INTRODUCTION

Heart rate (H.R) of an individual reflects an integrated physiological response comprising of autonomic system , central and peripheral reflexes as well as intrinsic cardiac conditions[1].

Normal heart beat originates from Sino-atrial node (SAN) and its rate determine the heart rate. The SAN is located superiorly in the right atrium at the junction of the crista terminalis, a thick band of atrial muscle at the border of the atrial appendage, and the superior vena cava. Human histologic studies have demonstrated that the sinus node has a crescent-like shape with an average length of 13.5 mm. A collection of cells known as paranodal cells, which are electrically and histologically distinct from the sinus node, are thought to facilitate electrical conduction from the sinus node to the rest of the atrium[2].

The impulse pass through atrial pathways to Atrio-ventricular node (AVN) and then bundle of His and through Purkinje system reach the ventricular muscle. As the blood volume is constant, one of the physiological ways to deliver more oxygen to an organ is to increase heart rate to increase blood volume to an organ. Normal HR is about 60 – 90 beat / min. Bradycardia is defined as a resting heart rate below 60 b/m. However, heart rates from 50 to 60b/m are common among athletic people and do not necessarily require special attention. Tachycardia is defined as a resting heart rate above 90b/m [3].

Heart is innervated by sympathetic and parasympathetic nerves fibres. Impulses in nonadrenergic sympathetic nerve to the heart increase heart rate (chronotropic effect). They also inhibit the effect of vagal stimulation through (**vasoconstrictor centre**), nerve fibers sent through cervical ganglia and superior thoracic ganglia to SAN and AVN, plus additional fibers to atria and ventricles. Its stimulation cause release of neurotransmitter of norepinephrine at neuromuscular junction and subsequently shortens the repolarization period and speed up the rate of depolarization and contraction which result in increase of heart rate [4]. (figure 1)

Another cardiac centre that affect the heart rate is (**Cardioinhibitory centre**), this comprise mainly of the dorsalis motor nucleus of the vagus plus parts of nucleus ambiguous and nucleus of tractus solitarious. It sends inhibitory signals to the heart via vagus nerve which sends branches to both SAN and AVN only. Vagal nerve stimulation releases neurotransmitter acetylcholine (Ach) at

neurotransmitter junction. Ach slow HR by slowing the rate of spontaneous depolarization [4].

