et al , 2012) In the 70's & 80's, SPECT was largely replaced by CAT and MRI scans because they provided superior resolution, Recently, SPECT has returned to prominent use, especially in diagnosing cardiac and neurological abnormalities, While CAT and MRI scans only provide images of static brain anatomy, SPECT offers clues to brain function by tracing blood allocation.

2.6 Radiopharmaceuticals:

Radiopharmaceutical is defined as a radioactive compound which, when administered for purposes of diagnosis or therapy, elicits no physiological response or an adverse reaction from the patient. (Adam, Sam, 2005)

Although ^{201}Tl was the first clinically successful myocardial perfusion imaging agent and is still used in many clinical settings, ^{99m}Tc labeled radiopharmaceuticals are now generally preferred. Because there are significant bio kinetic differences among these radiopharmaceuticals, protocols for imaging vary, although the basic underlying physiologic principles and rationale for interpretation remain the same. A major determinant of protocol design is whether the administered radiopharmaceutical remains fixed in the myocardium, washes out, or redistributes in the myocardium over time. Because of these differences, the choice of radiopharmaceutical influences almost every aspect of the approach to imaging, including the timing and acquisition of image sequences. Thus an understanding of the in vivo behavior of the radiopharmaceutical or combination of radiopharmaceuticals used to perform myocardial perfusion imaging is critical in determining the examination protocol and to the interpretation of the resulting images (Syed Sajid Husain,2007).

2.6.1 Common Cardiac Radiopharmaceuticals agents:

In the realm of NM there are some radiopharmaceuticals being used specifically in Myocardium Perfusion Imaging (MPI) study, for instance,

A) The most common widely used ^{99m}Tc scanning agents fall under four distinct groups of chemical compounds:

1. **^{99m}Tc-MIBI (sestamibi, Cardiolite)**
2. **Technetium-^{99m} tetrofosmin (Myoview)**

New Radiopharmaceuticals Emerging radiopharmaceuticals labeled with Tc-^{99m} and other radioisotopes suitable for SPECT imaging hold promise of providing more specific information regarding regional and global myocardial perfusion and viability status.

This is true of I-123 BMIPP, a labeled fatty acid.

B) Thallous Chloride Tl 201

2.6.1.1 ^{99m}Tc-MIBI (sestamibi, Cardiolite)

^{99m}Tc-sestamibi (^{99m}Tc-MIBI; Fig. 2.4) is a cationic, lipophilic complex that consists of 1 atom of ^{99m}Tc in a 1+ oxidation state and 6 molecules of 2-methoxyisobutylisonitrile (MIBI). Sestamibi contains isonitrile groups that form a complex with ^{99m}Tc after reduction with stannous ions. Since isonitriles are volatile and unstable compounds, MIBI is available in stabilized form as copper tetrafluoroborate adduct, [Cu(MIBI)4]BF4, which should be decomposed during radiolabelling carried out at elevated temperature. Lyophilized Sestamibi kits (Cardiolite, ^{99m}Tc-MIBI kit, CardioTop, Technescan Sestamibi, etc.) contain a mixture of [tetrakis(2-methoxy-2-methylpropyl-1-isocyanide)copper (1+)] tetrafluoroborate as the active substance .

Technetium-^{99m}-MIBI (methoxyisobutylisonitrile), or ^{99m}Tc-sestamibi, is a lipophilic complex with a positive charge that is in frequent clinical use , To ensure the positive charge of the complex, a technetium atom in a low oxidation state (+1) is reacted with the monodentate isonitrile ligand to obtain [Tc(-C=NR)6]+ with a hexacoordinated (octahedral) structure. Each carbon atom bound to the technetium possesses a non-paired electron (overlapping with the lone pair of the adjacent nitrogen), thus the technetium-sestamibi molecules are paramagnetic. Since isonitriles are volatile, not very stable compounds, MIBI is

available in stabilized form as copper tetrafluoroborate adduct, [Cu(MIBI)4]BF4, which should be decomposed during labelling, with the procedure carried out at an elevated temperature by immersing the vial in boiling water for 10 min ,Technetium-^{99m}-MIBI is taken up by the cells of the myocardium in passive diffusion ,and then appears in the cytosol and is localized in the mitrochondria. The uptake is proportional to the myocardial perfusion, and the washout is rather slow (excluding considerable redistribution). At stress, more than 3% of the injected dose is accumulated in the myocardium, while the nonbound part is eliminated via the hepatobiliary route. Technetium-^{99m}-MIBI is also taken up in tumours and metastases, expanding its clinical application.

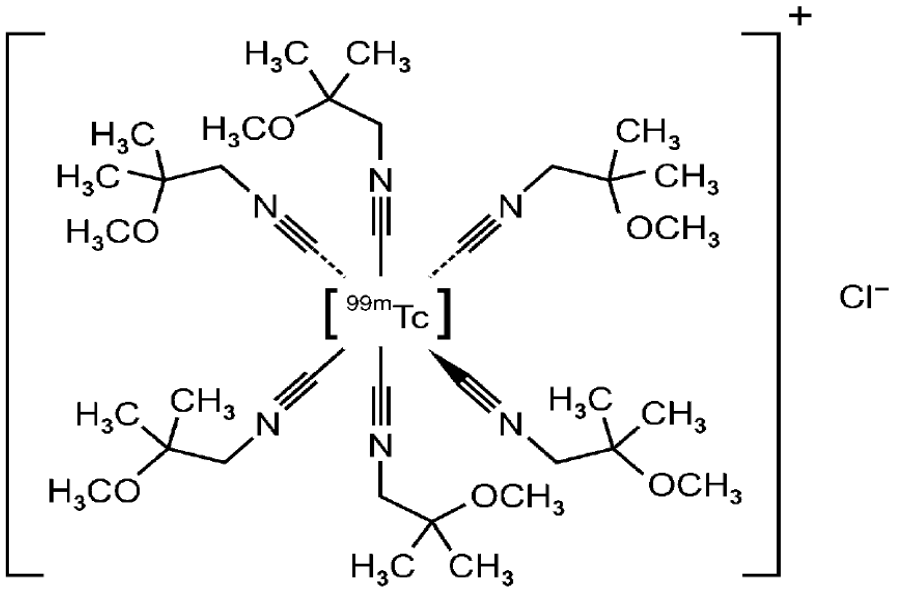


Figure 2.12: Structure of ^{99m}Tc-sestamibi ((OC-6-11)-hexakis[1- (isocyano-kC)-2-methoxy-2-methylpropane] [^{99m}Tc]technetium(I) chloride .

prime example of a radiopharmaceutical with this core is the lipophilic heart imaging agent ^{99m}Tcsestamibi, where the Tc(I) atom is coordinated by six monodentate 2-methoxy-isobutyl isonitrile (MIBI) ligands, forming a stable octahedral complex (Figure 3.3). Since the MIBI ligands are neutral the sestamibi complex retains the single positive charge of the Tc+ core. In the Cardiolite kit, the MIBI ligands are complexed into a copper/boron fluoride complex to facilitate lyophilization since MIBI alone is a volatile liquid.13 Cysteine and stannous chloride are reducing agents.35 Citrate forms complexes with Tc(V) and Tc(IV) and with Sn(II) and Sn(IV). Tin citrate complexes can increase the reducing power of the mixture because Sn(IV)-citrate is a much more stable complex than Sn(II)- citrate.7 Mannitol is a bulking agent in lyophilized samples but can also form a weak complex with reduced technetium.7 In the heating step of the radiolabeling process, the copper-MIBI complex is broken releasing the MIBI ligands. The MIBI ligands displace citrate from the preformed ^{99m}Tc-citrate intermediate to form ^{99m}Tc-sestamibi.

$$Step\ 1. \quad TcO_4^- + Citrate \xrightarrow{Sn^{2+}} Tc-Citrate$$

$$Step\ 2. \quad [Cu(I)(MIBI)_4]^+ + Tc-Citrate \xrightarrow{heat} [Tc(I)(MIBI)_6]^+$$

:

2.6.1.1.1 Image acquisition :

Begun approximately after 30-60 min after injection to allow for hepatobiliary clearance. Longer delay can be required for resting images and for stress with vasodilatators alone because of the risk of higher subdiaphragmatic technetium (^{99m}Tc) activity. There is no evidence for significant changes in myocardial tracer concentration or redistribution, therefore imaging for up to 6 hours post injection is possible. Test may be done in a one day or two days protocol.

2.6.1.2 ^{99m}Tc-Tetrofosmin

The most important technetium dioxo compound to date is the cationic complex [^{99m}Tc-(tetrofosmin)2O2]+ where tetrofosmin is the ether functionalized diphosphine ligand 1,2-bis[bis(2-ethoxyethyl)phosphino]ethane. Structural characterization of this dimeric complex has shown that the ^{99m}Tc and ^{99}Tc complexes are identical and possess the O=Tc=O+ core (*Figure 3.5).*

Because the donor ligands are neutral, the technetium complex has a net charge of 1+. The complex is labeled at room temperature employing a gluconate transfer ligand.

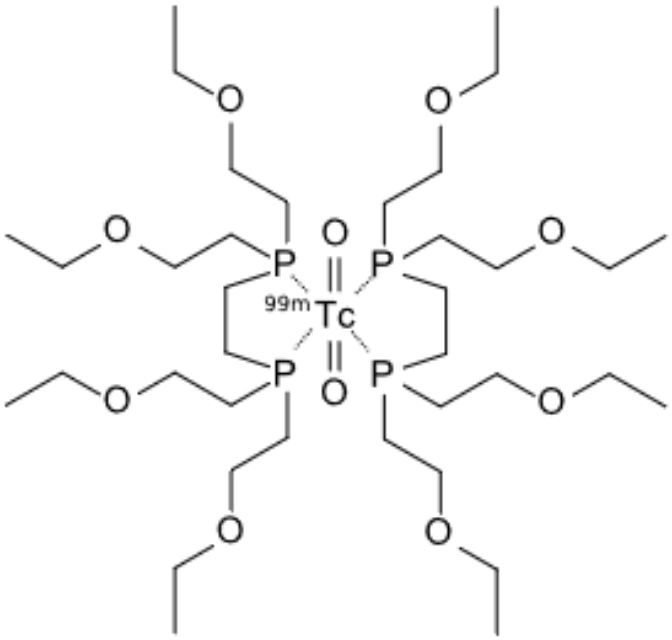


Figure 2.13: Structure of ^{99m}Tc-tetrofosmin dioxo compound.

The original formulation of ^{99m}Tc-tetrofosmin had a pH range of 8.3 to 9.1 and was prepared without admission of air to the reaction vial. It had a shelf life of 8 hours. Stability work at Amersham revealed that the complex was sensitive to autoradiolytic decomposition and that admission of 2 mL of air at the time of pertechnetate addition and a final pH range of 7.5 to 9.0 would result in a product that was stable for 12 hours. The increased stability is attributed to the ability of oxygen to scavenge reducing species (the hydrated electron eaq and the hydrogen radical H•)

$$H\bullet \quad + \quad O_2 \quad \longrightarrow \quad \bullet HO_2$$

$$e^-_{aq} \quad + \quad O_2 \quad \longrightarrow \quad \bullet O_2^-$$

.

After intravenous administration ^{99m}Tc-tetrofosmin is taken up into the heart in roportion to myocardial blood flow. Uptake does not involve cation channel transport but occurs by by potentialdriven diffusion of the lipophilic cationic complex across the sarcolemmal and mitochondrial membranes.96 ^{99m}Tc-tetrofosmin is bound in the intracellular cytosol of myocytes.97 Washout from the heart is slow being 4% per hour after exercise and 0.6% per hour at rest.98 ^{99m}Tc-tetrofosmin is used in nuclear medicine to assess myocardial perfusion in ischemia and infarction

Technetium (^{99m}Tc) tetrofosmin complex injection is a sterile solution of technetium^{99m} complexed with 1,2 bis[bis(2-ethoxy-ethyl)phosphino]ethane (tetrofosmin) that is present in excess. The injection is suitable for intravenous administration and contains sufficient sodium chloride to make the solution isotonic with blood. The content of technetium-^{99m} is not less than 90% and not more than 110% of the content of technetium-^{99m} stated on the label at the reference date and time stated on the label. Not less than 90% of the total technetium-^{99m} radioactivity is present as technetium (^{99m}Tc)

tetrofosmin complex. The injection contains a variable quantity of tin (Sn) not greater than 1 mg/ml.

2.6.1.3 Thallous chloride Tl201:

Tl^{201}-Thallium as thallous chloride 37 MBq/ml The specific activity is more than 18.5 GBq $(500\ mCi)/mg$ thallium.(Figure 3.6) Tl^{201} decays to Hg^{201} by electron capture with a half-life of 73.1 hours.

Most important radiation emitted

Energy level	Abundance (%)
69 keV-X-rays	27.4
80 keV-X-rays	20.5
135 keV-γ-rays	2.7
166 keV-γ-rays	1.6
167 keV-γ-rays	10.0

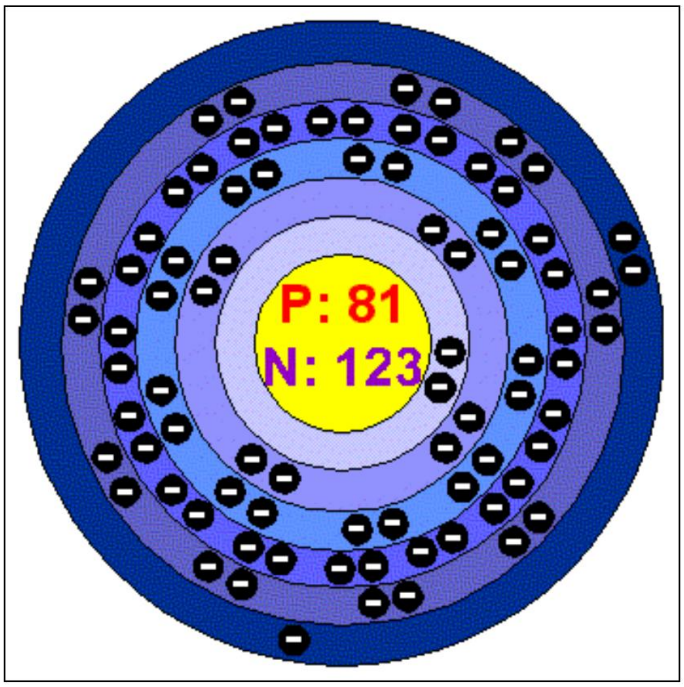


Figure 2.14: Elaborates chimical Structure of *Thallous chloride Tl201* *(www.chemicalelements.com/elements)*

Thallium Tl ^{201} is cyclotron produced with no carrier added. The radionuclidic composition at calibration time, expressed as percent of total activity is not less than 98 percent Thallium Tl ^{201} with not more than 0.1 percent Thallium Tl 200, not more than 1.2 percent Thallium Tl ^{202}; not more than 0.2 percent Lead Pb ^{203}, and not more than 0.3 percent all others. The concentration of each radionuclide contaminant changes with time. Therefore, it is recommended that Thallous Chloride Tl ^{201} Injection be administered close to calibration time to minimize the effect of higher levels of radionuclidic contaminants pre and post calibration. Graph 1 shows maximum concentration of each radionuclidic contaminant aS a function of time.

2.6.1.3.1 Patient preparation &Image acquisition

Fasting during 4 hours before the examination is recommended. Thallous chloride (^{201}Tl) injection can be done either at rest or during intervention tests: conventional stress test or a similar test like electro stimulation or pharmacological test. The first set of images can be acquired few minutes after injection. Thallium redistribution can be studied with a new set of images acquisition obtained between 3 to 24 hours after injection. In some cases, instead of the redistribution study (or after it), reinduction of 37 MBq of thallium can be done to evaluate myocardium viability.

2.6.1.1.3.2 Dosage

Must be handled with appropriate safety measures. measure patient dose by a suitable radioactivity calibration system immediately before administration.

• For myocardial imaging in adults:

– Planar 37 to 74 MBq (1 to 2 mCi)

– SPECT 74 to 111 MBq (2 to 3 mCi)

• For localization of parathyroid hyperactivity, planar

or SPECT – imaging, 75 to 130 MBq (2 to 3.5 mCi)

Chapter two-Section two

2.7 Literature Review

Ayalew A et al, 2000 has mentioned that the prognostic values of both radiopharmaceuticals (^{201}Thallium-^{99m}Tc-Sestamibi) depending of their biodistribution over particular myocardium territories is a matter of debate, **Raymond taillefer et al, 1997** have investigated with the isonitrile complexes have shown them to undergo pattern of biologic distribution different from that of^{201}TI, Another study revealed that patients could be shown to have significantly higher heart-to-lung ratios as compared to those in both other groups, both heart-to lung- and heart-to-whole body ratios tended to decrease with a higher degree of CAD **Agnieszka Manka-Waluch et,al 2007** , as classified by American Heart association **Cerqueira et al, 2002**, **Richard M. Fleming et. al 2011** explained that not only the loss of isotope to an ischemic myocardial region over time; but, also accounts for "wash-in." "Wash-in" was noted in 15% of the cases where regions of myocardium were supplied by "critically" narrowed arteries and arteries whose "vulnerable plaques" were ready to rupture. In these individuals the combination of severely disturbed flow through critically narrowed and/or unstable coronary lumen passages and relatively large regions of ischemic myocardium with impaired ability to accumulate ^{99m}Tc-sestamibi, results in a delay in initial isotope counts, **Moretti, J.L., et al 2005** mentioned that loss of influx in cells at an early stage of apoptosis owing to a decrease in their electrical gradient, lack of retention in resistant cells mediated by multidrug resistant proteins and/or overexpression of

the anti-apoptotic protein Bcl-2, preventing mitochondrial accumulation, means that there will be poor accessibility of ^{99m}Tc-MIBI to the tumor, decreased viability and electrical gradients in 'over-aged' and hypoxic cells, myocardial perfusion imaging (MPI) according to their specific territories within the myocardium, including Left Anterior descending Artery (LAD), Right anterior descending Artery (RCA), and Left circumflex Artery (LCX)*)* are divided into 17 segments as per the American Heart Association (AHA**), Ayalew et al, (2000)** stated that the myocardial fractional retention of both ^{201}Tl and MIBI is strongly correlated with the decrease in coronary flow during ischemia, **Sherif et al, (1998)** using ^{99m}Tc-MIBI mentioned that the quantitative analysis shows increased risk in relation to the severity of the abnormality with thallium-^{201}.

Baskot Branislav et al 2011 has mentioned that in case of expiration date of the radiopharmaceutical, the body treated as foreign body and further being captured in liver , Also **S.B. KHAMIS et.al,2013** have elaborated that sub-optimal heating of the respective radiopharmaceutical might cause the radiopharmaceutical to miss target and goes to salivary gland or thyroid in a form of pertechnetate ($^{99m}TcPCO_4$), several studies have correlated many factors (preventable or non-preventable factors) which will contribute in the development of coronary artery disease (CAD) leading to IHD for example **Boudi, 2014** has mentioned that mortality and morbidity are higher in the elderly. More than 80% of people who die of CAD are aged 65 years or older , American heart association also addressed that elderly women who have heart attacks are more likely than men are to die from them within a few weeks **AHA,**

2014, but in the other hand **Georgoulias et.al 2010** has mentioned that the prevalence of (IHD) among both genders falling within the age range of 40 to 60 years, Regarding gender as positive or negative factor, **Boudi, 2014** has mentioned that in the United States, 9.1% of men and 7.0% of women have the disease. Women tend to develop symptomatic coronary artery disease about 10 years later than men. In the United States, men over 40 years of age have a 49% chance of developing the disease in their lifetime, while the chance for women over the age of 40 years is 32% It is thought that the higher estrogen levels in premenopausal women protect them from some of the heart damage done by atherosclerosis, but this protection disappears after menopause, this study has handeled the human race as a factor for myocardium reversibility and the role of nuclear medicine to detect the ischemic portion within the myocardium in sudan and middle east, **Fox et al, 2001** stated that in the U.K Coronary artery disease is the cause of 52% (95% CI 43–61%) of incident heart failure in the general population under 75 years, **Moberg et al., 1972; Platia el al., 1975** have observed higher long- term mortality rates among patients with proximal as opposed to distal left anterior descending (LAD) coronary artery lesions regardless to the number of diseased vessels, **Boudi, 2014** for instant has mentioned that Americans of Asian Indian origin are 2 to 3 times as likely as European Americans to develop coronary artery disease , **McLaughlin, 2014**. Addressed that Patients who have a larger waist measurement than hip measurement are at increased risk for CAD, and individuals with familial hypercholesterolemia, an inherited metabolic disorder affecting the low-density

lipoprotein cholesterol (LDL) receptors, carry a genetic mutation that makes it difficult for their cells to remove LDL from their blood, he also mentioned that as Obesity increases the risk for heart disease by causing the heart to work harder, which leads to hypertension. With obesity, high blood cholesterol and triglyceride levels also increase, while HDL levels decrease, Patients with type 2 diabetes may have an increased risk of CAD because of disturbances in protein and fat metabolism, which may lead to weight problems. **American Heart Association (AHA,2014)** ,**Gibbons et al, (1997)** showed that: ischemic disease was higher incidence among male and increases as the age increases also mentioned that Obese patients are also at increased risk for developing metabolic syndrome and diabetes, **Burggraf and Parker, (1975) and Webster et al, (1974)** they have mentioned that in several natural history studies an increased mortality in patients with single-vessel disease of the left anterior descending coronary artery of 2-470 compared with 0.5-2% for isolated right coronary artery stenosis has been reported **,Fred et al, 2012** mentioned that nuclear medicine with utilization of ^{99m}Tc-MIBI and ^{201}TL Radiopharmaceuticals to determine the adequacy of blood flow to the myocardium, especially in conjunction with exercise or pharmacologic stress for the detection and evaluation of coronary artery disease (CAD). Although the basic principles are similar, protocols for imaging vary among the radiopharmaceuticals used, However **Brown et al, 1983** has mentioned that^{201}Tl showed some disadvantages for imaging due to its physical and biologic characteristics and its lower photon energy, and attenuation and scattering from overlying tissues.

Chapter Three

Chapter three-Section one

Methodology

3.1 Tools and equipment:

The following chapter will highlight all the experimental materials, equipments, measuring devices, procedures employed to perform measurements and the methods of analysis.

3.1.1 Single Photon Emission Computed Tomography (SPECT):

Gamma cameras which used for the study were dual headed gamma cameras (SPECT), **(**MEDISO – Nucline™ SPIRIT DH-V), and Philips/ADAC Forte SPECT (Philips Medical) Gamma Camera used for acquisitions, SPECT is using LFOV with LEHR Collimators.

3.1.2 Treadmill

The Bruce Treadmill Test is an indirect test that estimates VO2 max using a formula rather than using direct measurements that require the collection and measurement of the volume and oxygen concentration of inhaled and exhaled air. This determines how much oxygen the athlete is using.

The Bruce Protocol:

The Bruce Protocol is a maximal exercise test where the athlete works to complete exhaustion as the treadmill speed and incline is increased every three minutes (See chart). The length of time on the treadmill is the test score and can be used to estimate the VO2 max value. During

the test, heart rate, blood pressure and ratings of perceived exertion are often also collected.

Bruce Treadmill Test Stages

Stage 1 = 1.7 mph at 10%
Grade Stage 2 = 2.5 mph at 12%
Grade Stage 3 = 3.4 mph at 14%
Grade Stage 4 = 4.2 mph at 16%
Grade Stage 5 = 5.0 mph at 18%
Grade Stage 6 = 5.5 mph at 20%
Grade Stage 7 = 6.0 mph at 22%
Grade Stage 8 = 6.5 mph at 24%
Grade Stage 9 = 7.0 mph at 26%

The Bruce Protocol Formula for Estimating VO2 Max

For Men $VO2\ max = 14.8 - (1.379 \times T) + (0.451 \times T^2) - (0.012 \times T^3)$

For Women $VO2\ max = 4.38 \times T - 3.9$

T = Total time on the treadmill measured as a fraction of a minute (ie: A test time of 9 minutes 30 seconds would be written as T=9.5).

Because this is a maximal exercise test, it should not be performed without a physician's approval and without reasonable safety accommodations and supervision.

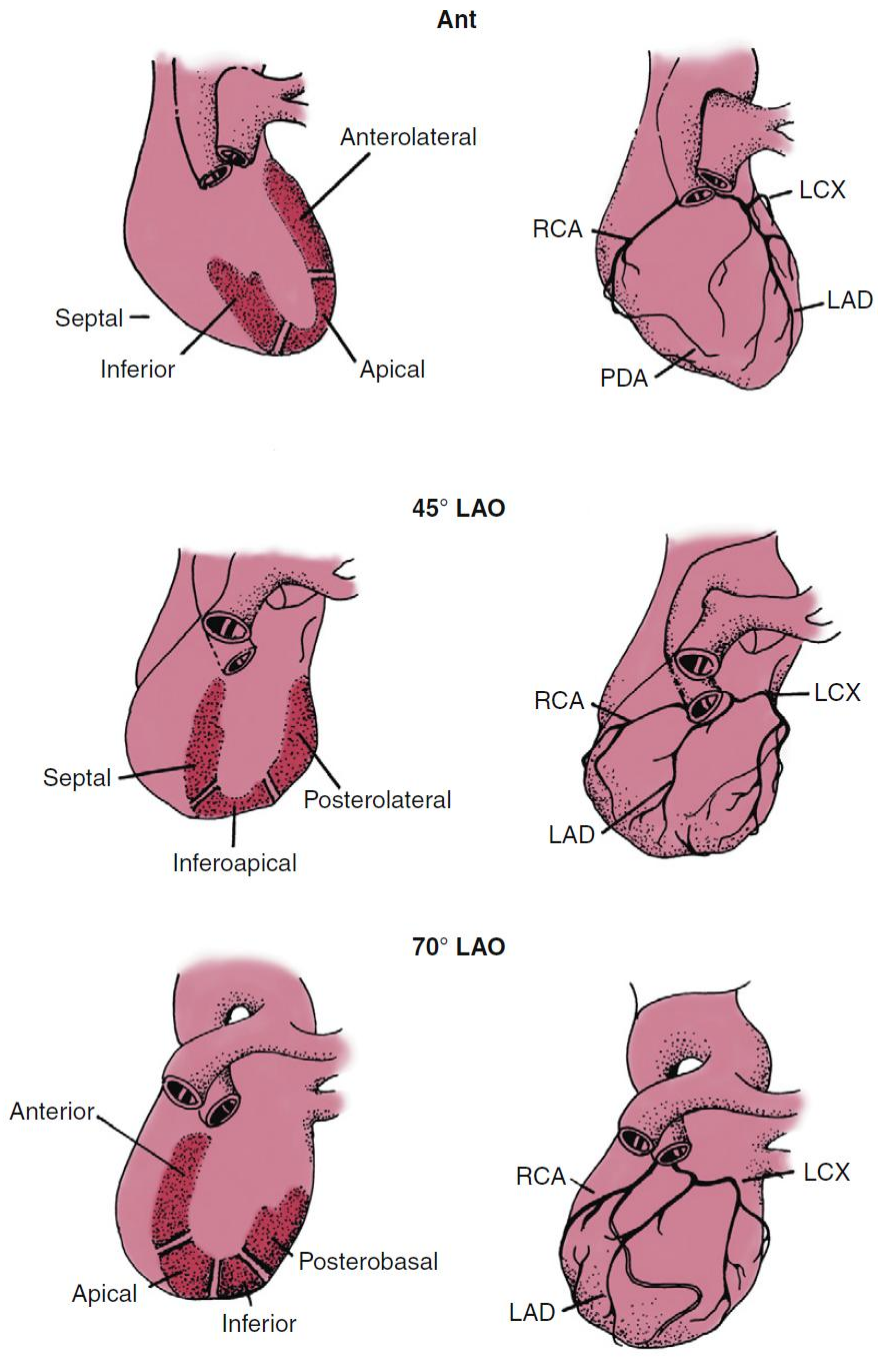


Figure3.1: Shows different orientations for imaging of myocardium (*Fred A. Mettler et al , 2012)*

3.1.3 Radiopharmaceuticals:

3.1.3.1 ^{99m}Tc-MIBI (sestamibi, Cardiolite)

^{99m}Tc-Sestamibi The range of intravenously administered radioactivity is 185–925 MBq (5–25 mCi); the typical dosage is 740 MBq (20 mCi). This radiopharmaceutical localizes in both parathyroid tissue and functioning thyroid tissue but usually washes out of normal thyroid tissue more rapidly than out of abnormal parathyroid tissue. (Hyperplastic parathyroid glands generally show faster washout than most adenomas.)

3.1.3.2 Thallous Chloride Tl ^{201}

Injection is supplied in isotonic solution as a sterile nonpyrogenic diagnostic radiopharmaceutical for intravenous administration. Each unit dose contains 1 mL and each milliliter contains 37 MBq, 1 mCi of Thallous Chloride Tl ^{201} Injection at calibration time. The pH is-adjusted to 4.5-7.5 with hydrochloric acid or sodium hydroxide. lt is made isotonic. with 9 mg sodium chloride/mL and is preserved with 0.009 mL benzyl alcohol/mL.

3.1.3 Post-processing softwares:

3.1.3.1 Syngo.via Server (VA20A/VB10)

Syngo.via is the universal imaging software (Siemens Healthcare) for 3D reading and advanced visualization. Multi-user, multi-modality, and multi-disciplinary,Syngo.via is including purchased applications dedicated for cardiac applications which has been used in this study such as (Cedars)&(Corridor4DM) QPS for processing purposes.

3.1.3.2 Cedars-Sinai Medical Center (CSMC)

It's a Cardiac Suite of applications is intended to enable an automated display, review, and quantification of Nuclear Medicine Cardiology medical images and datasets. CSMC Cardiac Suite may be used in multiple settings including the hospital, clinic, doctors office, or remotely. The results provided should be reviewed by qualified healthcare professionals (e.g., radiologists, cardiologists, or general nuclear medicine physicians) trained in the use of medical imaging devices.

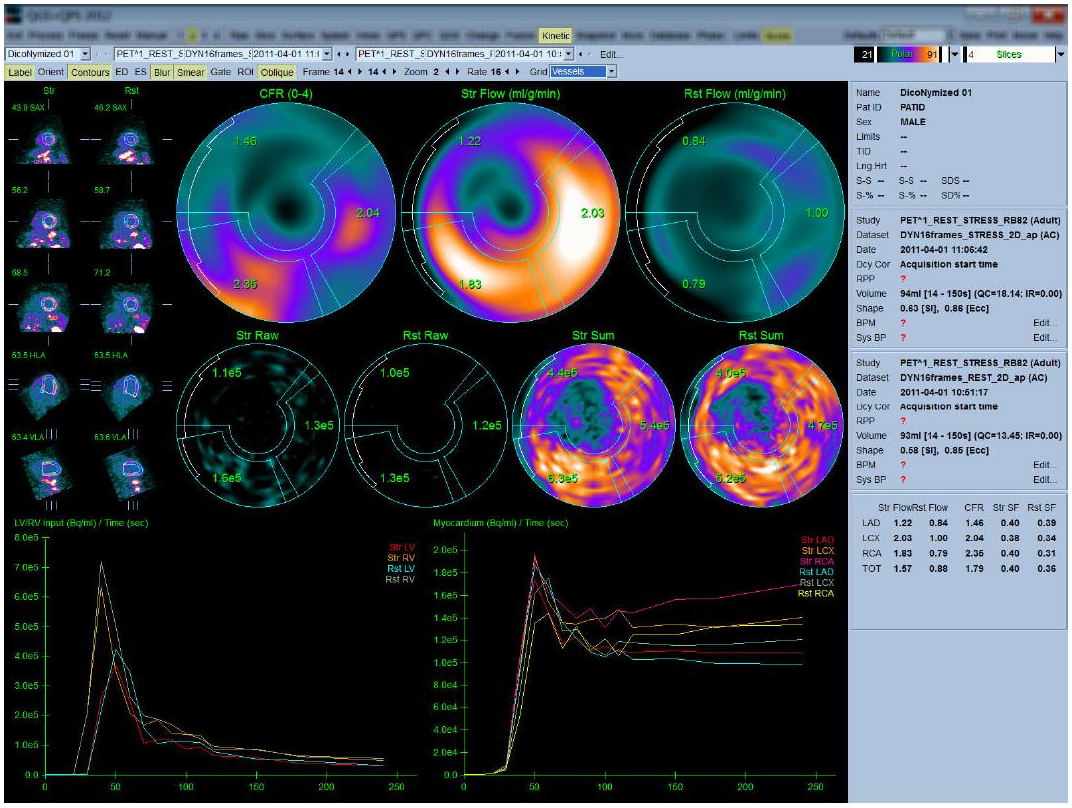
CSMC Cardiac Suite will be marketed as a comprehensive application suite that includes QGS+QPS (Quantitative Gated SPECT + Quantitative Perfusion SPECT) in a single application (aka AutoQUANT) and CSImport applications. This allows automatic

processing and review of quantitative and qualitative information generated by nuclear medicine studies. Purchasable options consist of Quantitative Blood Pool SPECT (QBS), QARG (for reporting purposes), Fusion (SPECT/CT/CTA and/or PET/CT/CTA), AutoRecon, Motion Correction (MOCO) and QPET. QPET also includes viability quantification and two additional databases (rubidium and ammonia) for processing PET studies. QGS+QPS is an application which combines both Quantitative Perfusion SPECT (QPS) and Quantitative Gate SPECT (QGS) into a common application. Quantitative Perfusion SPECT (QPS) is an application designed for LV (Left Ventricle) and RV (Right Ventricle) extraction and analysis. QPS provides a tool to review and quantify perfusion Cardiac SPECT and PET data sets to determine the location, orientation, and anatomical extent of the left ventricle of the heart, to construct 3D

contour maps of the heart, and to calculate the heart volume. Physicians use this information to assess the anatomical and physiological functionality of the heart and analyze the presence of myocardial defects through comprehensive imaging modalities. Stress-Rest Registration is a direct method for detecting changes between stress and rest images. It is a practical and fully automatic algorithm for quantification of stress-induced changed from paired stress and rest scans and does not use protocol-specific databases. Prone-supine quantification allows quantification of perfusion

on prone images as well as combined quantification of prone/supine datasets by applying heuristic rules, which allow automatic elimination of image artifacts based on the relative defect locations on prone and supine images. The shape index parameter defines 3D left ventricular (LV) geometry derived from LV contours in end systolic and end diastolic phases. QPS includes an algorithm for the quantification of myocardial perfusion, using normal limits created from studies of low-likelihood normal patients only. The algorithm has been validated in a large group of patients demonstrating equivalent diagnostic performance despite the use of simplified normal limits. The following databases are being provided (for male and female): Prone Stress MIBI, Rest MIBI, Rest MIBI AC (Attenuation Corrected), Rest Thallium, Stress MIBI, Stress MIBI AC, Stress Thallium. Optional normal limits databases offered are Rubidium for PET, Ammonia for PET. QPS provides the ability for user generated normal limits files using the simplified method. QPS also includes a variable, Total Perfusion Deficit (TPD), which combines defect extent and severity values. The new quality control (QC) automatically detects quantitative segmentation failures. In the event of a failure a different algorithm is applied. Quantitative Gated SPECT (QGS) is an application designed for LV (Left Ventricle) and RV (Right ventricle) extraction and analysis. QGS provides a tool to review and quantify function Cardiac SPECT and PET data sets to determine the location, orientation, and

anatomical extent of the left ventricle of the heart, to construct 3D contour maps of the heart, and to calculate the heart volume (for the left ventricular wall). Physicians use this information to assess the anatomical and physiological functionality of the heart and analyze the presence of myocardial defects through comprehensive imaging modalities. A new Phase page included in QGS page gives access to phase information for gated datasets. A new technique to create cardiac "motion-frozen" perfusion or viability images, by warping ECG-gated images to the end-diastolic position has been added. Such "motion-frozen" perfusion and viability images have improved resolution and contrast by removing blurring effect caused by cardiac motion. The new quality control (QC) automatically detects quantitative segmentation failures. In the event of a failure a different algorithm is applied,QGS+QPS can also generate and display TID (Transient Ischemic Dilation) and LHR (Lung Heart Ratio or Lung Heart Counts). A new group processing algorithm has been added which allows for simultaneously solving left ventricular geometry for all of the available datasets. It allows the algorithms, in regions where structure cannot be definitively determined for one or more of the datasets, to make decisions that exploit all the available information and that do not introduce arbitrary inter-study inconsistencies.(Cedars-Sinai Medical Center,2014)



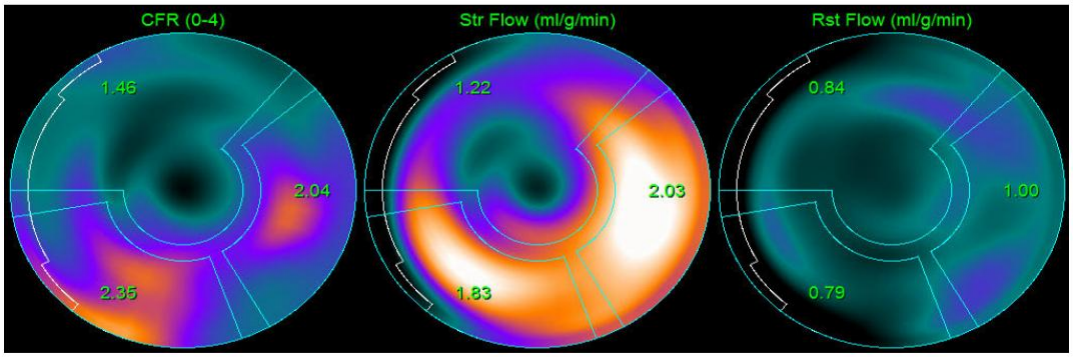


Figure3.2: Shows the user interface used by the researcher to quantify ratios fin cedars-sini application. ***(****Cedars-Sinai Medical Center,2014)*

3.3.4 *The Corridor4DM*

Is an application is intended to provide processing, quantification, and multidimensional review of the biodistribution of radionuclides in the body using planar and tomographic images. The application performs quantitative measurements of tracer uptake over time to aid in the interpretation of myocardial perfusion emission tomographic images to assist appropriately trained medical professionals in their assessment of cardiac health.

4DM algorithmically determines and displays the left ventricular endocardial and epicardial surfaces. These surfaces provide quantitative assessments of cardiac function, e.g. systolic and diastolic function, regional wall thickening, wall motion, transient ischemic dilation (TID), phase analysis, and generalized factor analysis of dynamic sequences (GFADS).

4DM provides regional assessments of myocardial perfusion, metabolism, wall thickening, wall motion, time to peak contraction, time to peak thickening, perfusion reversibility between stress and resting conditions, viability, and GFADS. 4DM provides this regional information in 2D polar maps and 3D surface-rendered images of the left ventricle and it provides a comparison of the patient-specific regional information in comparison to a similar patient population with a low likelihood of cardiac disease.