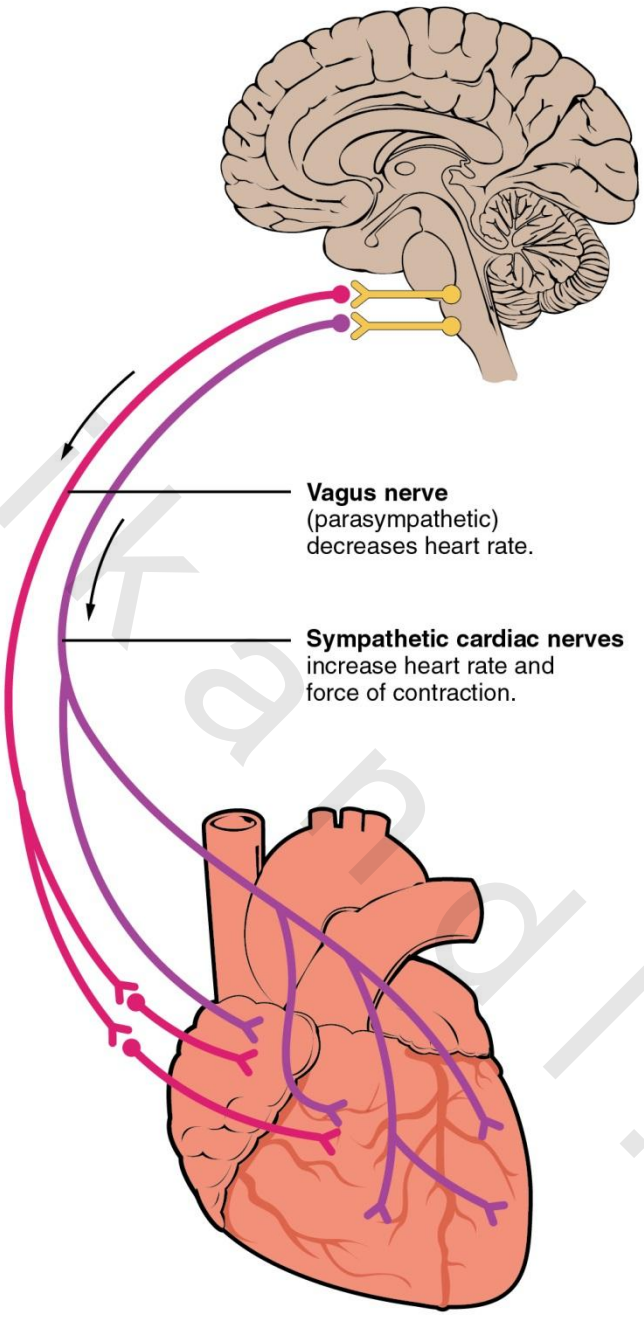

Figure 1: Autonomic Innervation of the Heart - Cardioaccelerator and cardioinhibitory areas are components of the paired cardiac centers located in the medulla oblongata of the brain[5].

Factors affecting heart rate:

Heart rate is nervously regulated through cardiovascular centres (as discussed before) which control the sympathetic and parasympathetic discharge to the heart.

The activity of these centers is affected by certain supraspinal centres and many reflexes initiated from the cardiovascular system itself [(6)].

A. Supraspinal centres:

1. Cerebral cortex:

Cortical influence on the heart rate is evident in emotions and conditioned reflex as the heart rate altered in seeing, hearing or thinking of certain events [(7)].

2. Hypothalamus and limbic system:

These structures with the cortex are concerned with emotional reactions.

3. Respiratory centre:

In children and young people increasing the heart rate during inspiration and decrease during expiration are common and called respiratory sinus arrhythmia, and this tachycardia is due to irradiation of impulses from inspiratory centre which excite vasoconstrictor centre, as well as lung inflation stimulate pulmonary stretch receptors which stimulate vasoconstrictor centre and lastly due to Bainbridge reflex [(8)].

B. Cardiac reflexes:

1. Marey's reflex [(9)] (Baroreceptor reflex):

A rise of arterial blood pressure leads to decrease of heart rate and vice versa. The carotid sinus and aortic nerves transmit the signals from the arterial baroreceptors.

Stimulation of these arterial baroreceptors stimulate cardioinhibitory centre, inhibition of respiratory centre (temporary apnea may occur) and inhibition of secretion of antidiuretic hormone.

Abnormal hypersensitivity of carotid sinus may produce bradycardia and hypotension and may lead to syncopal attacks with mild compression on carotid sinus area during shaving or by a tight collar (**carotid sinus syndrome**) [10].

2. Bainbridge reflex:

Bainbridge reflex was first described by Francis Aurther Bainbridge in 1915. Bainbridge found that infusion of blood or saline into animal increase the heart rate. This phenomenon occurred even if arterial blood pressure did not increase. **Bainbridge reflex and baroreceptor reflex act antagonistically to control heart rate.** The baroreceptor reflex act to decrease heart rate when blood pressure increases. When blood volume is increased the Bainbridge reflex is dominant but when blood volume decrease baroreceptor reflex is dominant [8-11].

3. Ventricular or coronary stretch reflex:

Distention of left ventricle leads to bradycardia and hypotension. Their receptors located near coronary vessel which send signals through vagus nerve to medulla oblongata to stimulate cardioinhibitory centre.

4. Bezold – Jarisch reflex:

Injection of certain substances like serotonin into the coronary arteries leads to hypotension, bradycardia and apnea. This reflex is also mediated by vagus nerve [12].

C. Extravascular reflexes affect heart rate:

1. From skeletal muscles:

Voluntary contraction of skeletal muscle (exercise) leads to an increase of the heart rate. Receptors within muscles and joints stimulated during contraction and pass through somatic afferent nerve fibres to medulla oblongata where they stimulate the vasoconstrictor centre [7]. As well as during contraction the venous return is increased and HR increased by Bainbridge reflex [8].

2. From the skin and viscera:

Exposures to cold and painful stimuli usually result in reflex increase of heart rate while severe pain especially visceral pain is commonly associated with bradycardia.

3. From the eye:

Applying pressure to the eyeball results in reflex bradycardia. This reflex mediated through oculomotor nerve to cardioinhibitory centre.