4DM provides several options for verifying the quality of the input data and processing of that data. Data cines, image co-registration, surfaces, valve plane, and polar map QA displays of all selected studies are provided and available both during processing and subsequently during image interpretation. (*Corridor4dm Invia, Llc,2015*)

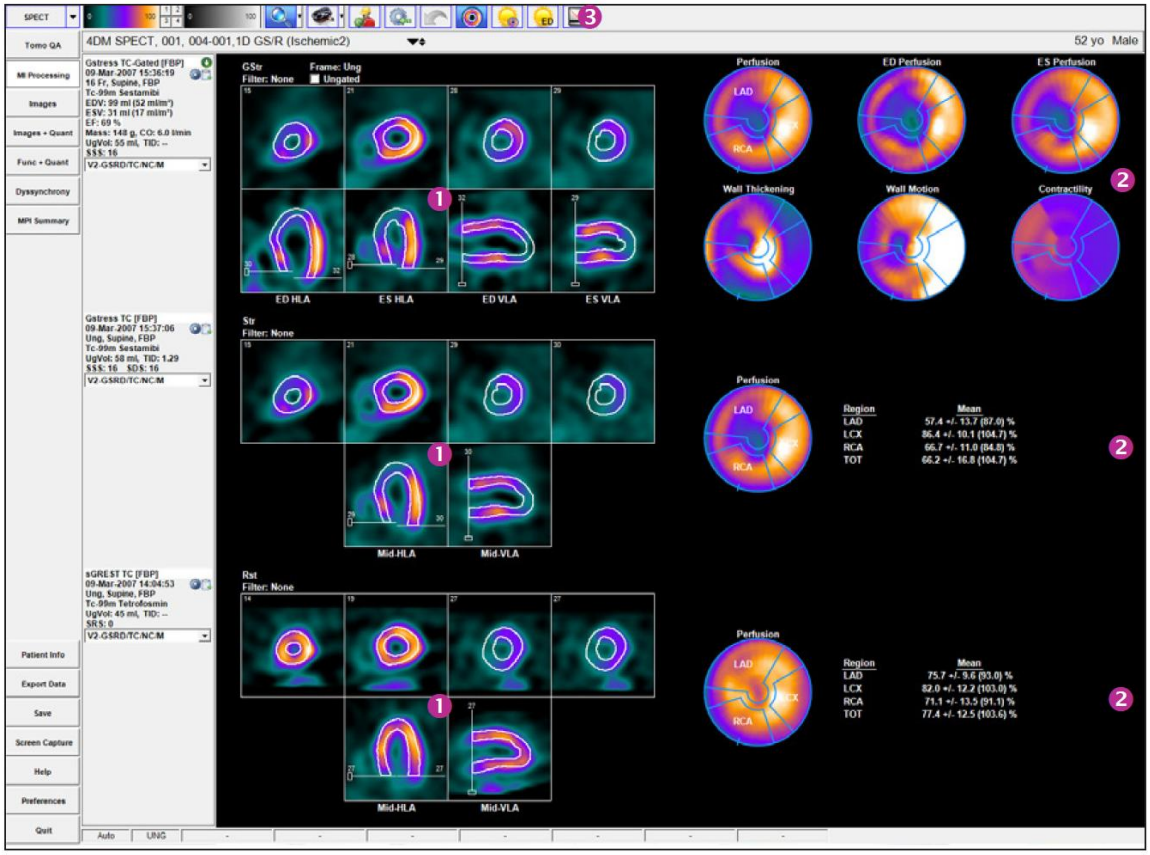


Figure3.3: Shows the user interface used by the researcher in corridor 4DM application.*(Corridor4DM INVIA, LLC,2015)*

Chapter three-Section two

3.2Methodology

3.2.1 Procedure and technique:

In this thesis the researcher used the descriptive and explanatory methods to cover the thesis issue ,A sample of consecutive one hundred and fifty patients underwent treadmill stress, Bruce's model of stress, using Philips/ADAC Forte SPECT (Philips Medical) Gamma Camera used for acquisitions, SPECT is using LFOV with LEHR Collimators, Atypical Bruce technique of treadmill exercise Nuclear medicine myocardial perfusion imaging MPI has been applied, in which all the patients undergo The sequence of serially acquired images in conditions of stress and rest , Images will be obtained over a 76° orbit from the right anterior oblique 45° view to the left posterior oblique 45° view, using a dual-head SPECT, variable-angle gamma camera equipped with (LEHR)collimators.

3.2.2 Study group:

Group (I): patients with known Ischemic Heart Disease (IHD) sample of 73 patients (42 males) (31 Females) injected with 740MBq 20-25mci ^{99m}Tc-Sestamibi undergo ^{99m}Tc-MIBI nuclear medicine investigation in (RICK) hospital (archived).

Group (II): A sample of 77 patients suffering from (IHD) (56 males) (21 females) injected with 2-3 mCi undergo TL-^{201} nuclear medicine investigation. (Practical)

All patients in both groups were suffering from (IHD) either (Reversible or non-reversible) and both patients in both groups were injected and had the acquisitions according to the specific radiopharmaceutical. *(*^{201}*Thallium and 20 mCi* ^{99m}*Tc-MIBI).*

3.2.3 Samples of Measurements:

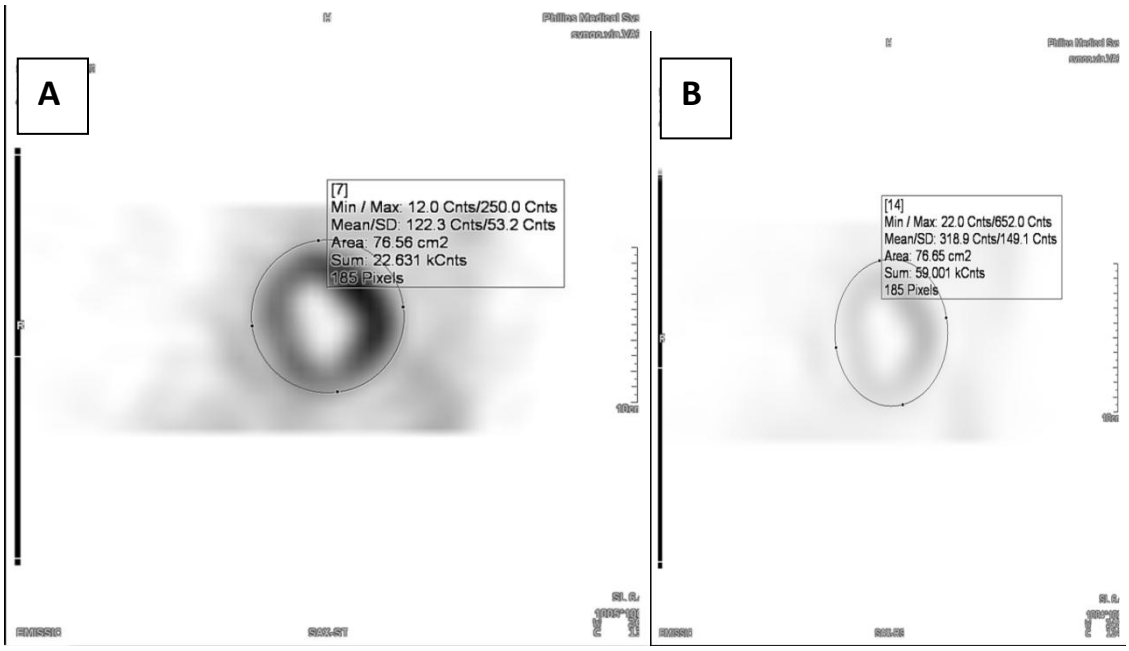


Figure3.4: Shows measurement of the whole heart sum counts/second/Pixel (c/s/p) using ROI in both conditions Stress/Rest

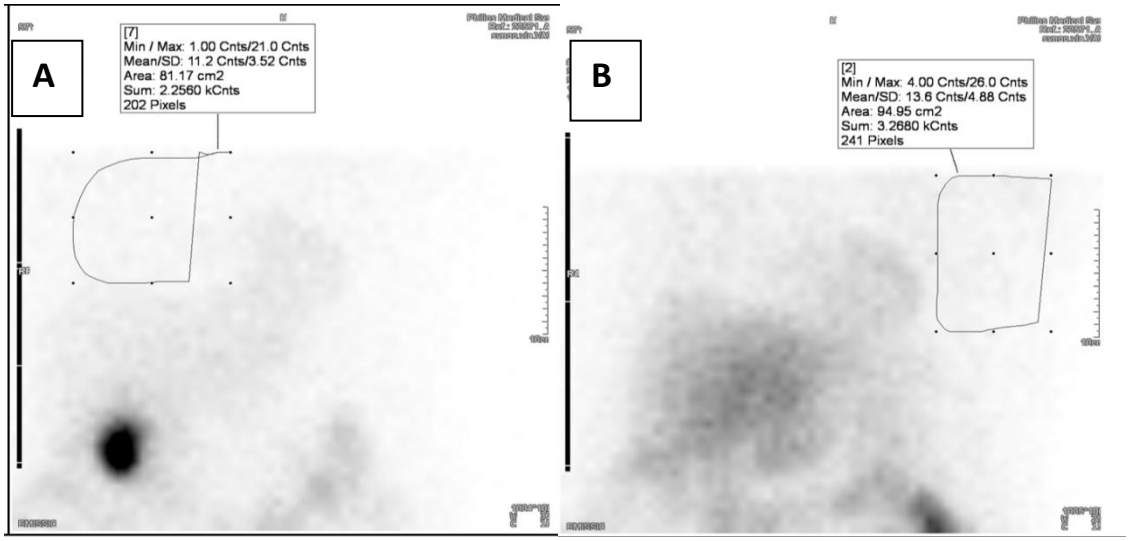


Figure 3.5: Shows measurement of the Right (A) and Left (B) Lungs sum counts/second/Pixel (c/s/p) using ROI in both conditions Stress/Rest

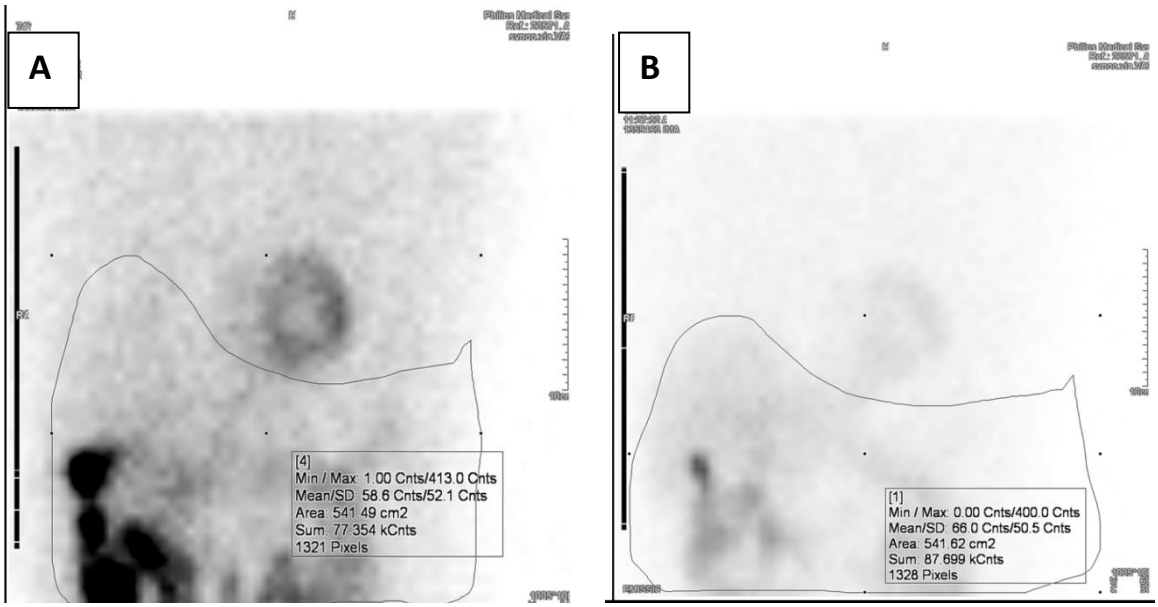


Figure3.6: Shows measurement of gastrointestinal track (GIT) at Stress (A) and Rest (B) Lungs sum counts/second/Pixel (c/s/p) using ROI in both conditions Stress/Rest

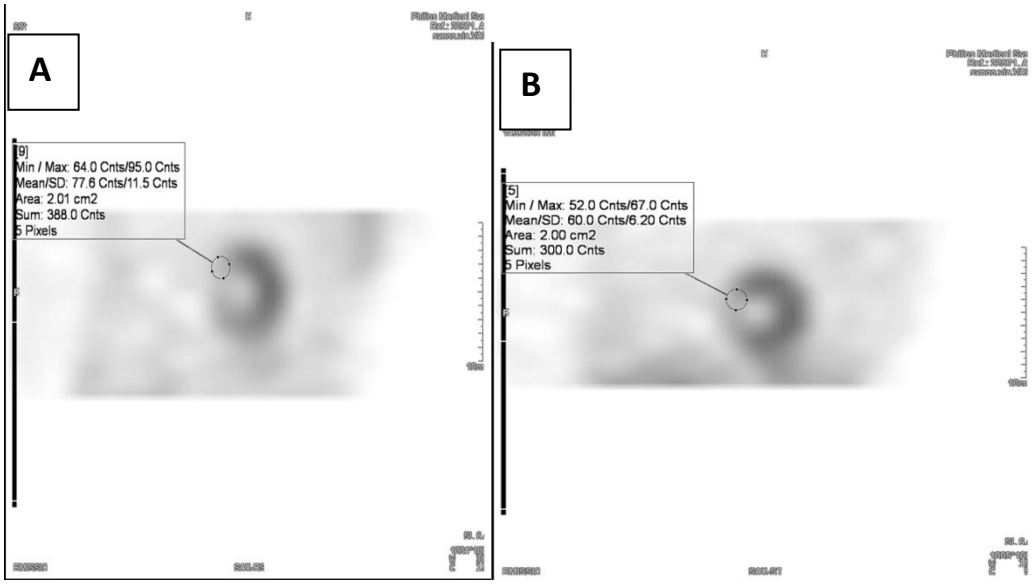


Figure3.7: Shows measurement of the Affected LAD territory of myocardium at rest(A) and stress (B) Lungs sum counts/second/Pixel (c/s/p) using ROI in both conditions Stress/Rest

3.2.4 Image interpretation and data analysis:

A number of relatively fixed size ROI's drown around different myocardium territories i.e. LAD,RCA and LCx, portions using the static projections of LV SPECT within two different sets of images (Stress, Rest), using two basic executing systems", Synogo.via (Siemens Healthcare) and (Cedars)&(Corridor4DM) QPS for processing purposes. The mean counts per second per pixels (c/s/p) of the ROI's have been measured to determine the volume of radiopharmaceutical concentration within the ischemic portion, of the heart, This steps were taken to measure the 1st pass of the radiopharmaceuticals into ischemic portion using stress set of DICOM images, The resulted variables of each ROI were maximum, minimum counts, mean counts, slandered deviation , area, and number of pixel, Next, Rt. Lung to Heart Ratio, Lt. Lung to Heart Ratio, Whole Heart to ischemic portion ratio, GIT to Heart ratio, Taking into consideration the functional values of LVEF, Another number of ROI's were drown and measured for reversibility estimation of both radiopharmaceuticals, A fixed the time post injection for the ^{201}Thallium and ^{99m}Tc-MIBI were calculated in reference to the injected dose *(2 mCi~111 MBq of ^{201}Thallium and 740 MBq 20 mCi ^{99m}Tc-MIBI),* Counts of ROI were next analyzed and set to tables using Excel (Microsoft).

Chapter Four

Chapter Four

4.1Results

In this chapter highlights the estimated results from the collected data (Reversibility) of the myocardium using both radiopharmaceuticals ^{201}TL and ^{99m}Tc-MIBI, the selective factors effects reversibility in patients suffering of (IHD) such as Age of the sample, distribution of sample based on pathological condition of (IHD) and the gender involved by (IHD) in the forms of bar, Pie and curves followed by discussion and analysis.

The results also shows factors affecting the tissue reversibility in left anterior descending artery (LADR),(RCA),(LCx) of the heart as well as the radiopharmaceutical uptake ratio in whole heart, right/left lungs, gastrointestinal tract (GIT- (*Liver, Gallbladder, spleen*)) and the affected heart segment (territory) for the stress and rest.

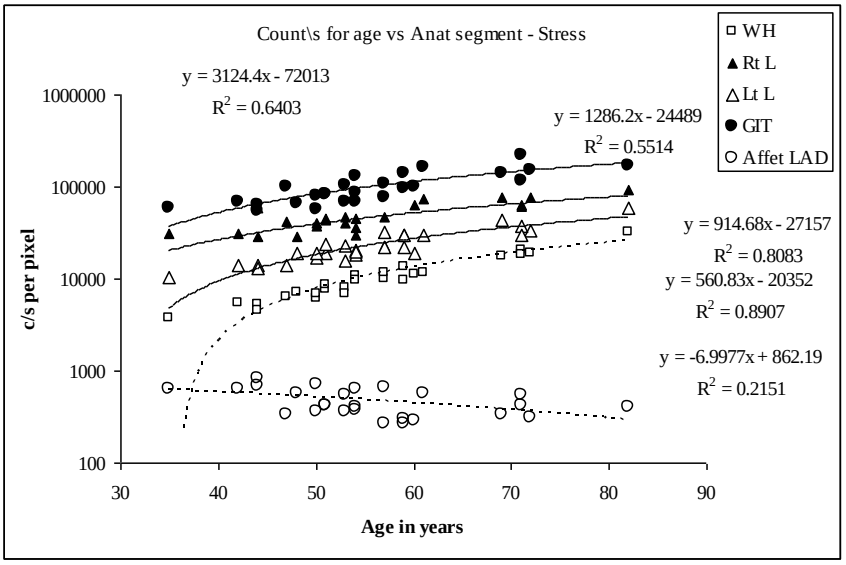


Figure 4.1: shows the correlation between Age versus count/sec at stressed cardiac study for whole heart, Rt\Lt lungs, GIT and the ischemic heart segment.

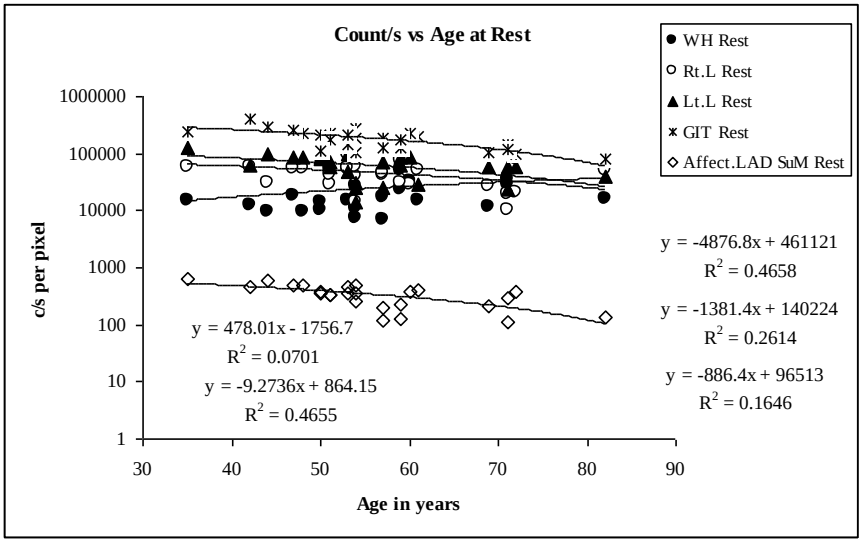


Figure 4.2 shows the correlation between Age versus count/sec at rest cardiac study for whole heart, Rt\Lt lungs, GIT and the ischemic heart segment.

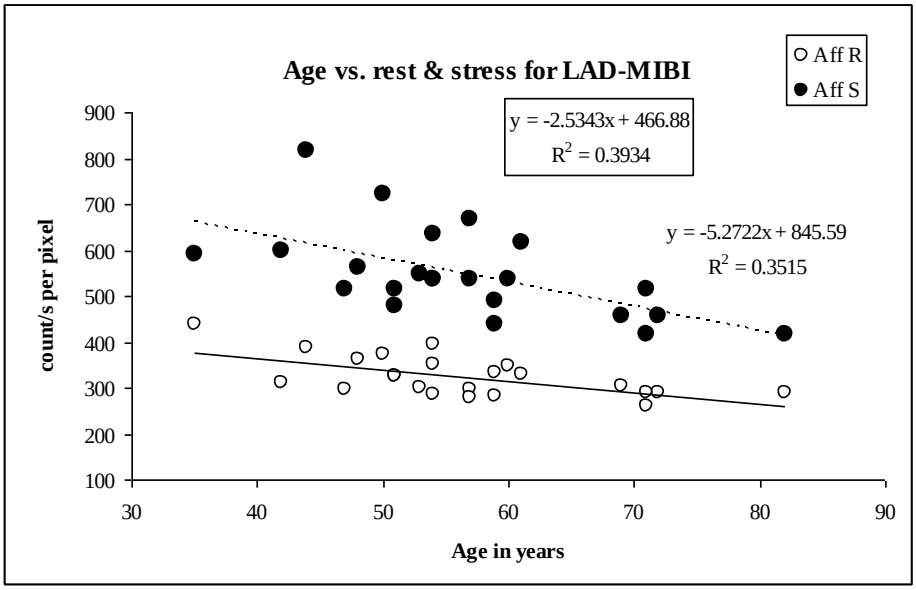


Figure 4.3 shows the correlation between Age versus count/sec at rest & stress cardiac study for and the ischemic heart segment.

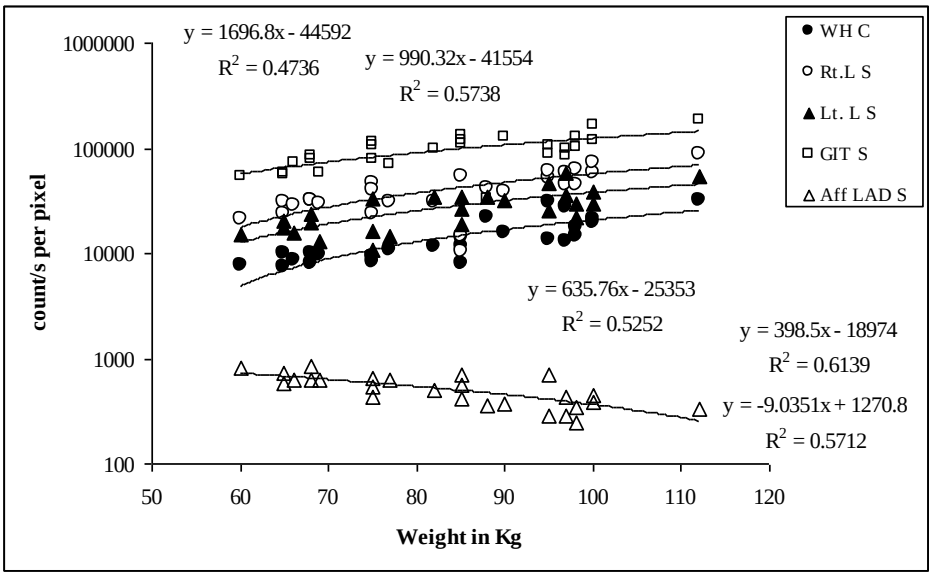


Figure 4.4 shows the correlation between weight in Kg versus count/sec at stressed cardiac study for whole heart, Rt\Lt lungs, GIT and the ischemic heart segment.

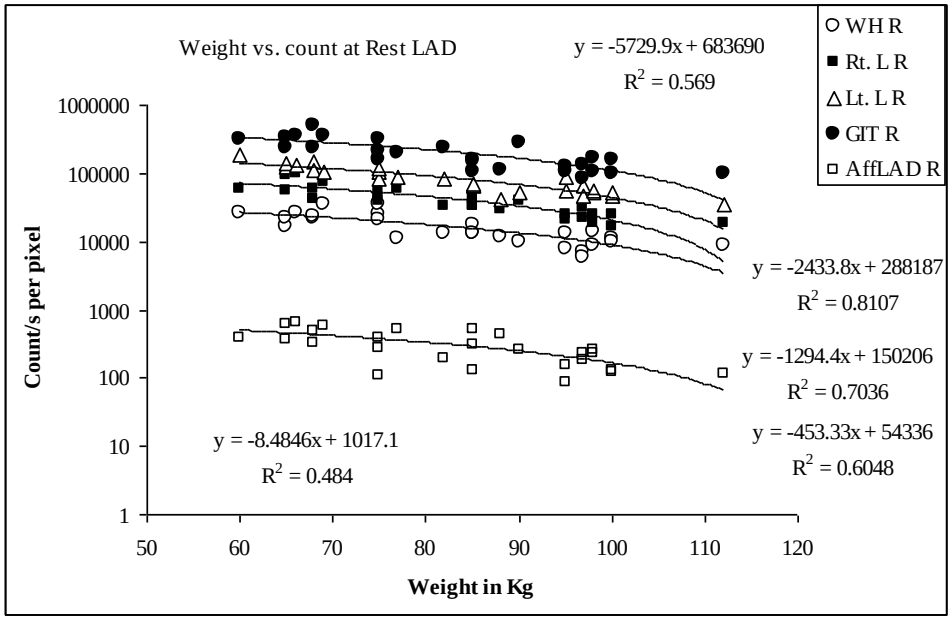


Figure 4.5 shows the correlation between weight versus count/sec at rest cardiac study for whole heart, Rt\Lt lungs, GIT and the ischemic heart segment.

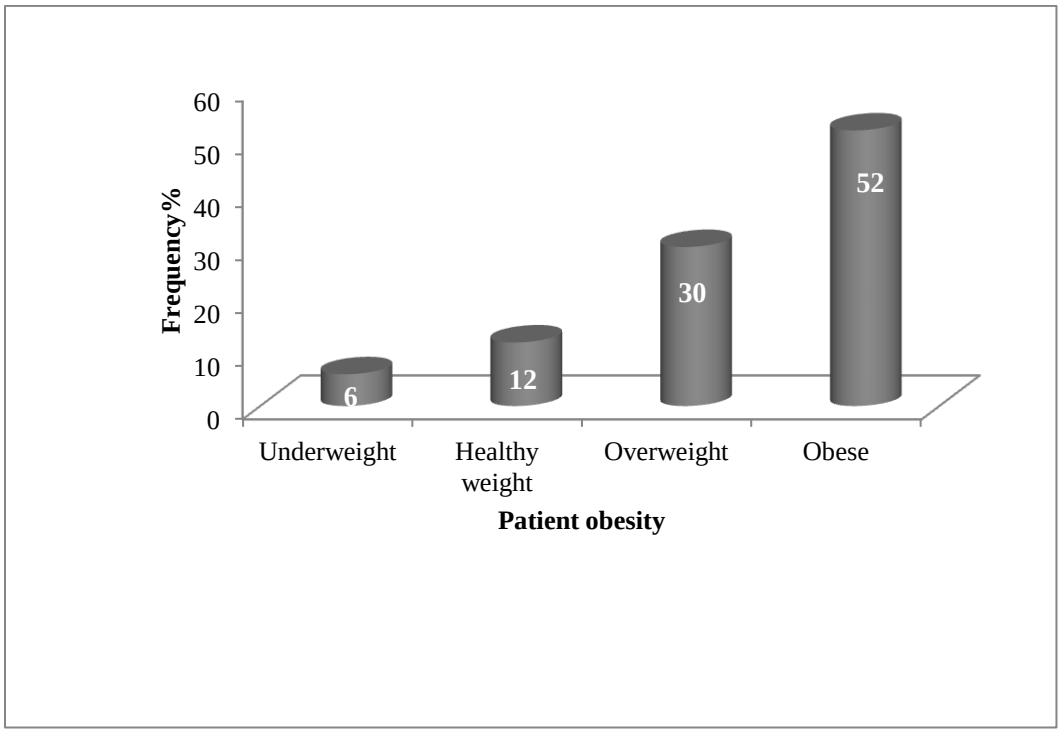


Figure 4.6: shows the general patient weight distribution based on the body mass index (BMI)

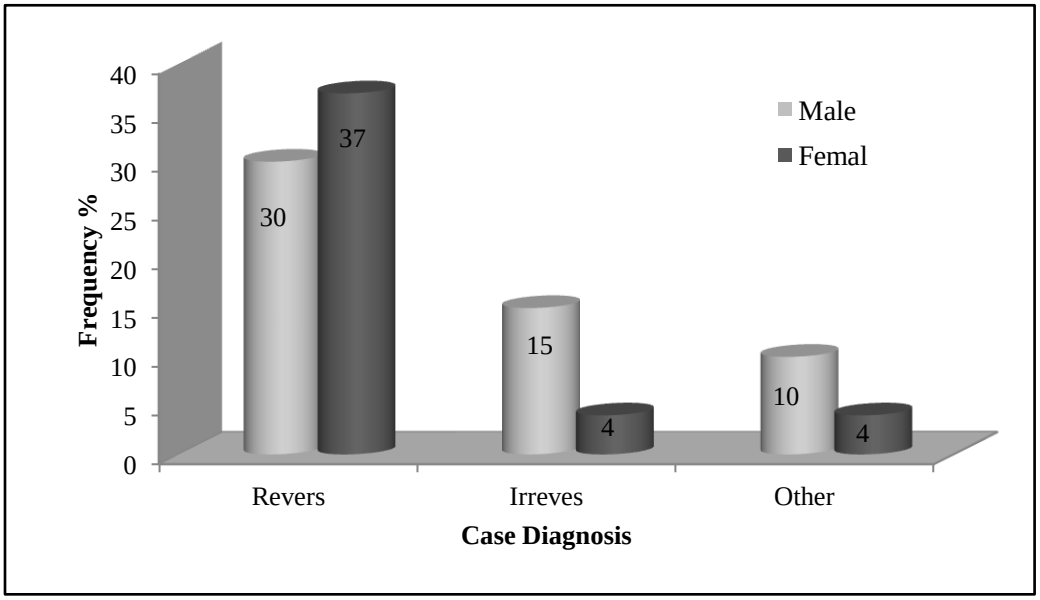


Figure 4.7 : shows the frequency of reversibility% for ischemic heart segment among the gender

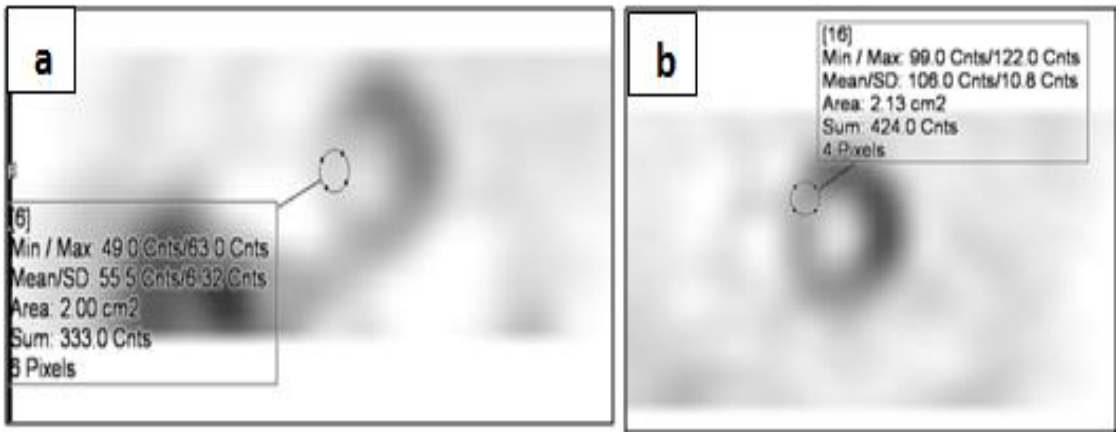


Figure 4.8: shows the uptake of apical heart & at ROI during rest (a) and stress (b) where the ischemic segment (17) manage to take a little amount of radiopharmaceutical, indicating the reversibility of the case

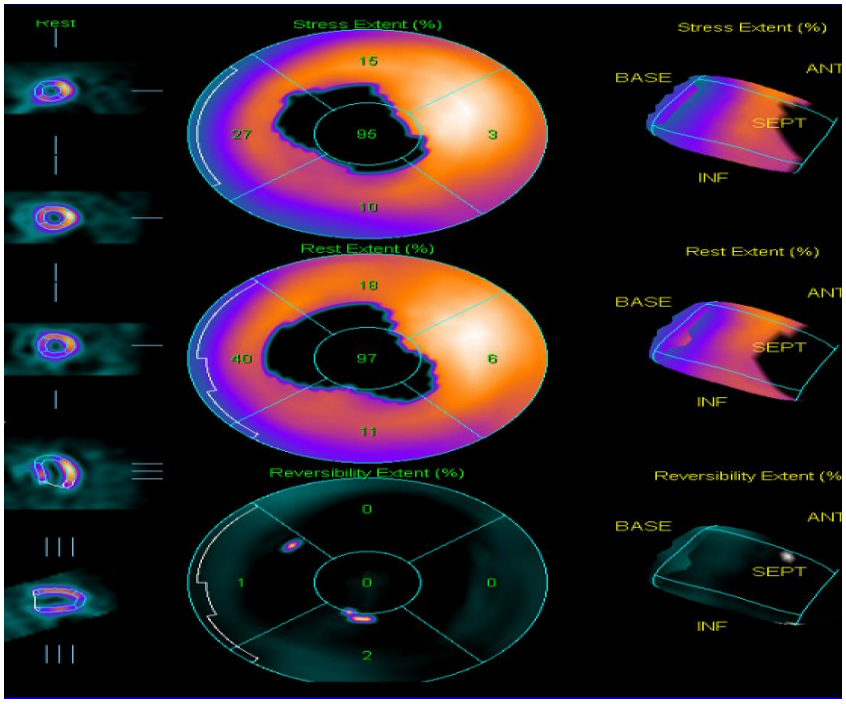


Figure 4.9: shows the lack of distribution of ^{99m}Tc-MIBI (Sestamibi) at apical segments within myocardium typically (Seg.No. 17) during stress and rest as per AHA (American Heart Assosication) Model

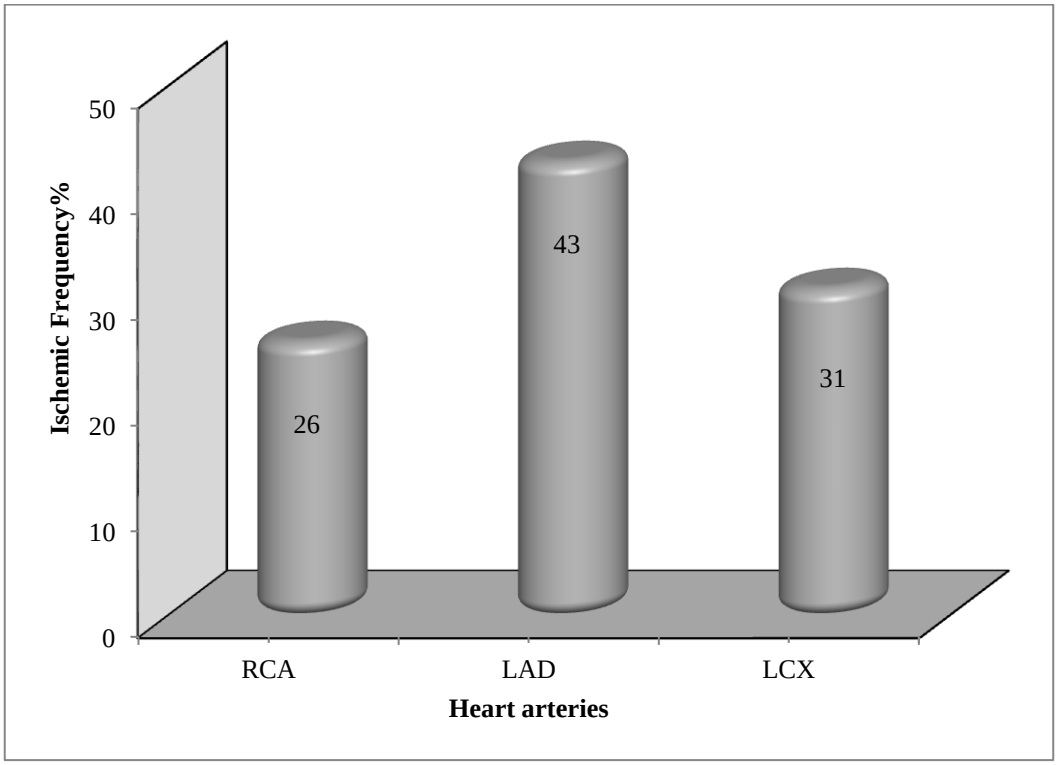


Figure 4.10: shows the common heart arteries (RCA, LAD and LCX) involved by Ischemic Diseases in percent

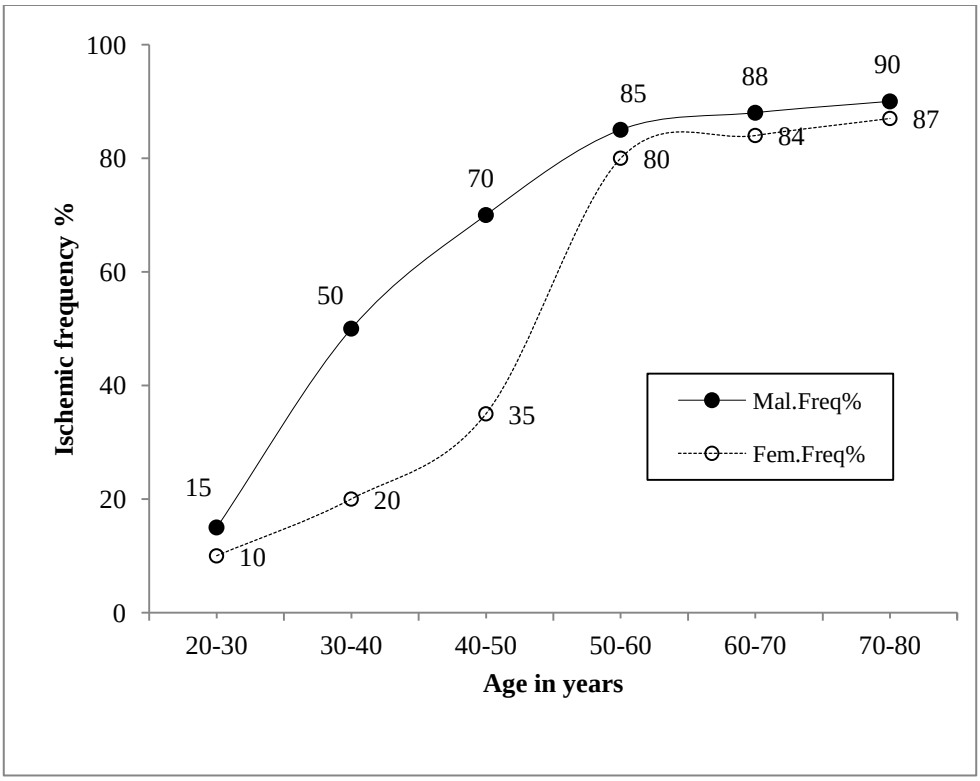


Figure 4.11: shows the correlation of age versus ischemic frequency percent among male and female

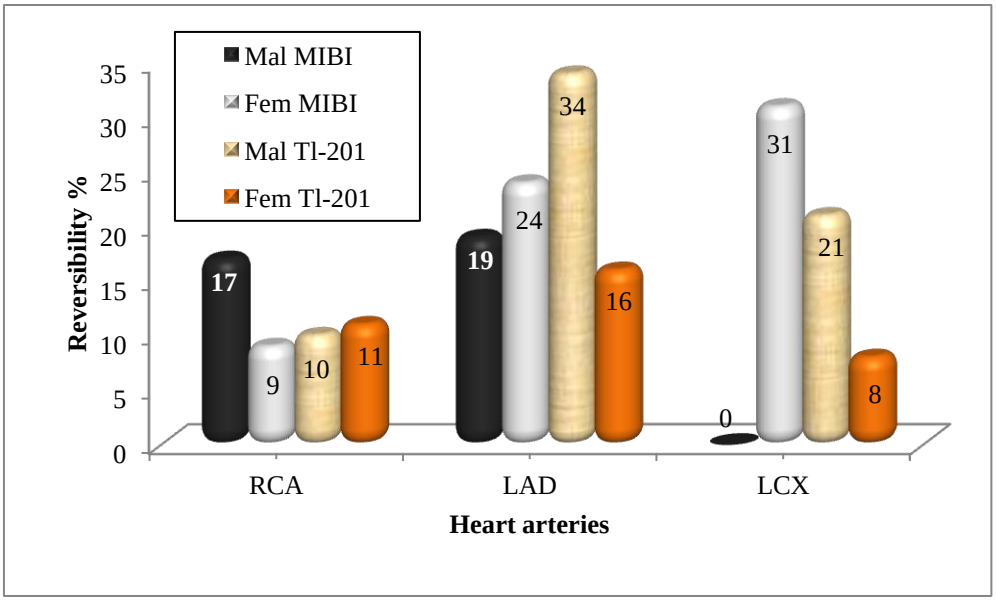


Figure 4.12: shows the reversibility% in coronary arteries Left Anterior descending (LAD) Right coronary artery (RCA) Left Circumflex (LCX) using ^{99m}Tc-MIBI &^{201}Tl, (M = mala, F = female)