D. Chemical regulation of heart rate:

1. Effect of changes in blood gases[13]:

Moderate hypoxia increases heart rate by direct stimulating of SAN, direct inhibition of cardioinhibitory centre and by stimulating vasoconstrictor centre through stimulation of peripheral chemoreceptors in carotid and aortic bodies. On the other hand, **severe ischemia** causes severe bradycardia that may lead to death due to inhibition of SAN and paralysis of cardiovascular centres in the medulla oblongata.

Moderate hypercapnea and acidosis stimulate central and peripheral chemoreceptors and subsequent stimulate the vasoconstrictor centre and produce tachycardia. But in **severe hypercapnea** or acidemia produce severe bradycardia due to SAN inhibition and cardiovascular centre paralysis.

2. **Effects of hormones, drugs and chemicals[14]:**

- **Adrenaline** [15]: small doses increase the heart rate by direct action on β1 receptors in SAN but in large doses it elevate arterial blood pressure which decreases heart rate through Marey's reflex.
- **Noradrenaline**: potent vasoconstrictor that decrease heart rate through Marey's reflex [9].
- **Thyroxin** [16]: increase heart rate by direct stimulation of SAN and by increasing sensitivity to catecholamines.
- **Atropine** [17]: accelerates the heart rate by blocking parasympathetic activity.
- **Histamine**: potent vasodilatory substance which leads to drop in blood pressure and tachycardia by Marey's reflex.
- **Autonomic drugs**: sympathomimetic drugs (e.g. amphetamine) cause tachycardia while parasympathomimetic cause bradycardia.
- **Other drugs**: calcium channel blockers, beta blockers, digoxin, dipyridamole and procorolan.

Maximum heart rate is the highest heart rate an individual can achieve without severe problem through exercise stress. Dr. William Haskell and Dr. Samuel Fox devised the most widely formula that determine the maximal heart rate HR_{Max} which contains no reference to any standard deviation. ($HR_{Max} = 220 - age$) [18].

Importance of heart rate refers to becoming non-invasive tool to measure index of myocardial work [19]. Heart rate response during stress and heart rate decline post-stress are also very good marker of cardiac autonomic control [20]. There is a plethora of studies suggesting that the findings of blunted heart rate elevation during progressive exercise (chronotropic incompetence) [21] and attenuated heart rate decline during recovery are important for underlying autonomic dysfunction associated with increased cardiovascular morbidity and mortality [22]. So, high resting heart rate (tachycardia) and abnormal heart rate responses during or after stress test may preceed manifestation of cardiovascular disease and may contribute to the early identification of persons at high risk [10]. An impaired heart rate response to exercise and failure to reach >80% of age predicted heart rate response known as aschronotropic incompetence [23].

Increase circulating level of catecholamines augment sympathetic outflow and causes a long term reduction in vagal drive [12]. It is also

associated with impaired baroreflex function leading to a marked increase in resting heart rate [24].

Another study suggests that sustained tachycardia interact with inflammation at several level of cardiovascular system [25] and exert synergistic effect on cardiovascular morbidity and mortality and this could be explained by elevated heart rate increases tensile stress which apart from inducing endothelial injury as well as increases mediators [26]. So, autonomic nervous system dysfunction may underlie both progression of inflammation and elevating resting heart rate [27]. In other way, stimulation of vagus nerve has been associated with normalizing tachycardia and this process inhibits inflammation via stimulation of cholinergic anti-inflammatory pathway [28]. So, European society of hypertension/ European society of cardiology guidelines recently proposed the inclusion of elevated heart rate when elevating the cardiovascular risk profile of an individual [29].

Single-photon emission computed tomography (SPECT)

Singe photon emission computed tomography (SPECT) myocardial perfusion imaging is a well-established method of evaluating for coronary artery disease with over 30 years of experience supported by literature validating its diagnostic and prognostic value [30].

The most widely used nuclear cardiology procedure is myocardial perfusion imaging (MPI) using SPECT study. It is a non-invasive imaging modality routinely used in the diagnosis of and for assessing the prognosis of coronary artery disease and heart muscle damage following an infarction. MPI SPECT images provide a visual three dimensional image of the perfused myocardium for assessment. In addition, if the MPI SPECT studies are gated to the electrocardiogram (ECG) it is possible to make a functional assessment of the perfusion images. The clinical success of MPI SPECT, and gated MPI SPECT, relies on an understanding of the physics and technical aspects of SPECT imaging, as well as the technical [31].

The excellent procedural and clinical guidelines published by ACCF and ASNC have made this testing modality widely available in the outpatient and in-patient setting. In the United States, more than 6 million SPECT MPI studies performed annually. This versatile technique may be combined with exercise, dobutamine or vasodilator stress, providing stress, providing flexibility for various patient populations [32].

To perform MPI a patient is intravenously given a radiopharmaceutical or tracer (a pharmaceutical labeled with a small amount of radioactivity, which emits gamma rays). The ideal tracer would have the following desirable properties:

1. Distribute in the myocardium in linear proportion to blood flow.
2. Efficient myocardial extraction from the blood on the first pass through the heart.
3. Stable retention within the myocardium during the scan but also rapid elimination allowing repeat studies under different conditions.
4. Be readily available; and have good imaging characteristics, limitations and quality assurance requirements of the system.

SPECT (tomography) imaging produces full 3D images and has several advantages over planar imaging. In particular, tomography allows separation of target regions from overlying structures, and therefore gives improved diagnostic results over planar imaging. By performing MPI SPECT, it is possible to create a 3D volume representation of the perfused myocardium. By selecting appropriate planes through the myocardium, the cardiac shape can be assessed, together with regional and global perfusion patterns. The sensitivity of CAD detection has been shown to be far superior with SPECT (93%) than with planar imaging (77%). Specificity is also improved in SPECT compared with planar imaging (88% and 82%, respectively). SPECT is, however, a much more complex technique, and there is scope for more image artifacts to appear during the image acquisition and subsequent image processing. However, by paying strict attention to detail throughout the whole imaging procedure (acquisition and processing) and by regularly performing quality control tests on the gamma camera, the chance of these image artifacts appearing is much reduced [(33)].

Other advantages of SPECT image over planar one include ability to differentiate overlying and underlying structures, ability to reconstruct image in same orientation irrespective to cardiac position and ability to reconstruct images in format comparable with other cardiological images[(34)].

ACCF/ASNC 2009 Appropriate use criteria (AUC) consist of 67 most common clinical scenarios, and scored based on the level of appropriateness, using a rigorous scientific method (33 appropriate, 9 uncertain and 25 inappropriate). An appropriate imaging study is one in which the expected incremental information, combined with clinical

judgment, exceeds the expected negative consequences by a sufficient margin for a specific indication. A hierarchical approach facilitates the use of AUC so that the patients are classified for a true clinical indication as some might fall into clinical table [35]. (figure 2)