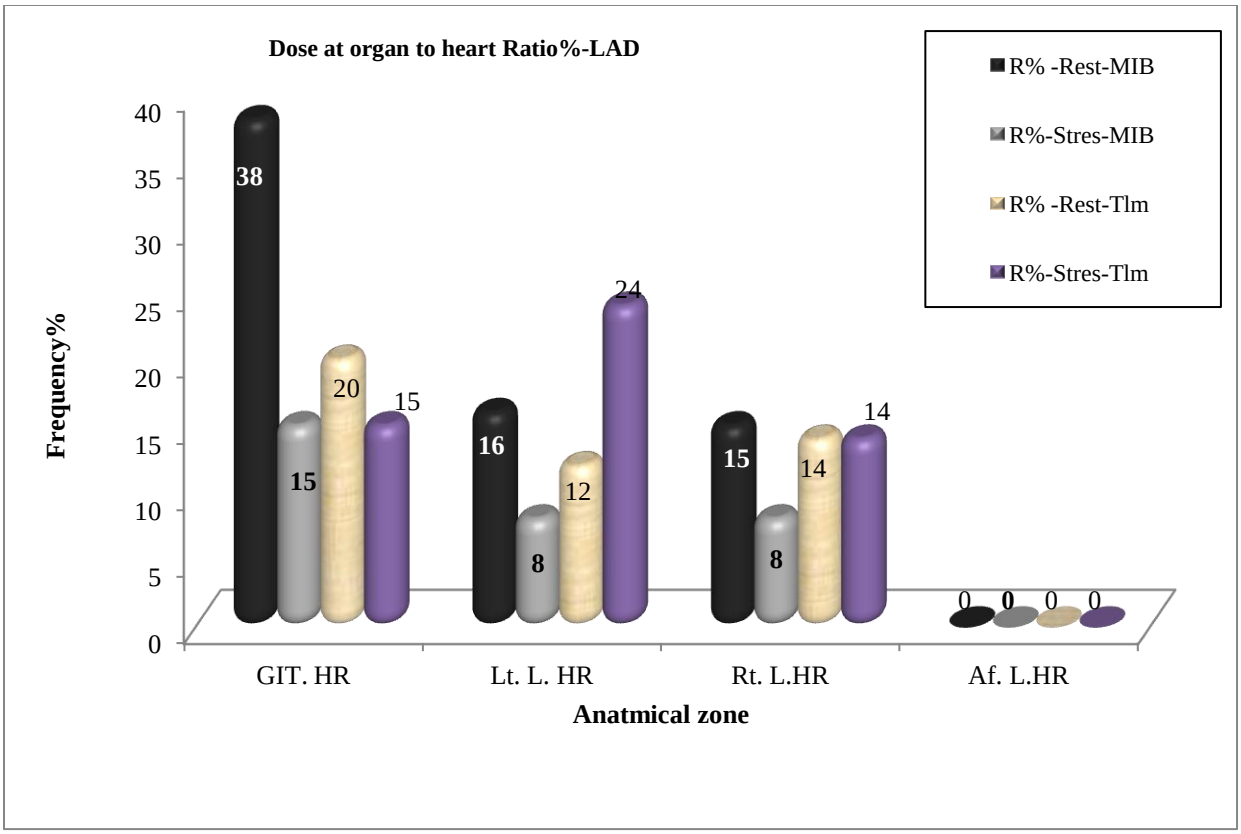


Figure 4.13: shows the dose at organs to heart ratio% for the common ischemic disease involving (LAD)

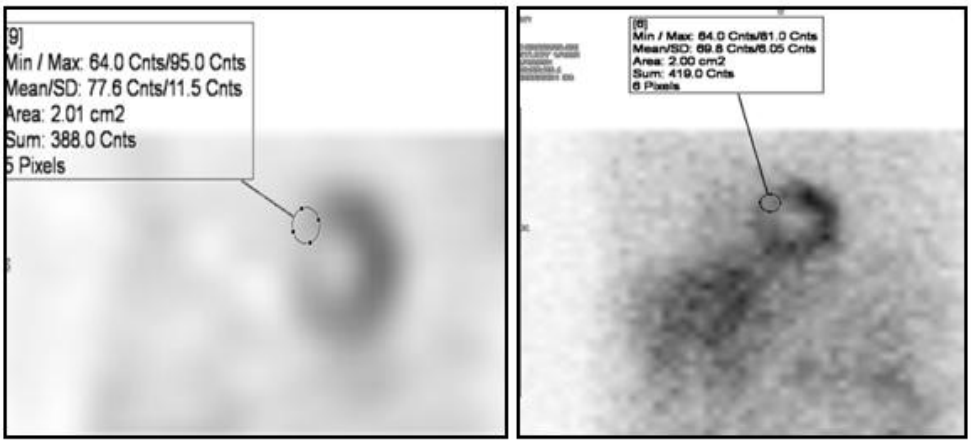


Figure 4.14: shows the uptake in count/second during stress and rest for involved heart segment by ischemia to assess the reversibility of myocardial ischemia

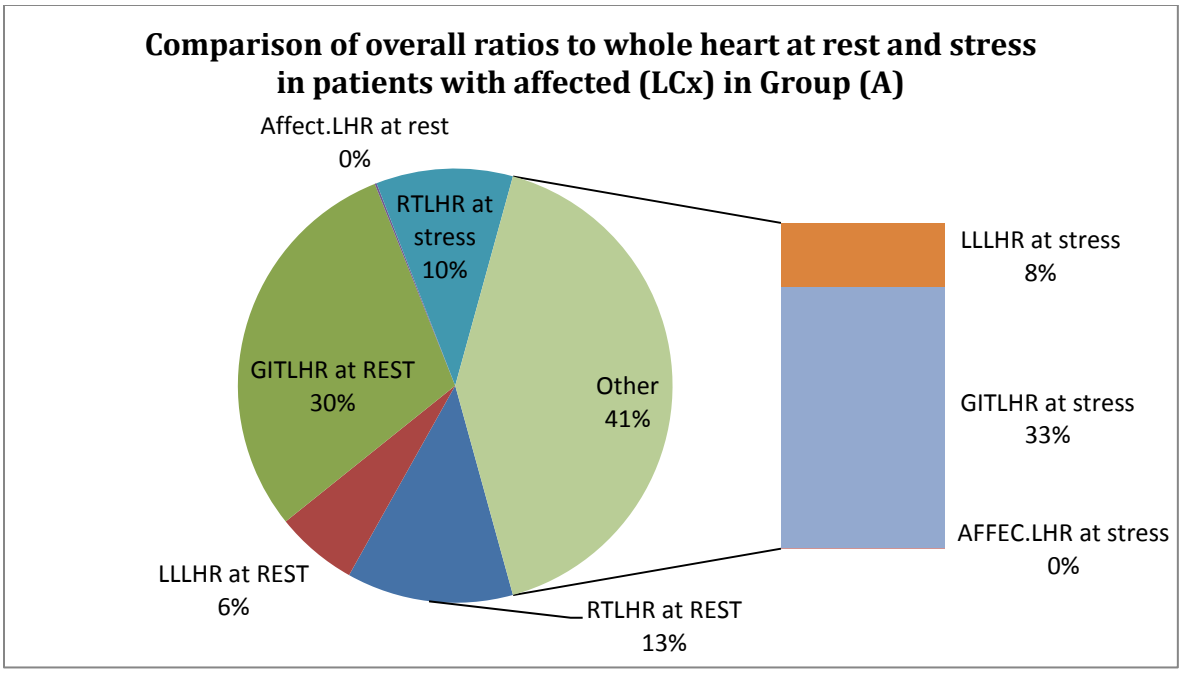


Figure 4.15: shows the percentage calculated ratios on patients with affected LCX to the whole heart uptake using ^{99m}Tc-Sestamibi Group (I)

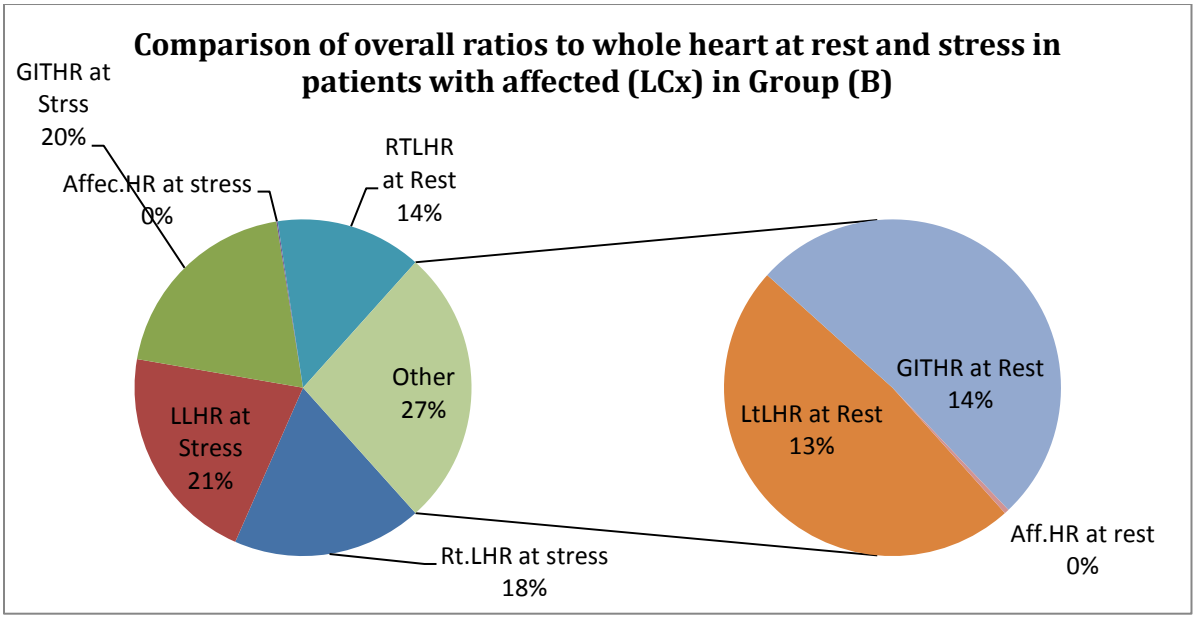


Figure 4.16: shows the percentage calculated ratios on patients with affected LCXto the whole heart uptake using ^{201}Tl in Group (II).

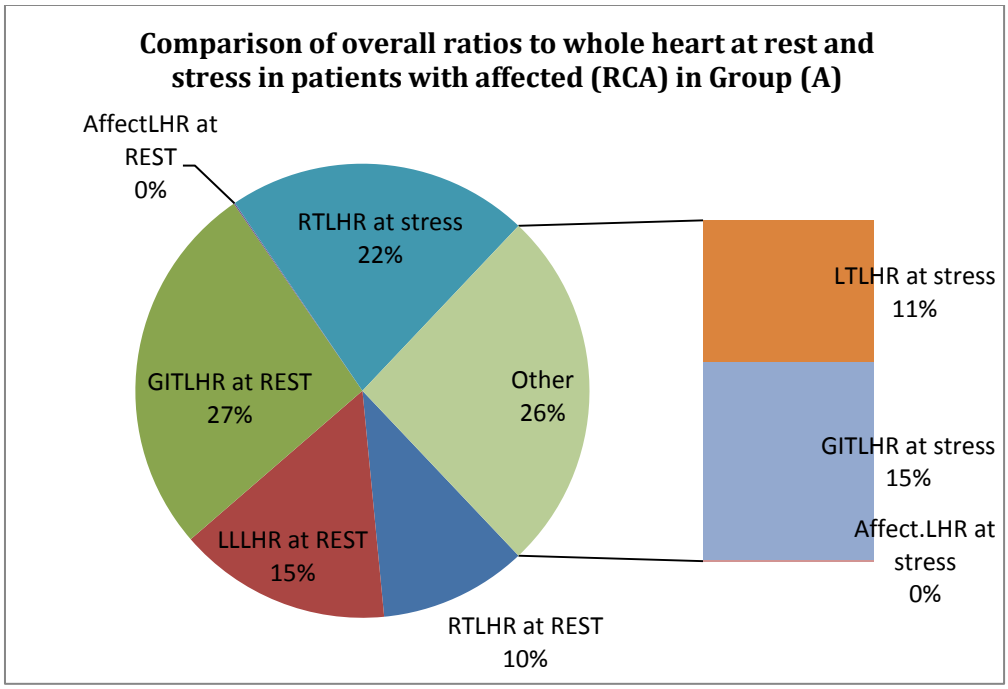


Figure 4.17: shows the percentage calculated ratios on patients with affected RCA to the whole heart uptake using ^{99m}Tc-Sestamibi .

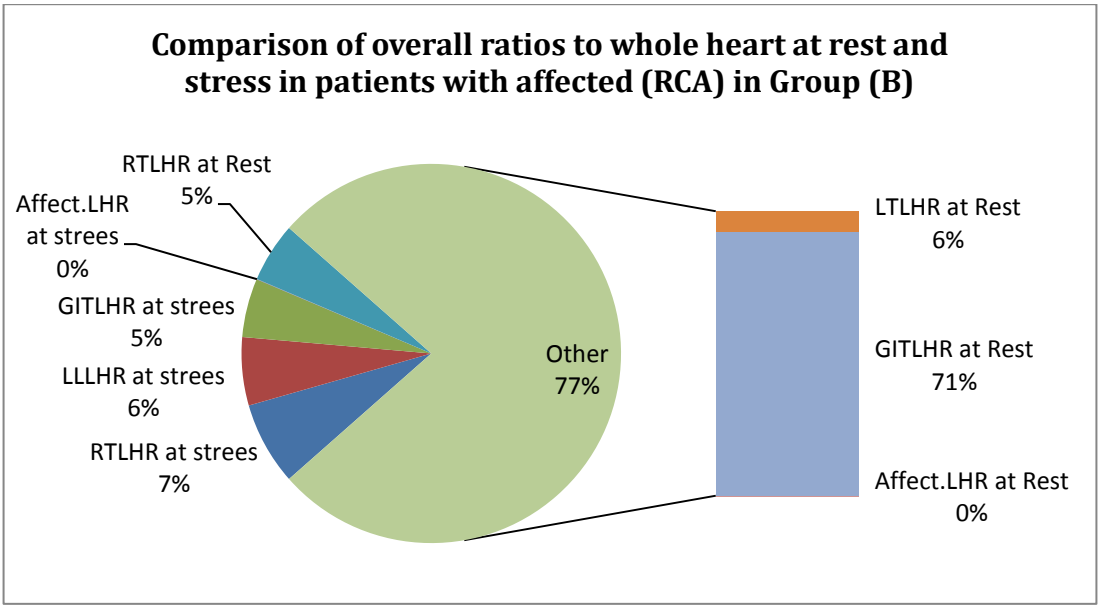


Figure 4.18: shows the percentage calculated ratios on patients with affected RCA to the whole heart uptake using ^{201}Tl.

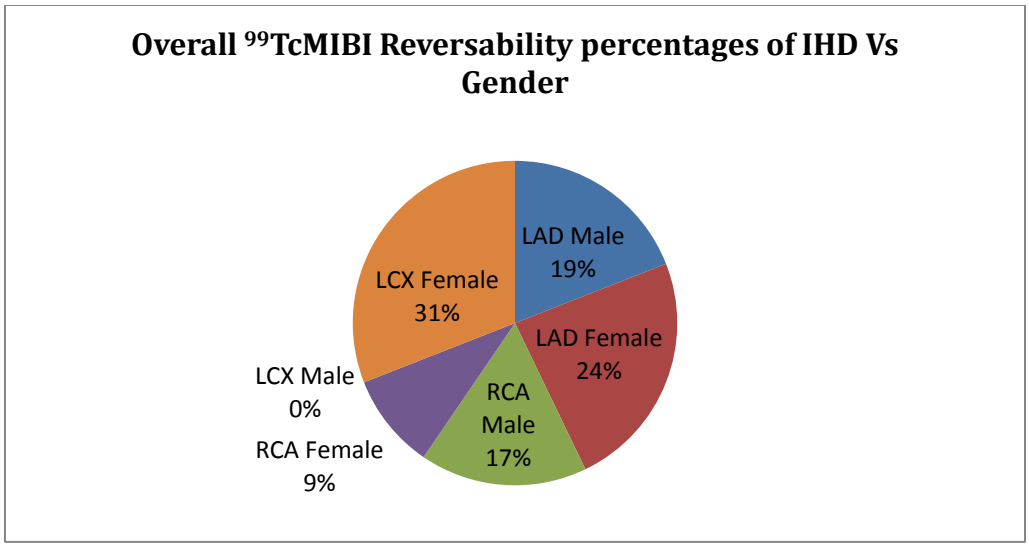


Figure 4.19: shows the percentage of reversibility (Reversible &Irreversible Myocardial territory) in all of three coronary arteries Left Anterior descending (LAD) Right coronary artery (RCA) Left Circumflex (LCX) using ^{99m}Tc-MIBI.

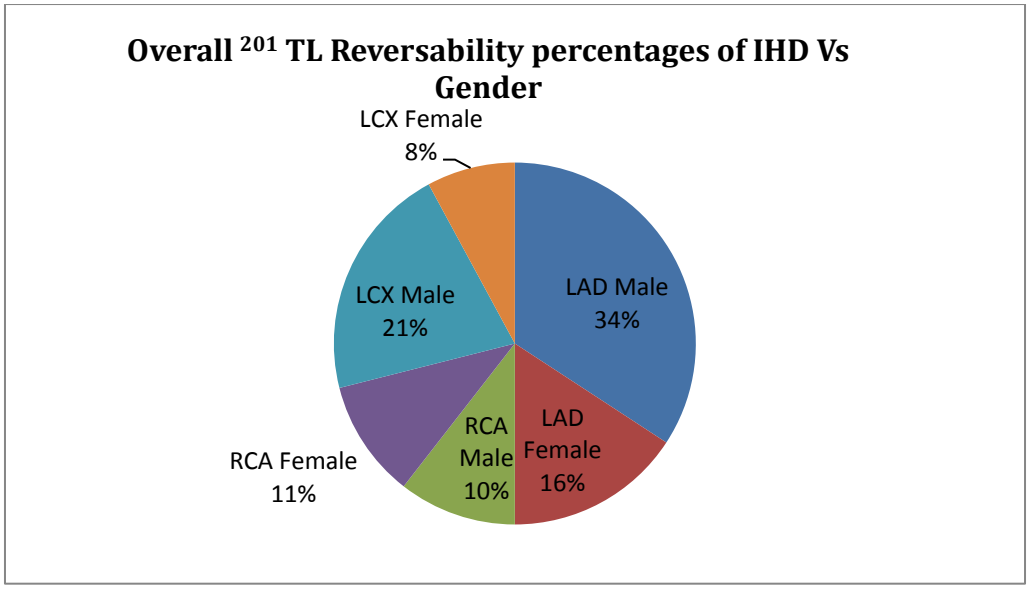


Figure 4.20: shows the percentage comparison between Left Anterior descending (LAD) Right coronary artery (RCA) Left Circumflex (LCX) of prevalence of (IHD) and reversibility over both genders in the sample injected with ^{201} Tl.

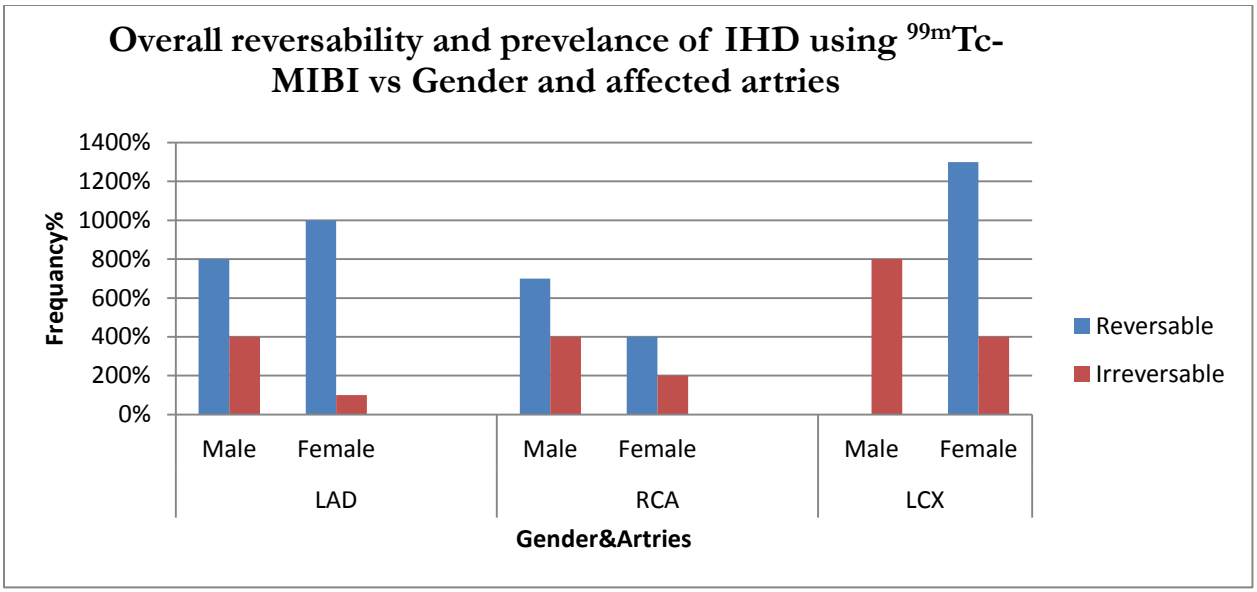


Figure 4.21: Shows the percentage of prevalence of (IHD) and reversibility over both genders, among the three main arteries Left Anterior descending (LAD) Right coronary artery (RCA) Left Circumflex (LCX).