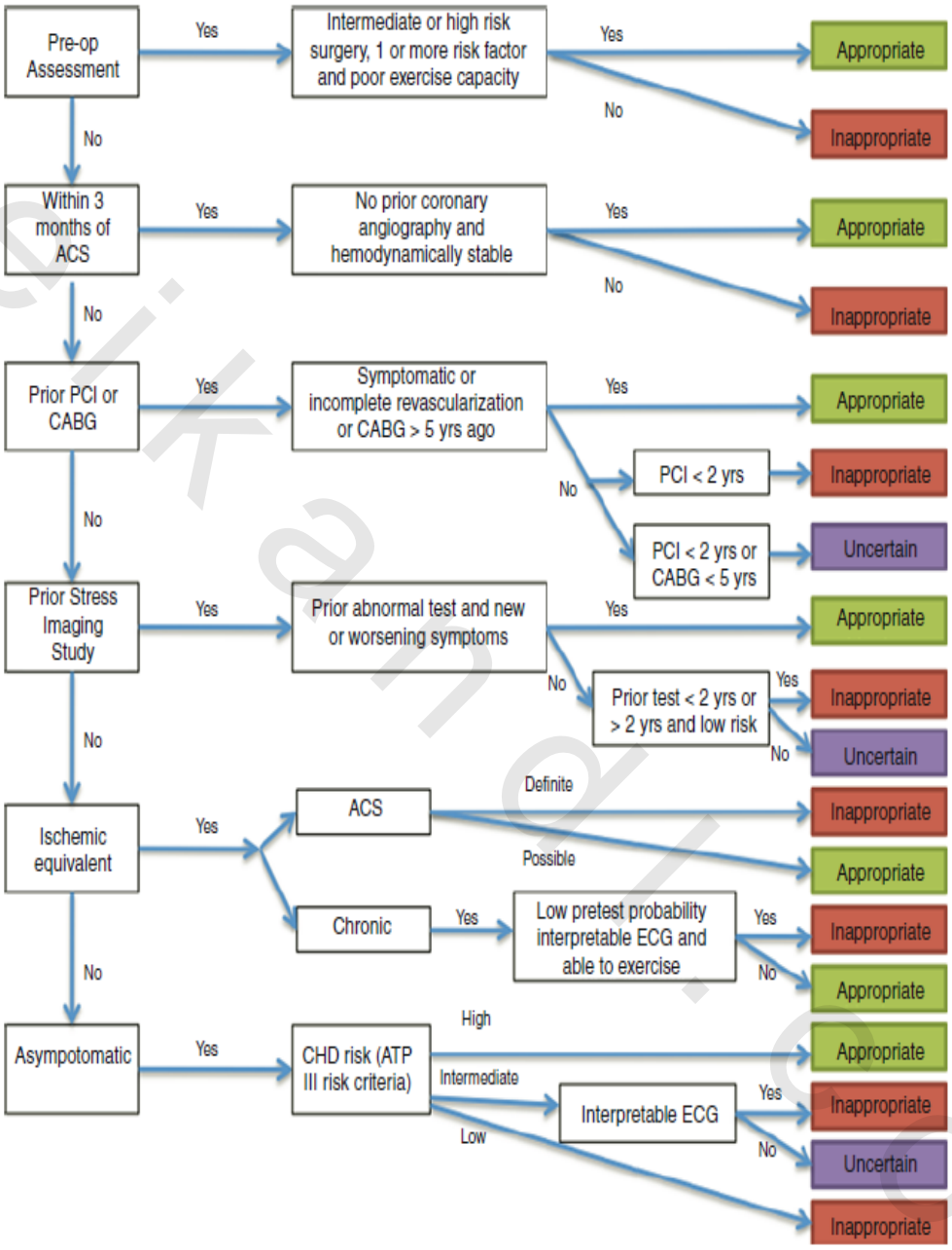

Figure 2: Heirarchial approach for test ordering using AUC.[35]

Gated SPECT:

Gated SPECT scans have increased temporal resolution, and so it is possible to analyze individual phases of the cardiac cycle. In a gated

acquisition each phase of the cardiac cycle are associated with a temporal frame within the computer. Reconstruction of each interval of a gated MPI SPECT into a tomographic image set allows for visual or quantitative estimation of functional parameters, such as myocardial motion and thickening. The most common gating rate is eight frames per R–R interval per projection, although 16 frames are sometimes used. Gated MPI SPECT wall motion is often visualized using bulls eye plots or a 3D surface display or mesh method. (Figure 3)

In 1971 Strauss et al. introduced the concept of using ECG to trigger image frame acquisition. Combined perfusion/function studies became commonplace in the late 1980s with the advent of Tc-99m labeled myocardial perfusion agents and has rapidly evolved into a standard for myocardial perfusion imaging in the USA [(36)].

In its position paper in March 1999, The American Society of Nuclear Cardiology recommended the routine incorporation of ECG gating during SPECT cardiac perfusion scintigraphy [(37)]. Over 90% of all myocardial perfusion SPECT studies in the USA are now gated.