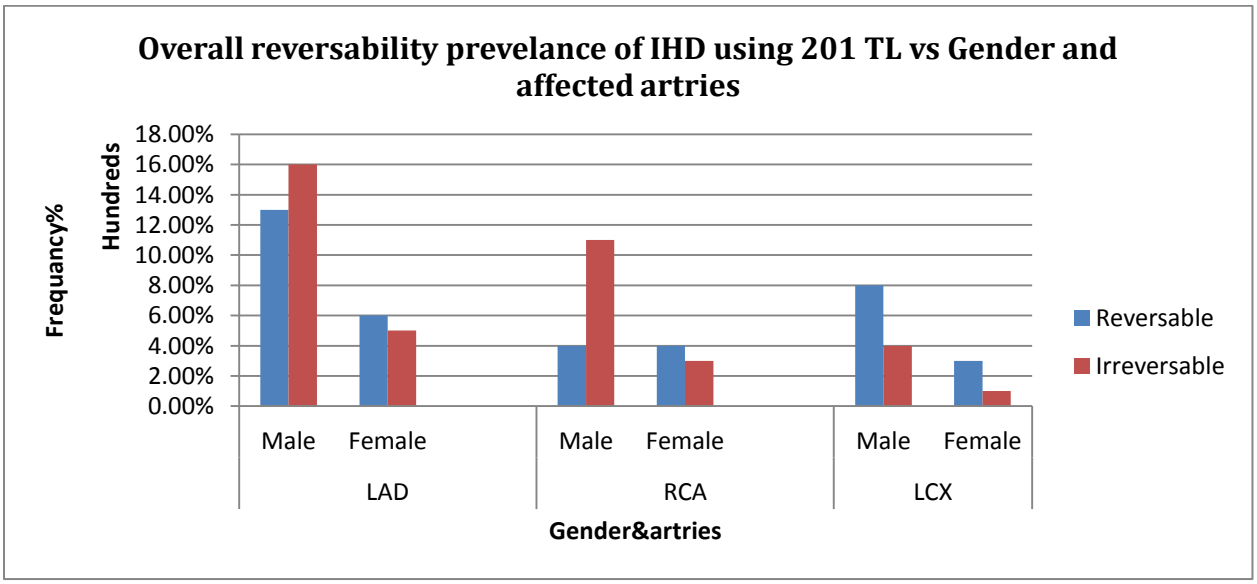


Figure 4.22: Shows the percentage of prevalence of (IHD) and reversibility over both genders, among the three main arteries Left Anterior descending (LAD) Right coronary artery (RCA) Left Circumflex (LCX).

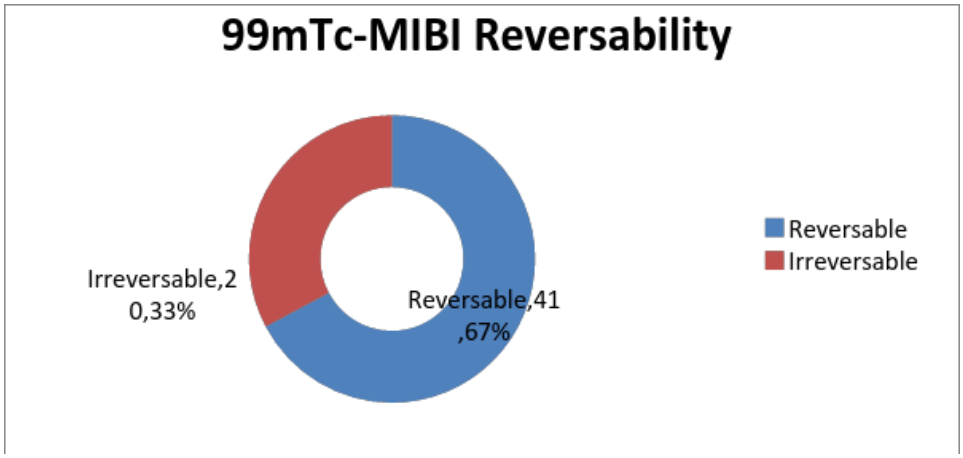


Figure4.23: shows the reversibility Percentage versus irrevocability with reference to the control group within the tested sample with ^{99m}Tc-MIBI

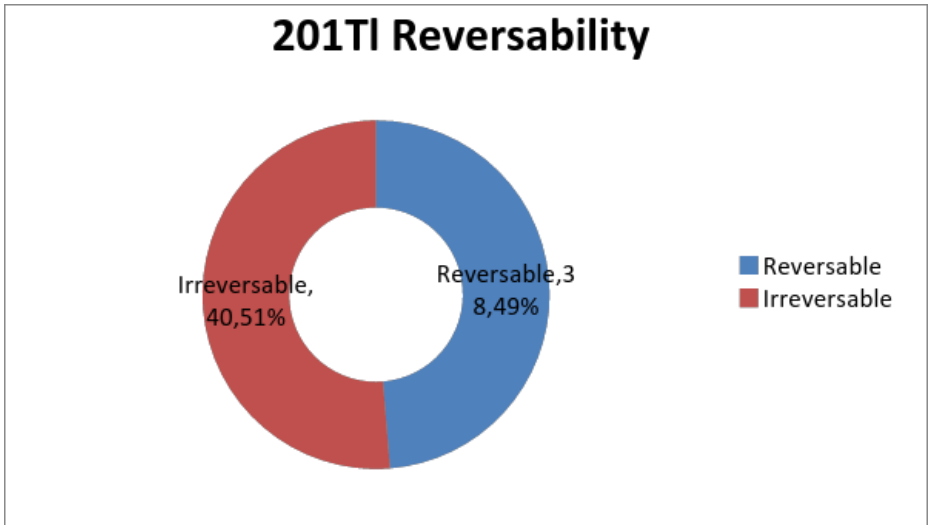


Figure 4.24: shows the reversibility Percentage versus irreversibility with reference to the control group within the tested sample with ^{201}TL.

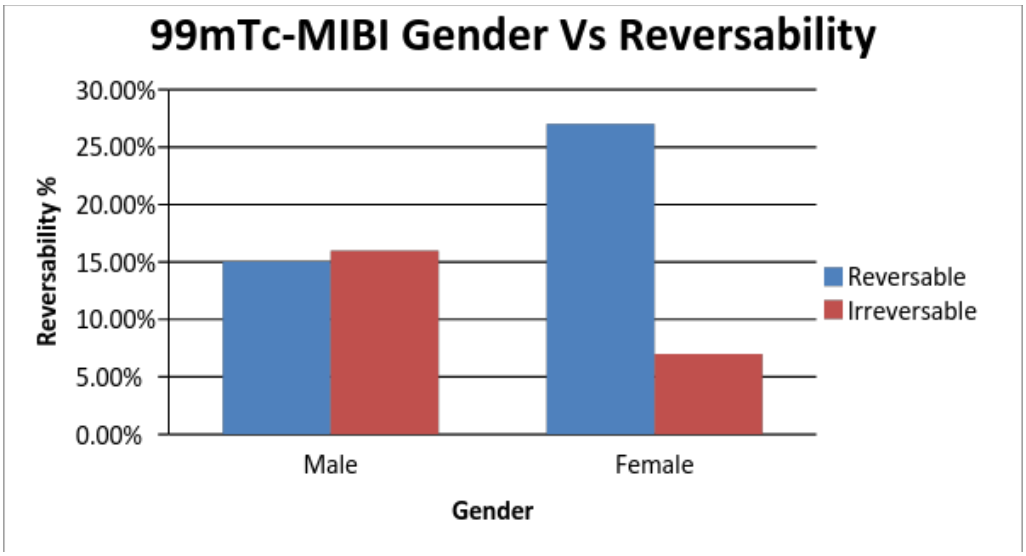


Figure 4.25: Percentage of the distribution of (IHD) over the gender of (sample) injected with ^{99m}-Tc-Sestamibi, in addition to the percentage of reversibility.

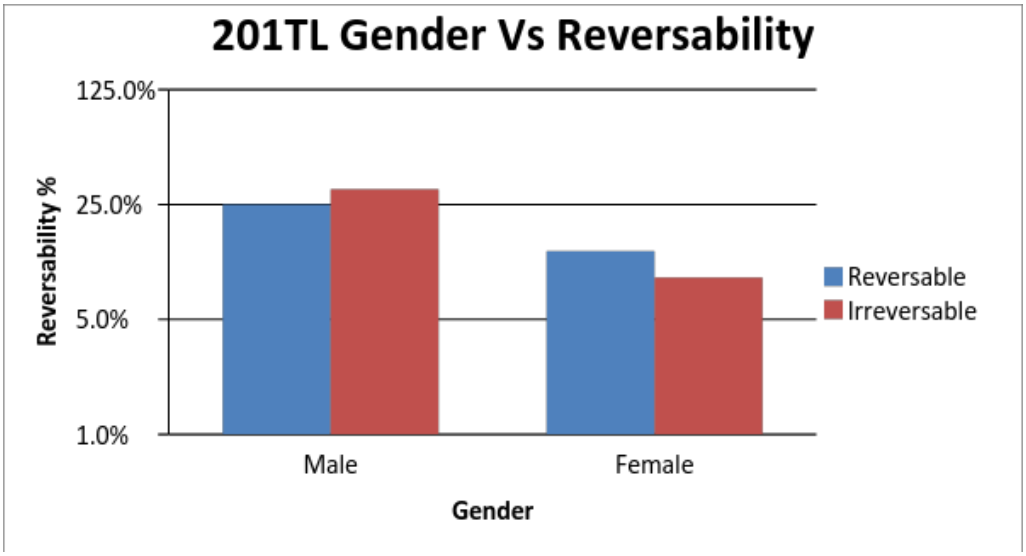


Figure 4.26: Percentage of the distribution of (IHD) over the gender of (sample) injected with ^{201}TL, in addition to the percentage of reversibility.

Chapter Five

Chapter Five

5. Discussion conclusion and recommendations

This chapter will discuss all estimated results from the collected data, and highlight the most important findings of the research, next. It highlights the estimated conclusion, then, the researcher will mention the outcome and the recommendations of the research

5.1 Discussion:

Regarding the study of myocardial ischemic heart disease; which is ascribed to defect of the Left Anterior Descending Artery (LADA) that supplying the heart segments (17, 13, 14, 7, 8, 1, 2) as classified by American Heart association (Cerqueira etal, 2002) and as well it is commonly involved by stenosis due to atherosclerosis, such segments radiopharmaceutical perfusion or uptake in count/second per pixel indicating the extend of LADA defect, which in turn reveals the vitality of the myocardial territory, the Bio distribution of the injected radiopharmaceutical as well as the ischemic reversibility. In Figure (4.1), which shows the correlation between Age versus count/sec at stressed cardiac study for whole heart, Rt\Lt lungs, GIT and the ischemic heart segment, it revealed that: the c/s per pixel for the affected segment has been decreased as the age increases, such decrement could explain that: the aging is a negative factor for ischemic reversibility if occur or it could be ascribed to the fact that: elderly people likely to develop complete or partial occlusion of one or more coronary arteries (Earl et al, 2002). While the aging effect in c/s for the whole heart uptake, Rt/Lt lungs and the GIT was a significant increasing uptake during

the stress phase where R^2 = 0.6, 0.6, 0.8 and 1 respectively, such results could be ascribed to significant promoted blood flow and increasing of blood pooling of heart, muscles and GIT (Mitchell & Blomqvist, 971; João and Dominique, 2004) by exercise, also the higher uptake of MIBI by GIT is considered as a part of MIBI normal bio distribution property, as well it could be ascribed to un optimum heating of MIBI (100^{o}C); that causing the radiopharmaceutical miss its target and goes to salivary gland or thyroid in a form of pertechnetate ($^{99m}TcPCO_4$). And in case of expiration date of the radiopharmaceutical, the body treats the radiopharmaceutical as foreign body and further being captured in liver (Baskot et al, 2011). Figure (4.2) shows the correlation between Age and count/sec at rest cardiac study for whole heart, Rt\Lt lungs, GIT and the ischemic heart segment, it revealed that: there were decreasing uptakes by whole heart, GIT and Rt/Lt lungs as the age increases, however the GIT shows significant uptake (R^2 = 0.5) relative to other anatomical structures; but less significant when compared with the values of stress where R^2 = 0.6, and the Rt/Lt lungs came secondly with less significance at R^2 = 0.3, and 0.2 respectively. Figure (4.3): shows the correlation between Age in years versus count/sec at rest & stress for cardiac study of ischemic heart segment (*left anterior descending artery*). It revealed that: there is decreasing uptake by the affected heart segment following the patients aging; such decreasing correlation following aging indicates bad prognosis of IHD or irreversible tissue vitality, however there is obvious higher uptake in case of stress relative to rest which is ascribed to exercise that increase the heart ejection fraction and further

increasing the blood flow in tissue (João and Dominique, 2004). In Figure (4.4) which shows the correlation between weight in Kg versus count/sec at stressed cardiac study for whole heart, Rt\Lt lungs, GIT and the ischemic heart segment. It is analysis revealed significant increased uptakes by GIT, Rt lung, Lt lung, and whole heart ($R^2 \approx 0.6$) as the weight increases, with same superior radiopharmaceutical uptake by GIT relative to other organs. Such results could be ascribed to the fact that obesity can alter the biodistribution of ^{99m}Tc-MIBI specifically with patients suffering from (IHD). These obtained results are agreed with the results mentioned by Agnieszka et al, (2007). While the affected heart segment remains with same decreasing uptake as the weight increases; this ascertains the irreversibility of tissue vitality of the affected heart segment among elderly people. In comparison with Figure (4.5) where patient at rest, however the same organs (GIT, Lt lung, Rt lung and the whole heart) showing significant ($R^2 \approx 0.7$) decreasing uptake as the weight increases as well as the affected heart segment, which might ascribed to the "uptake/retention" theory. Such results are agreed with the results mentioned by Richard et al, (2011) in which they ascribed the loss of isotope in ischemic myocardial region by time and as well accounts for "wash-in" as the regions of myocardium supplied by "critically" narrowed arteries and arteries whose (vulnerable plaques) were ready to rupture. Also in the studied sample; the combination of severely disturbed flow through critically narrowed and/or unstable coronary lumen passages and relatively large regions of ischemic myocardium with impaired ability to accumulate sestamibi, results in a delay in initial isotope counts.

Regarding the sample distribution based on weight or body mass index (BMI) as in Figure (4.6), the high frequencies were the obese and overweight patients (52% and 32% respectively), which is consider as a factor for CHD as mention by Canoy et al, (2013) that stated: "CHD risk increased with increasing BMI and waist circumference" and although BMI could be influenced by many other factors such as age, socioeconomic status, habits and physical activity (Whitlock et al, 2009; Wormser et al, (2011) as well as altitude living, however even these proved having direct impact in CHD risk Roger et al, (2012). Figure (4.7): shows the ischemic heart segment reversibility and irreversibility% among both genders, in which the reversibility% was high among females and represents 37% relative to male 30%, while the irreversible cases were greater among male 15% relative to only 4% among female, such irreversibility of IHD among male could be due to the causative factors which are more common among male. And also the graph deduces that: the incidence % of IHD is predominant among male 55% compared with 45% among female, such high incidence among male is agreed with Jackson et al, (1997). While Figure (4.8) shows that: the uptake of apical heart & at ROI during rest (Figure 8a) with obvious lack of ^{99m}Tc-MIBI uptake and faint distribution, while at stress (Figure 8b) there was increased uptake by myocardium with significant (P = 0.5) uptake at ischemic zone of tissue which correspond to the apical segment number (17) within myocardium ,in Figure (4.9): shows the lack of distribution of ^{99m}Tc-MIBI (Sestamibi) at apical segments within myocardium typically (Seg.No. 17) during stress and rest as per AHA (American Heart Assosication) Model ,in (Figure 4.10) which

shows the common heart arteries right coronary artery, left anterior descending artery, and left circumferential artery (RCA, LAD and LCX) involved by ischemic diseases in percent. The analysis reveals that: the common artery of the heart involved by ischemia was the left anterior descending artery (LAD) which represented 43% relative to 31% and 26% for LCX and RCA respectively. Such result could be ascribed to the massive muscle coverage supplied by this artery and the less probability of partial occlusion and more probability of complete occlusion which include the following segments (17, 13, 14, 7, 8, 1, 2) as per American heart association (AHA), this results agreed with Burggraf and Parker, (1975) and Webster et al, (1974) as they have mentioned that in several natural history studies an increased mortality in patients with single-vessel disease of the left anterior descending coronary artery of 2-470 compared with 0.5-2% for isolated right coronary artery stenosis has been reported ,In (Figure 4.11) which shows the correlation of age versus ischemic frequency percent among male and female. It is analysis showed that: the male were more common involved by ischemic disease compared to female during the age hood, and the risk of ischemic increases as the age increase for both gender with plateau occurring among age group of 50-70 years old, however the female were more less susceptibility to ischemic disease during the first forth decades. Such result could be ascribed to the fact that: elder people are more suffering of elevated resting heart rate, increase in heart rate, life stress, and arteriosclerosis (Andrews et al, 1993). Same results have been highlighted by Gibbons et al, (1997) in which they showed that: ischemic disease was higher incidence among male and

increases as the age increases. Also these obtained results agreed with the results mentioned by Boudi, (2014b) in which he mentioned that In the United States, men over 40 years of age have a 49% chance of developing the disease in their lifetime, while the chance for women over the age of 40 years is 32%, such results can be ascribed as estrogen levels in premenopausal women protect them from some of the heart damage done by atherosclerosis, but this protection disappears after menopause. However this obtained results is disagree with the results mentioned by Go et al, (2013) in which they mentioned that elderly women who have heart attacks are more likely than men and are more likely to die from them within a few weeks, in (Figure 4.12) shows the reversibility% in coronary arteries Left Anterior descending (LAD) Right coronary artery (RCA) Left Circumflex (LCX) using ^{99m}Tc-MIBI &^{201}Tl. And based on the predominant of ischemic disease in LAD, the analysis reveals that: the reversibility of LAD ischemic disease detected by ^{201}Tl was higher (34%) compared with that detected by ^{99m}Tc-MIBI (19%) among male, while among female,^{201}Tl detected only 16% as reversible of the sample compared with 24% detected by ^{99m}Tc-MIBI. The reversibility of RCA ischemia was 10% detected by ^{201}Tl compared with 17% by ^{99m}Tc-MIBI among male while among female the detection was 11% and 9% by ^{201}Tl and ^{99m}Tc-MIBI respectively. And the detected reversibility of LCX ischemia among male and female was 21% by ^{201}Tl and 0%by ^{99m}Tc-MIBI respectively. These obtained results are agreed with the results mentioned by Agnieszka et al, (2007) .In this realm, the ischemic reversibility judgment remains a subject of debate, as other factors such as race

and heredity can play major role to determine the accurate statement, and Mc Laughlin, (2014) has mentioned that individuals with familial hypercholesterolemia, an inherited metabolic disorder affecting the low-density lipoprotein cholesterol (LDL) receptors, carry a genetic mutation that makes it difficult for their cells to remove LDL from their blood, also Boudi, (2014b) has mentioned regarding race that Americans of Asian Indian origin are 2 to 3 times as likely as European Americans to develop coronary artery disease, in (Figure 4.13) shows the dose at organs to heart ratio% for the common ischemic disease on LAD. The analysis showed that: the assessment of ischemic heart diseases using ^{201}Tl gives least dose ration to GIT, Lt L, Rt L which were 20%, 12%, and 14% compared with ^{99m}Tc-MIBI that gives high dose ratios as 38%, 16% and 15% respectively during patient rest, such fact indicates that low dose of ^{201}thalium can perform the study relative to ^{99m}Tc-MIBI and it showed more interpretation confidence in (Segmental Reading) than ^{99m}Tc-MIB as mentioned by Sherif et al, (1998) using ^{99m}Tc-MIBI mentioned that the quantitative analysis shows increased risk in relation to the severity of the abnormality with ^{201}TL,At the same time both ^{201}Tl and ^{99m}Tc-MIBI can detect the affected artery successfully during rest and stress which shows no uptake by the heart segment, these results are similar to those obtained by Ayalew et al, (2000) that the myocardial fractional retention of both ^{201}Tl and MIBI is strongly correlated with the decrease in coronary flow during ischemia, (Figure 4.14) shows the uptake in count/second during stress and rest for involved heart segment by ischemia to assess the reversibility of myocardial ischemia. It reveals that: the

ischemic heart segment (8) within an area of 2 cm^2 i.e. about 5 pixels, at rest (a) and stress (b) where the ischemic segment (17) manage to take a little amount of radiopharmaceutical, indicating the reversibility of the case. Figures 5 (a) and (b) have an uptake of 388 and 410 count for rest and stress respectively, which indicating that: there is a probability of ischemic reversibility and returning of myocardium to normal blood supply. Such finding could add a new fact upon which the ischemic diagnosis could be confirmed or not, this result is agreed with the study mentioned by Mohammed et al, (2016).

In (Figure 4.15 and 4.16) Shows the ratios of the previous trend for patients suffering from defected (LCx) in Groups (I) injected with ^{99m}Tc-Sestamibi at Stress/Rest, GIT and Rt/Lt lungs showed 30% ,6%and 13% respectively at rest , at stress GIT ,and Rt/Lt Lungs showed 33%,8%and 10 respectively ,When compared to the same group of patients suffering from (LCX) defect in Group (II) injected with ^{201}TL , GIT Rt/Lt Lungs showed rations of 14%,14% and 13% respectively , such results reveals that patients in Group (II) injected with ^{201}Tl who's suffering from (LCX) defect had a very low distribution of ^{201}Tl within regions other than heart in comparison to the same set of patients in Group (I) injected with ^{99m}Tc-Mibi,this might occur due to significant promoted blood flow and increasing of blood pooling of heart, muscles and GIT during exercise in relevant to the injected dose as described by Mitchell & Blomqvist, (1971), João and Dominique (2004), in (Figure 4.17 and 4.18) which demonstrates the ratios of the previous trend for patients suffering from defected (RCA) in Groups (I) injected with ^{99m}Tc-Sestamibi ,GIT,Rt/Lt Lungs showed ratios of

27%,10%,15% respectively at rest while at stress GIT Rt/Lt Lungs showed 15%,22%,11% respectively, However, relating the same group of patients suffering from (RCA) defect in Group (II) , GIT and Rt/Lt Lungs showed percentages of 71%,5% and 6% respectively at rest , while at stress GIT Rt/Lt Lungs showed percentages of 5%, 7% 6% Respectively at stress, Such results reveals no correlation with results of ^{201}Tl uptake ratios within the other two coronary arteries i.e. (LAD) and (LCX) as GIT is higher with 71% at rest in comparison to (LAD) and (LCX) ,Such results can be ascribed as (LCX) is considered as the narrowest branch compared to coronary arteries i.e. (LAD) and (RCA) indicating that the probability of distribution of radiopharmaceuticals to regions other than heart remains high, However this obtained result agreed with Agnieszka Manka et.al,(2006) an they have mentioned that the myocardial tracer uptake is closely related to the extent of ischemic disease as evaluated under stress conditions, Therefore, evaluation of resting imaging with regard to myocardial tracer distribution seems to be more appropriate. (Figure 4.19 and 4.20) Elaborates the percentage comparison between Left Anterior descending (LAD) Right coronary artery (RCA) Left Circumflex (LCX) demonstrating the prevalence of (IHD) and reversibility over both genders i.e. (males and females) in the sample injected with ^{99m}Tc-Sestamibi,and ^{201}Tl , in Group (I) (LCX)(LAD) and (RCA) showed 0% ,19% and 17% of incidence of (IHD) in males of the sample (33 males) respectively, while showed (31%,24,and 9% respectively in females (32 females), When compared to the results from Group (II) the prevalence in percentage for (LCX),(LAD) and (RCA) was 21%,34%

and 10% for males respectively , while shown 8% ,16%and 11 % for females respectively ,such results reveals that the prevalence of (IHD) among population is clearly higher with (LAD) myocardial territory as it shows the highest percentages of incidence with the sample in Group (I) and (II) with 24% and 16% in females while 19% and 34% in males in both groups respectively, However, this study also elaborated that the prevalence of (IHD) is more likely to occur in men than females , these obtained results agreed with the results mentioned by Boudi, (2014b) in which he mentioned that In the United States, men over 40 years of age have a 49% chance of developing the disease in their lifetime, while the chance for women over the age of 40 years is 32%, such results can be ascribed as estrogen levels in premenopausal women protect them from some of the heart damage done by atherosclerosis, but this protection disappears after menopause, (Figure 4.21 and 4.22) is clarifying the percentage of prevalence of (IHD) and reversibility over both genders, among the three main arteries Left Anterior descending (LAD) Right coronary artery (RCA) Left Circumflex (LCX), Group (I) reveals that (LAD) is higher in reversibility in males than female the figure also reveals that the likelihood for reversible myocardial territory of affected (LAD) segment is higher in females with poor possibility of reversibility for men affected within the same segment i.e. (LAD) , for patients with (RCA) defected territory in sample the possibility to recover after revascularization is less likely for females (Irreversible territories), while showed relatively the same percentage for both genders in terms of reversible myocardium tissue, (LCX) showed remarkable increment of prevalence in males

in comparison to females , on the other hand patients of Group(II) revealed higher irreversibility percentage for males with (LAD) defect and high reversibility percentage for females , (RCA) results agreed with the results in Group (I) estimated that less likelihood of reversibility for males (irreversible) with high reversibility percentage for females,(LCX) uncovered a very low likelihood of reversibility for men while the results for females followed the same trend of the previous coronary arteries, Such results can be ascribed as Only 17.0% of women compared to 24.9% of men met the 2008 Federal Physical Activity Guidelines in Women 2012 (AHA,2015), these results reveals that the capability of both radiopharmaceutical in detection of affected (reversible or irreversible territory) is reasonable, However, these results are similar to those obtained by Ayalew et al, (2000) that the myocardial fractional retention of both ^{201}Tl and ^{99m}Tc-MIBI is strongly correlated with the decrease in coronary flow during ischemia, Nevertheless, in (Figure 4.23 and 4.24) ^{201}TL showed better efficiency in detection of ischemic heart portion with less false/negative results i.e. to confirm irreversibility against reversibility for the interprtator as it showed 41% versus 49 % (positive Irreversible) patients within Group (II) respectively when compared to Group (I) with only 20.33% of the patients were confirmed with (irreversible myocardium territory) versus 67% (reversible myocardium territories) in which percentage of false/positive diagnose might occur , these obtained results disagree with the results mentioned by AHA, (2014a) whereby they have mentioned that elderly women who have heart attacks are more likely than men are to die from them within a few weeks,

But regardless to the specified classification mentioned i.e. ‘’elderly women’’ still reversibility judgment remains a subject of debate, as other factors such as race and heredity can play major role to determine the accurate statement, McLaughlin,et,al (2014) have mentioned that Individuals with familial hypercholesterolemia, an inherited metabolic disorder affecting the LDL receptors, carry a genetic mutation that makes it difficult for their cells to remove LDL from their blood, also Boudi, (2014b) has mentioned regarding race that Americans of Asian Indian origin are 2 to 3 times as likely as European Americans to develop coronary artery disease, Figure: shows the percentage of reversibility (Reversible &Irreversible Myocardial territory)in all of three coronary arteries Left Anterior descending (LAD) Right coronary artery (RCA) Left Circumflex (LCX) using ^{99m}Tc-MIBI **,** in Figure (4.25 and 4.26) in which it follows the same trend as the previous findings showing the Percentage of the reversibility of (IHD) over the gender of (sample) in Group (I) and Group (II) OF ^{99m}-Tc-Sestamibi and ^{201}TL, However , it reveals less likelihood of reversibility for men versus females and these obtained results can be ascribed as what have been mentioned within the previous trend of results regarding gender reversibility.

5.2 Conclusion:

In regard to the obtained results the researcher can conclude that the myocardial perfusion imaging (MPI) used in Nuclear Medicine is a well-established method for clinical evaluation of patients with suspected or known ischemic heart disease. This study revealed that factors such as age, weight, gender and obesity have great effect in IHD reversibility or tissue vitality that supplied by the left anterior descending artery, This study also reveals and confirmed the common involved coronary artery by ischemia which was the LAD and the male were more common involved by ischemic disease compared to female and the risk of IHD increases as the age increases among both gender. ^{201}Tlalium has been the radiopharmaceutical of choice for detection of ischemic portion due to its efficient uptake mechanism (Na^{+}/K/H pump), low dose administrated and higher reliability in diagnosis of chronic IHD, in addition to the diagnosis of ischemic reversibility depending on the count per pixels. Also the study confirmed that: IHD is common among male relative female and as well the frequency of reversibility% for ischemic heart is high among female relative to male.

5.3 Recommendations:

This study is paving the way for more reliability on quantitative evaluation of obtained myocardial perfusion images using different radiopharmaceuticals in nuclear medicine, according to the research out comes the researcher recommendations came as follows:

- ^{201}TL is recommended to be used as radiopharmaceutical of choice in detection of ischemic heart disease (IHD).
- Hormones such as estrogen can be involved in future researches to help determining reversibility % indexes among gender.
- ^{99m}Tc-Sestamibi is the radiopharmaceutical of choice for detection of coronary artery disease (CAD) in women.
- More researches are recommended by researcher of average counts/second/Pixel (C/S/P) for evaluation of other cardiomypathies.
- It recommended to apply slandered Quality control procedures for radiopharmaceuticals to ensure optimum bio-distribution of the tracer post administration.
- Factors such as obesity can be announce to public as a risk factor and since it's preventable other effective committees in community can help underlining it within preventive medicine list, this will help to reduce (IHD) indicator in community.
- The researcher also recommends applying researches for reversibility% over areas in Sudan.

Appendix A

WH	SUM counts Rest (c/s/p)	SUM Counts Stress(c/s/p)	RT L	SUM counts Rest (c/s/p)	SUM Counts Stress(c/s/p)	LT L	SUM counts Rest (c/s/p)	SUM Counts Stress(c/s/p)	GIT	SUM counts Rest (c/s/p)	SUM Counts Stress(c/s/p)	Affected	SUM counts Rest (c/s/p)	SUM Counts Stress(c/s/p)

Table 4.1: Shows overall summed counts (c/s/p) of whole heart-Right lung, left lung, gastrointestinal track ,and affected territory within heart at stress and rest

WH	Weight (Kg) Calculated BMI	**WH Sum Counts at Rest**	RT L	Weight (Kg) Calculated BMI	Rt.Lung counts at Rest	LT L	Weight (Kg) Calculated BMI	Lt.Lung counts at Rest	GIT	Weight (Kg) Calculated BMI	GIT's counts at Rest	Affected	Weight (Kg) Calculated BMI	Affected LAD Segment c/s/p at Rest

Table 4.2: Shows the summed counts of whole heart-Right lung, left lung, gastrointestinal track ,and affected territory. Within heart verses weight at rest condition.

WH	Age (Years)	**WH Sum Counts at Rest**	RT L	Age (Years)	Rt.Lung counts at Rest	LT L	Age (Years)	Lt.Lung counts at Rest	GIT	Age (Years)	GIT's counts at Rest	Affected	Age (Years)	Affected LAD Segment (c/s/p) at Rest

Table 4.3: Shows the summed counts of whole heart-Right lung, left lung, gastrointestinal track ,and affected territory. Within heart verses age at rest condition.

WH	Weight (Kg) Calculated BMI	**WH Sum Counts at Stress**	RT L	Weight (Kg) Calculated BMI	Rt.Lung counts at Stress	LT L	Weight (Kg) Calculated BMI	Lt.Lung counts at Strss	GIT	Weight (Kg) Calculated BMI	GIT's counts at Stress	Affected	Weight (Kg) Calculated BMI	Affected LAD Segment (c/s/p) at Stress

Table 4.4: Shows the summed counts of whole heart-Right lung, left lung, gastrointestinal track, and affected territory . Within heart verses Weight at stress condition.

WH	Age (Years)	**WH Sum Counts at Stress**	RT L	Age (Years)	Rt.Lung counts at Stress	LT L	Age (Years)	Lt.Lung counts at Strss	GIT	Age (Years)	GIT's counts at Stress	Affected	Age (Years)	Affected LAD Segment (c/s/p) at Stress

Table 4.5: Shows the summed counts of whole heart-Right lung, left lung, gastrointestinal track ,and affected territory. Within heart verses age at stress condition.

Affected LAD Segment (c/s/p) at Stress and Rest	Reference group *3 Segments (c/s/p) at Stress and Rest

Table 4.6: Shows the affected territories counts/second/pixel versus reference (control group) counts at stress and rest.

	Male	Female
Reversable		
Irreversable		

Table 4.7: Shows reversibility percentage versus irreversibility versus gender.

Appendix B

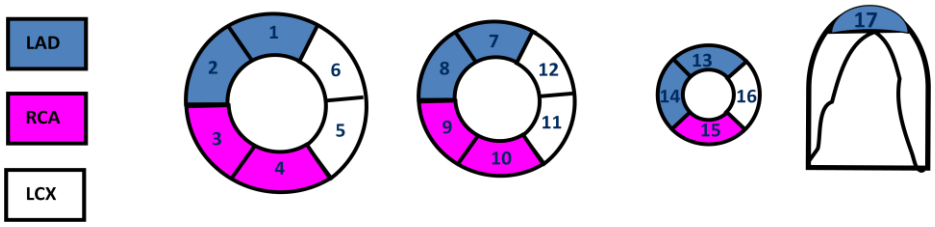


Figure 1.1. Shows different myocardium territories as per AHA classification

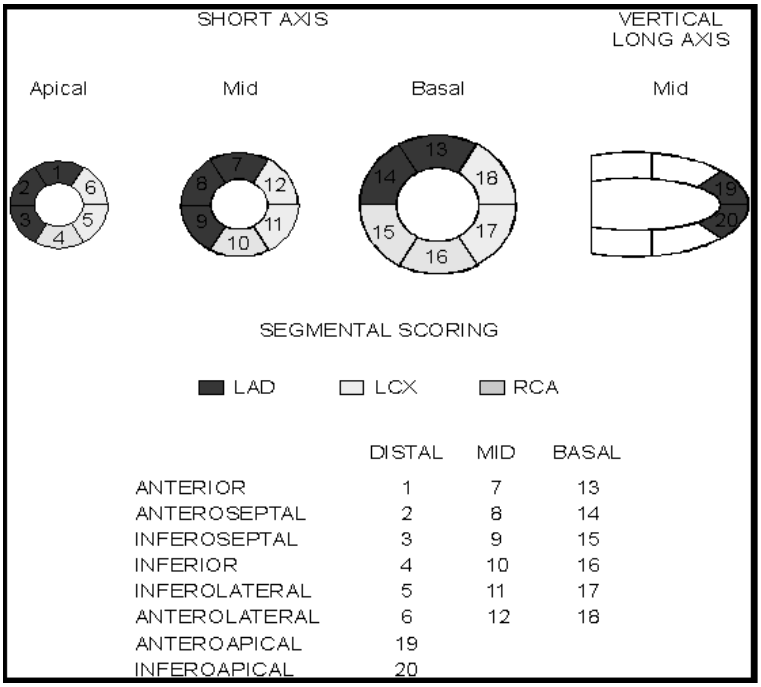


Figure 1.2 shows different heart territories to be evaluated by ROI's.

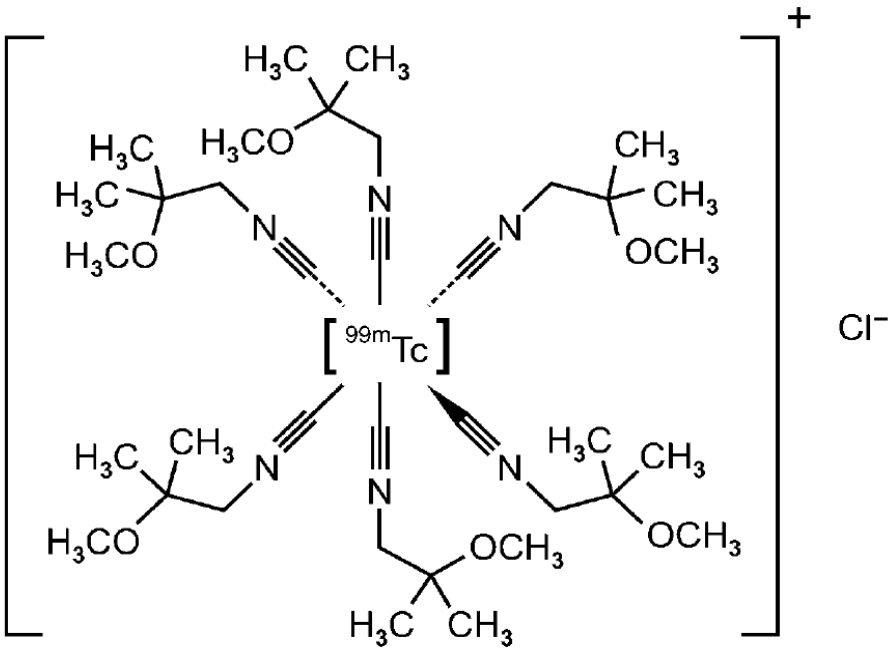


Figure3.4: Structure of ^{99m}Tc-sestamibi ((OC-6-11)-hexakis[1- (isocyano-kC)-2-methoxy-2-methylpropane] [^{99m}Tc]technetium(I) chloride .

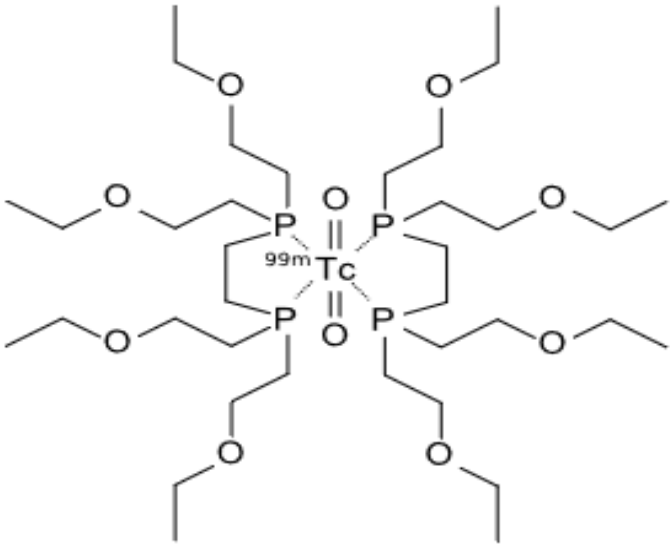


Figure3.5: Structure of ^{99m}Tc-tetrofosmin dioxo compound.