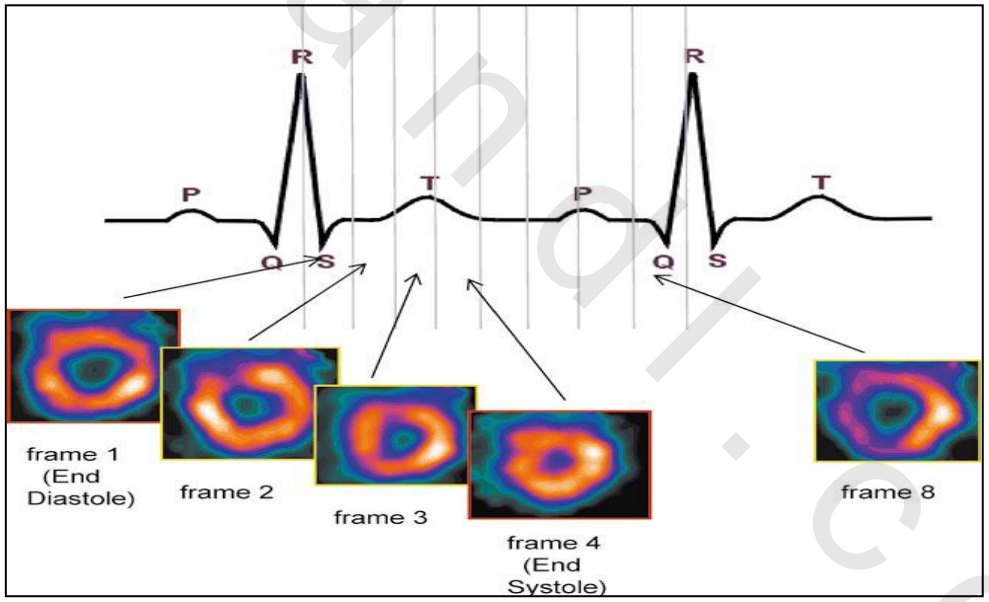

Figure 3: 8frames ECG gated SPECT study[(37)]

DePuey and Rozanski demonstrated that false-positive perfusion studies could be reduced from 14% to 3% by incorporating regional wall motion data in the interpretation of perfusion imaging. In women, where the false-positive rate of stress ECGs is relatively high and breast soft-tissue attenuation artifact is common, ECG gating has been shown to further enhance the diagnostic specificity of 99mTc perfusion imaging from 84% to 94% [(38)].

Smanio et al. demonstrated that the number of "borderline-normal" or "borderline-abnormal" interpretations was significantly reduced. In patients with a low likelihood of CAD, the normalcy rate increased from 74% to 93%. In patients with a high likelihood of CAD, the trend was also toward a higher number of unequivocally abnormal interpretations [39].

In the case of multivessel disease or left main disease, balanced global hypoperfusion comes into play. According to several reports, only 13–50% of patients with three-vessel CAD or left main disease actually have perfusion abnormalities in multiple territories. In the setting of diffuse ischemia, a perfusion defect may not be seen, because of image normalization. Transient ischemic dilatation (TID) in myocardial perfusion imaging (MPI) refers to a significant enlargement in left ventricular (LV) size on the stress images compared with the rest images. In the case balanced ischemia, TID due to stunning results in an increase in ESV and a decrease in EF. This is helpful to correctly identify significant CAD for predicting severe proximal left anterior descending artery or multivessel critical coronary lesion, even though there is no perfusion abnormality due to balanced ischemia [40].

Advantages of gated SPECT :[41]

1. Allows the reporting physician to distinguish between fixed defects from artifacts.
2. End diastolic and end-systolic images or polar map displays also help assess apparent perfusion abnormality.
3. Used to calculate the end-diastolic and end-systolic volumes, and as a result, calculate the left ventricular ejection fraction (LVEF), which is a fundamental diagnostic and prognostic predictor of CAD.
4. Assessment of both perfusion and function in a single-injection, single-acquisition sequence.
5. Gated SPECT helps to differentiate soft tissue attenuation artifact from scar. Artifact will show normal function and thickening, while scar will show as a fixed defect, with diminished or lack of wall thickening and motion.

Indications of gated SPECT [42]:

- Known or Suspected CAD:
  1. Diagnosis of physiologically significant CAD (presence and severity).

2. Determine prognosis (risk stratification based on extent and severity of myocardial perfusion abnormalities and left ventricular function.
3. Differentiate between coronary and non-coronary causes in patients with acute chest pain syndromes seen in the emergency rooms.

- Follow-Up of Patients with Known CAD:
  1. Evaluate the immediate and long-term of effect of:
     a. Revascularization procedures (such as coronary artery bypass grafting, angioplasty, stent placement, use of angiogenic growth factors, etc.).
     b. Medical or drug therapy, whether designed to prevent ischemia (e.g., drugs that alter myocardial metabolic oxygen supply/ demand relationship) or modify lipids and other features of atherosclerotic plaque (e.g., statin drugs).