(www.chemicalelements.com/elements)

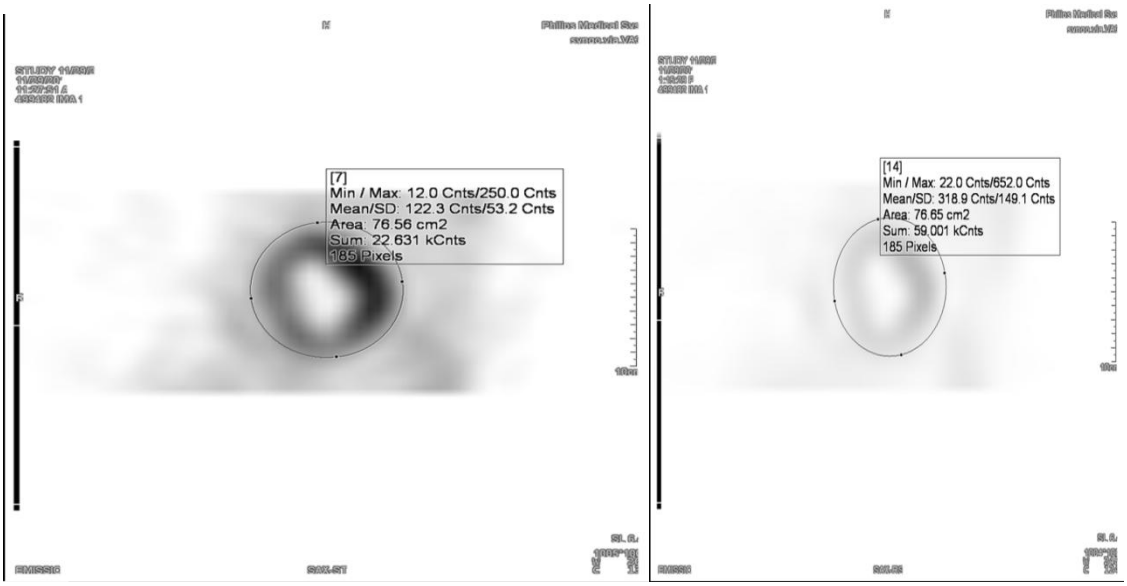


Figure3.7: Shows measurement of the whole heart sum counts/second/Pixel (c/s/p) using ROI in both conditions Stress/Rest

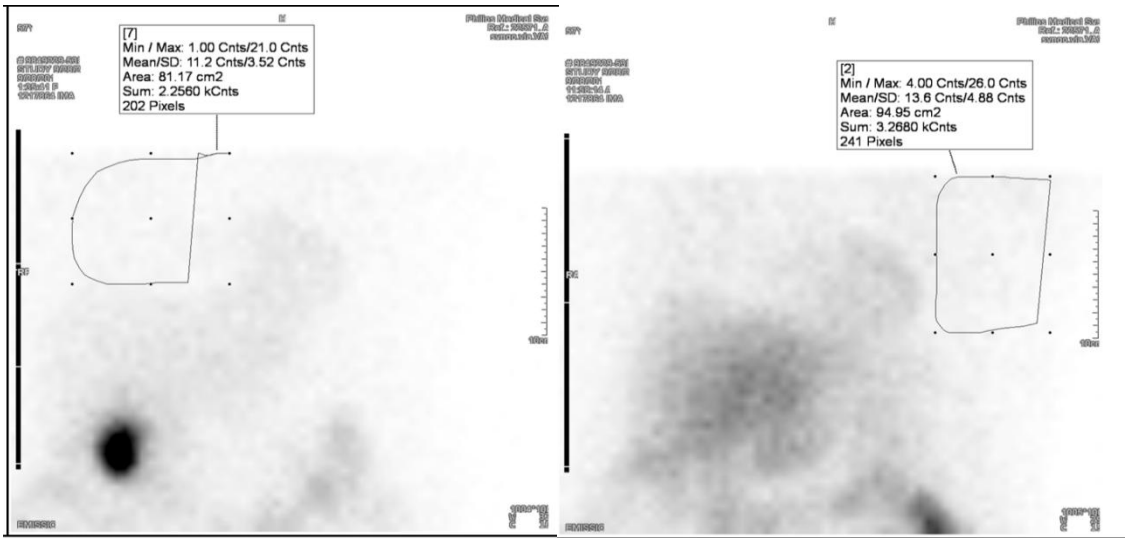


Figure 3.8: Shows measurement of the Right (A) and Left (B) Lungs sum counts/second/Pixel (c/s/p) using ROI in both conditions Stress/Rest

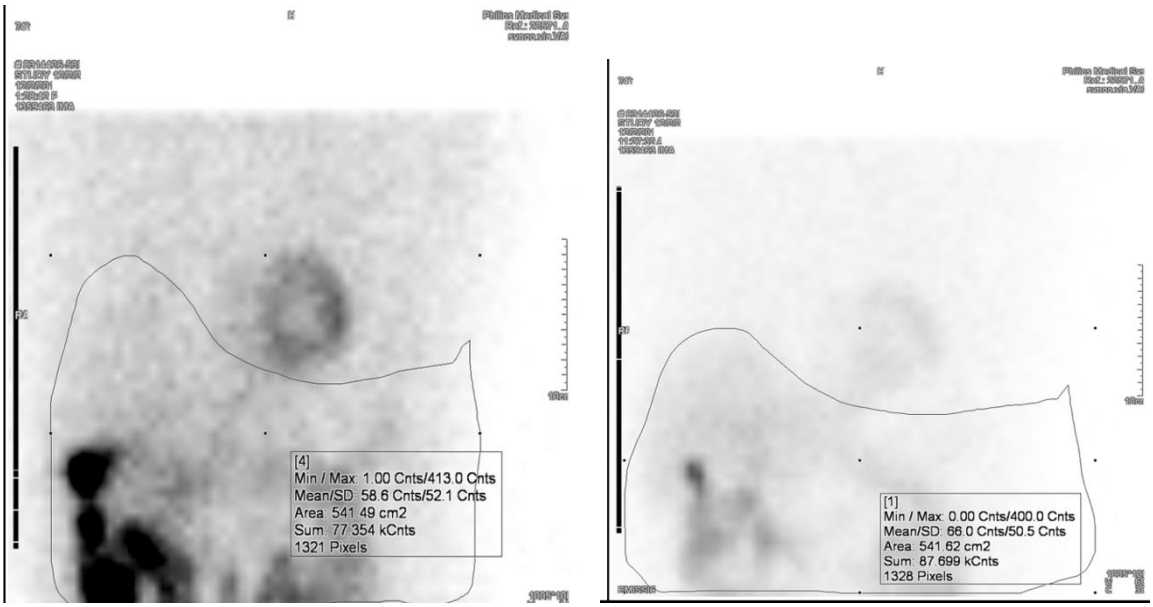


Figure3.4: Shows measurement of gastrointestinal track (GIT) at Stress (A) and Rest (B) Lungs sum counts/second/Pixel (c/s/p) using ROI in both conditions Stress/Rest

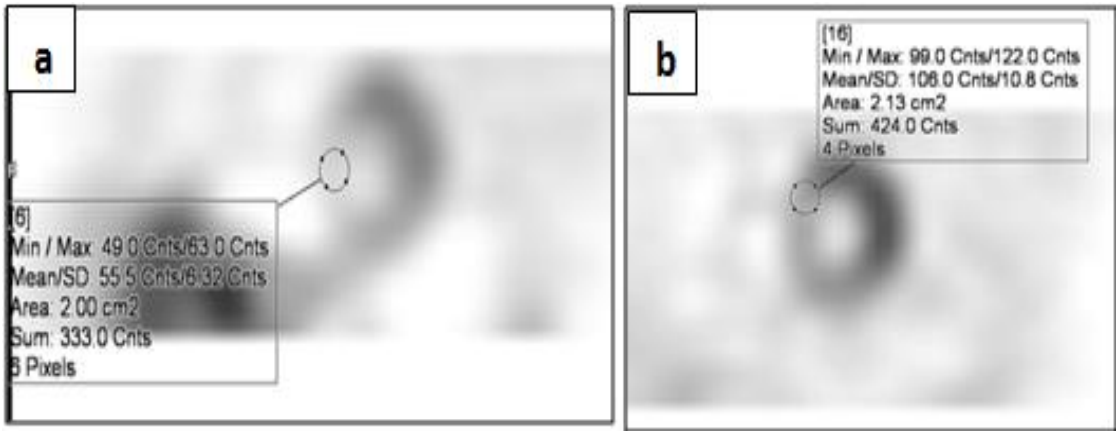


Figure 4.8: shows the uptake of apical heart & at ROI during rest (a) and stress (b) where the ischemic segment (17) manage to take a little amount of radiopharmaceutical, indicating the reversibility of the case

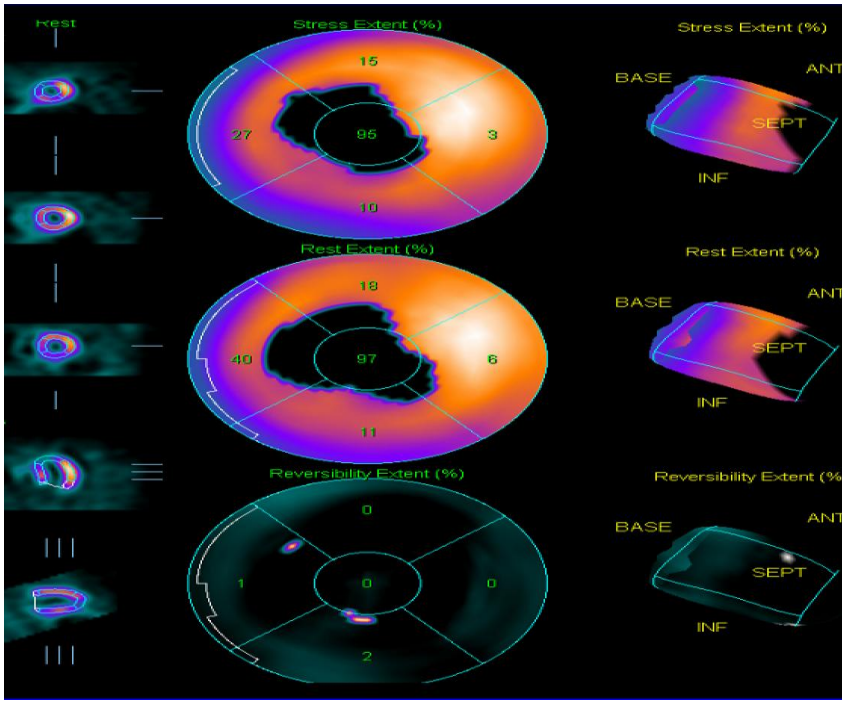


Figure 4.9: shows the lack of distribution of ^{99m}Tc-MIBI (Sestamibi) at apical segments within myocardium typically (Seg.No. 17) during stress and rest as per AHA (American Heart Assosication) Model

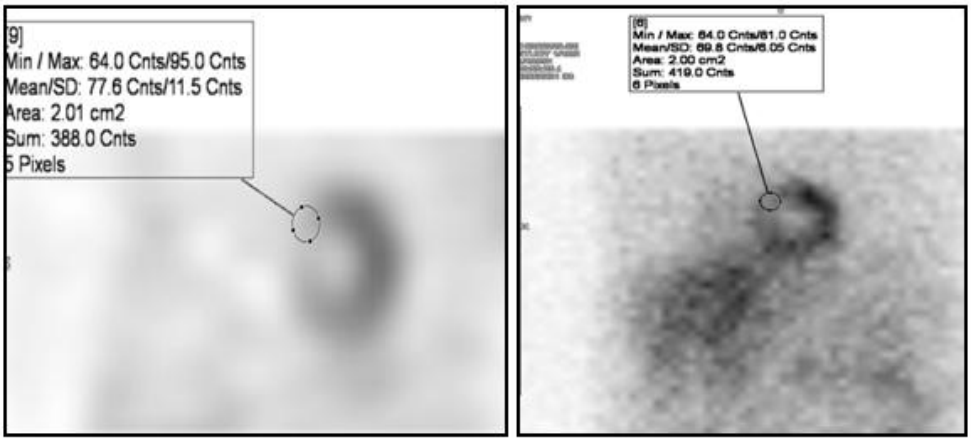


Figure 4.14: shows the uptake in count/second during stress and rest for involved heart segment by ischemia to assess the reversibility of myocardial ischemia

Appendix C

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Original Research Paper Medical Science

Assessment of Ischemic Coronary Arteries Prevalence, Reversibility and Relative Dose Ratio% Using ^{99}Mtc-Sestamibi and ^{201}TI

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ABSTRACT

The aim of this study was to assess the ischemic coronary arteries prevalence, reversibility and the relative dose ratio% using 99mTc-Sestamibi and 201TL. The method was adapted from the heart scintigraphy protocol i.e. a sample of one hundred and forty four patients with known or suspected ischemic heart disease (IHD)were administrated to a typically dose of 740 MBq (20 mCi) of 99mTc-MIBI and 74 to 111 MBq (2 to 3 mCi)of 201 Tl, Patients under beta-blockers or calcium channel antagonists were asked to discontinue administration for 24 - 48 hours before the stress test, using the standered Bruce protocol exercise followed by immediate SPECT study for stress ,One to two hours after injection, a rest 201 Tl SPECT acquisition was performed, While acquiring rest images for 99mTc-MIBI were obtained two to three hours post stress phase, SPECT acquisition was acquired with 90 degree configuration using contouring centered on the heart. The results analysis was carried out using EXCELL software in form of bars and correlation, which showed that: the male were more common involved by ischemic disease compared to female during the age hood with plateau occurring among age group of 50-70 years old. And the common artery of the heart involved by ischemia was the left anterior descending artery (LAD) which represented 43% relative to 31% and 26% for LCX and RCA respectively. The reversibility of ischemia in heart arteries were high in case of LAD (43%) and LCX (31%) when detected by 201 Tl among male and 99mTc-MIBI among female respectively while RCA shows the less reversibility of ischemia as17% for male by 99mTc-MIBI, 10% for male by 201Tl, 9% for female by 99mTc-MIBI and 11% for female by 201Tl.Also both Tlalium-201 and 99mTc-MIBI can detect the ischemic artery successfully during rest and stress with considerable limited and low exposure dose to other anatomical organs as GIT, Left Lung, and Right Lung.

KEYWORDS Coronary, Arteries, Ischemia, Reversibility, 201Thallium, 99mTc-MIBI.

INTRODUCTION

Coronary arteries diseases (CAD) recently have been consider as one of the major reasons of morbidity among males and females in Sudan, These coronary arteries give rise to rich capillary networks that bathe the cardiac muscle cells with blood. All arteries inside the heart walls are fed by branches of either the right or left coronary arteries, the blood flow through the heart usually keeps up with the body's demand. The demand is increased by exercise and strong emotions, both of which make the heart pump more quickly and more forcefully, causing the heart to use more oxygen, as the heart beats twice as fast it needs double as much oxygen [1]. Normally, the extra oxygen needed during exercise is supplied by a faster and a more voluminous blood flow through the coronary arteries [2]. In UK Coronary artery disease is the cause of 52% (95% CI 43–61%) of incident heart failure in the general population under 75 years [3]. Other studies have observed higher long- term mortality rates among patients with proximal as opposed to distal left anterior descending (LAD) coronary artery lesions regardless to the number of diseased vessels [4, 5]. Furthermore higher prevalence of chronic obstruction of the proximal left anterior descending coronary artery in comparison to other major coronary arteries was seen in patients dying of atherosclerotic disease [6]. Schuster and Bulkley, [7] stated that: Ischemic heart disease (IHD) can be caused mainly by atherosclerosis, Myocardial Infarction (MI) and Angina pectoris in which the ischemia is less severe and does not cause death of cardiac muscle. Angina pectoris implies three types: *(stable angina, prinzmetal angina, and unstable angina)*, the latter is the most threatening as a frequent harbinger of MI. Based on American Heart Association (AHA), all the seventeen (17) segments of the myocardium are supplied with those small branches *(right coronary artery (RCA), left anterior descending artery (LAD) and the left circumferential artery(LCX))*, If one of these branches blocked, will ceased the blood supply to the relevant segment of myocardium and will be deprived of oxygen [8] and the prevalence of atherosclerosis in a population consider as an index of IHD, [9]. IHD can be manifested through electrocardiographic and enzymatic changes with rare exceptions could be due to congenital anomalies of the coronary vessels, emboli, or ostial occlusion, while detection of IHD could be obtained by using echocardiogram (ECG) with correlation to wall motion abnormality (WMA) and Ejection fraction percentage of different myocardium territories [10], Delayed Enhancement method (DE) in Magnetic resonance imaging (MRI) which showed good capability of detection of (IHD) [11], diagnostic x-ray, contrast-enhanced multi-detector computerized tomography (MDCT) which is widely used as a noninvasive method of ruling out significant CAD [12] and nuclear medicine with utilization of ^{99m}Tc-MIBI and ^{201}Thallium Radiopharmaceuticals to determine the adequacy of blood flow to the myocardium, especially in conjunction with exercise or pharmacologic stress for the detection and evaluation of coronary artery disease (CAD). Although the basic principles are similar, protocols for imaging vary among the radiopharmaceuticals used [13]. However ^{201}Tl showed some disadvantages for imaging due to its physical and biologic characteristics [14] and its lower photon energy, and attenuation and scattering from overlying tissues.

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RESEARCH ARTICLE

ASSESSMENT OF SELECTIVE FACTORS AFFECTING MYOCARDIAL REVERSIBILITY IN ISCHEMIC HEART DISEASE USING ^{99M}TC-MIBI

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ABSTRACT

The aim of this retrospective study was to assess selective factors affecting the reversibility of the ischemic heart. The methodology carried out based on cardiac study at stress and rest for the distribution of ^{99m}Tc-MIBI with consideration to age, weight and gender. The results revealed that: the uptake in cunt/second/pixel (c/s/p) in stressed cardiac study for the affected heart segment (ischemic segment) has been decreased as the age increases, indicating the aging is a negative factor for ischemic reversibility, while there was a significant ($R^2 = 0.8$) increasing uptake during the stress phase for whole heart uptake, Rt/Lt lungs and the gastrointestinal tract (GIT). And there were significant ($R^2 = 0.7$) decreasing uptakes by whole heart, GIT and Rt/Lt lungs as the age increases with superior significant uptake by GIT during stress and rest at $R^2 = 0.6$ and 0.5 respectively. And in the correlation between weights in Kg versus count/sec at stressed cardiac study, the analysis revealed significant increased uptakes by GIT, Rt lung, Lt lung, and whole heart ($R^2 \approx 0.6$) as the weight increases whereas the same organs (GIT, Lt lung, Rt lung and the whole heart) showing significant ($R^2 \approx 0.7$) decreasing uptake as the weight increases as well as the affected heart segment The study also showed there were high frequencies percent of obese and overweight patients 52% and 32% respectively with ischemic heart segment reversibility of 37% among female relative to 30% among male, while the irreversible cases were greater among male 15% relative to only 4% among female and the incidence % of IHD is predominant among male 55% compared with 45% among female. The stress cardiac study enhance the uptake by the reversible ischemic segment hence gives further knowledge about ischemic reversibility% that could be managed by simple medications.

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INTRODUCTION

Ischemic (or ischemic) heart disease (IHD) is a disease characterized by reduced blood supply to the heart; Ischemia means a "reduced blood supply". The coronary arteries supply blood to the heart muscle and no alternative blood supply exists, so a blockage in the coronary arteries reduces the supply of blood to heart muscle. Most ischemic heart disease is caused by atherosclerosis, usually present even when the artery lumens appear normal by angiography, initially there is sudden severe narrowing or closure of either the large coronary arteries and/or of coronary artery end branches by debris showering downstream in the flowing blood, coronary artery (CAD) is presenting the start of many cardiomyopathy including reversible and irreversible ischemic diseases or myocardial infarction (MI), This disease is also affecting the myocardium wall motion causing wall motion abnormalities (WMA) due to lack of blood supply to different myocardium territories, ^{201}Thallium (*half-life ~72 hr emitting 70~80 Kev*) is considered as highly specific agent in detection of perfusion deficits of the myocardium in patients with severe coronary artery disease (CAD) compared to Methoxy Isobutyl Isonitrile (MIBI) which can be labeled with ^{99m}Tc (*Technetium half-life ~ 6 hrs emitting 141 Kev*) known as Sestamibi or Cardiotle, also proven high specificity and sensitivity in detection Ischemic heart disease (IHD), Nevertheless, the prognostic values of both radiopharmaceuticals (^{201}Thallium, ^{99m}Tc-Sestamibi) depending of their bio-distribution over particular myocardium territories is a matter of debate (Babak *et al*, 2014), investigations with the isonitrile complexes have shown them to undergo pattern of biologic distribution different from that of ^{201}TI (Raymond *et al*, 1997), Another study revealed that patients could be shown

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