- Known or Suspected Congestive Heart Failure:
  1. Differentiate ischemic from idiopathic cardiomyopathy.
  2. Help assess whether patient has sufficient viable myocardium overlying the infarction to consider revascularization.

Stress modalities of SPECT study:

Exercise stress test:

This is usually performed with a treadmill or bicycle ergometer with continuous patient monitoring and it is the preferred stress modality in patients who can exercise to an adequate workload. Exercise testing has a limited value in patients who cannot achieve an adequate heart rate and blood pressure response due to non-cardiac physical limitations such as pulmonary, peripheral vascular, musculoskeletal abnormalities or due to a lack of motivation. A treadmill is the most widely used exercise modality, with Bruce and modified Bruce being the most widely used exercise protocols. Departments may decide not to offer exercise stress MPI routinely if the patient population within the catchment area of the department is likely to include a high proportion of patients with non-cardiac physical limitation [(43)].

It allows for a physiologic assessment of functional capacity, symptoms and hemodynamics. When compared to pharmacologic stress testing, exercise is associated with less extensive hepatic and gastrointestinal tracer uptake, which significantly improves image quality [(44)].However, for several reasons plain exercise ECG may not be adequate and in such conditions it should be combined with an imaging modality to increase the sensitivity and specificity of diagnosis like Electronically paced ventricular rhythm, Pre-excitation syndrome example Wolff-Parkinson-White, 1 mm of ST segment depression at rest, Previous PCI/CABG and Left bundle branch block [(44)].

Myocardial perfusion imaging (MPI) with exercise stress testing enhances diagnostic sensitivity and specificity, particularly among patients with resting ECG abnormalities that preclude the interpretation of ST-segment deviation. MPI helps to differentiate true-positive from false-positive ST-segment depression and provides a more accurate assessment of the extent and severity of disease. Importantly, it can also localize ischemia to a particular vascular distribution. MPI is useful when patients are unable to achieve their target heart rate during exercise, because myocardial perfusion abnormalities in response to stress occur earlier than ECG changes [(45)].

When combined with exercise, MPI not only improves diagnostic capability, but it is also predictive of short- and long-term cardiac events. This prognostic ability does not apply to ECG interpretation without concurrent use of the Duke Treadmill score [(46)].

Duke treadmill score =Exercise time (in minutes) – 5 × maximum ST depression – 4 × angina score (0 = none, 1 = present, 2 = reason for test termination)

Low risk: > 5
Intermediate risk: = -10 to +4
High risk: < -10

The indications and contraindications for exercise MPI are listed in (Table 1 and 2) respectively.

Table (I): Indications of exercise stress myocardial perfusion imaging [32]:

Diagnosis of ischemic heart disease in patients with intermediate pretest probability of CAD and/or risk stratification of patients with intermediate or high pretest probability of CAD based on age, gender, and symptoms :	**Class**
Identify location, severity, and extent of ischemia.	I
In patients with Intermediate Duke treadmill score.	I
Assessment of functional significance of intermediate (25–75%) coronary lesion.	I
Repeat testing in patients whose symptoms have worsened/changed to redefine the risk for cardiac event.	I
Repeat testing every 1–3 years in high likelihood patients.	IIb
Asymptomatic patients who have a high-risk occupation.	IIb
Severe coronary calcification with uninterpretable ECG.	IIb
Screening of asymptomatic patients with low probability of CAD.	III
Prior to non-cardiac surgery Class:	
Intermediate risk surgery or vascular surgery AND risk factors with poor functional capacity.	IIb
Intermediate risk surgery or vascular surgery and adequate functional capacity (≥ 4 METS).	III
Low risk surgery.	III
Assessment of therapy and interventions in ischemic heart disease:	
3–5 years after revascularization in high risk, asymptomatic patients.	IIa
Evaluation of therapeutic efficacy (anti-ischemic drug therapy)	IIb
Routine assessment after PCI or CABG in asymptomatic patient	III

Table (II): Contraindications of exercise stress testing **:**[47]

Absolute	Relative
Acute myocardial infarction (within 2 days).	Left main coronary stenosis or its equivalent.
Unstable angina.	Electrolyte abnormalities.
Acute pulmonary embolism or infarction.	LBBB, pacemaker or pre-excitation.
Symptomatic severe aortic stenosis.	Moderate valvular stenosis.
Uncontrolled symptomatic heart failure.	HCM or other forms of out flow tract obstruction.
Acute myocarditis or pericarditis.	High-degree atrioventricular block
Aortic dissection.	Significant tachy- or bradyarrhythmias.
Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise.	Mental or physical impairment leading to inability to cooperate.
Patient unable to sign consent.	Extreme obesity, with weight exceeding the recommendations of the equipment capacity (usually >159 kg [350 lb]).
Uncontrolled hypertension (systolic ≥ 200 mmHg and/or diastolic ≥ 110 mmHg).	Respiratory distress.
Pregnant or breastfeeding.	

Pharmacological stress test:

The pharmacological stress test has proven to be an excellent alternative to the physical exercise test and can be performed using vasodilator agents (such as Dipyridamole or Adenosine) or Dobutamine. Adenosine is a direct coronary vasodilator and leads to a 3.5 to 4-fold increase in myocardial blood flow and is routinely given as a continuous infusion at a rate of 140 µg/kg/min over 6 minutes. Patients who cannot perform exercise stress for various reasons and those who are on concomitant treatment with medications which blunt the heart rate response (such as beta-blockers and calcium channel blockers) are better suited to Adenosine stress. Dipyridamole is an indirect coronary artery vasodilator that increases the tissue levels of Adenosine by preventing the intracellular reuptake and deamination of Adenosine [48].

It induces hyperemia, which lasts for more than 15 minutes. Although the incidence of side effects is less than with Adenosine, they last for a longer period and additional intervention such as IV

Aminophylline may be required to reverse side effects. The onset and duration of action of dipyridamole are usually prolonged. The peak pharmacological effects occur about 6 to 8 minutes following initiation of the infusion [49].

Effects persist for 15 to 30 minutes, but may last as long as 60 minutes. Half-life of dipyridamole is approximately 12 hours. Prolonged pharmacological activity could occur in the setting of hepatic insufficiency. The heterogeneity in blood flow in dipyridamole-induced ischemia is probably due to the steal phenomenon, where the normal coronary arteries dilate and augment blood flow leaving a reduced pressure for flow of blood across the compromised arteries. It is reported that during pharmacological stress, dipyridamole (0.56 mg/kg dose) increases heart rate by 11± 7 beats/ minute and the mean arterial blood pressure decreases by – 10 ± 3 mmHg[50].

Patients should be without oral intake for at least 6 h prior to the test and caffeine ingestion should be restricted for at least 12 h. Additionally, if the test is being carried out to establish a diagnosis of coronary artery disease, all anti-anginal medications should be withheld. Adverse effects are common with pharmacologic stress testing (50–80% incidence), although these are usually mild and predominantly bothersome, not issues of safety. Death and major cardiac complications are very rare (<1/10,000) in properly selected patients [51].

Indications and contraindications are listed in (table III).

Table (III): Indications and contraindications of pharmacologic stress testing **:**[52]

A. Indications for Pharmacologic stress testing	B. Contraindications for Pharmacologic Stress Imaging
Contraindications to exercise testing:	Hypotension.
Unsteady gait.	Hypersensitivity to the stress agent.
Critical aortic stenosis.	Recent ACS.
Large abdominal aortic aneurysm.	Decompensated heart failure.
Left Bundle Branch Block.	Severe aortic stenosis.
Ventricular Paced Rhythm.	Severe hypertension (vasodilators are acceptable).
Pre-excited pattern.	Uncontrolled atrial fibrillation (vasodilators are acceptable).
Inability to perform adequate exercise:	Asthma or COPD with ongoing wheezing (dobutamine is acceptable).
Orthopedic, neurologic limitations.	Methylxanthine use such as caffeine (dobutamine is acceptable).
Underlying lung disease (i.e. COPD, asthma).	Dipyridamole use (dipyridamole or dobutamine is acceptable).
Medication limiting heart rate response.	High grade AV block (dobutamine is acceptable).
Poor motivation.	
Peripheral vascular disease.	

INTERPRETATION AND REPORTING:

The interpretation of myocardial perfusion SPECT images should be performed in a systematic fashion to include: (1) evaluation of the raw images in cine mode to determine the presence of potential sources of image artifact and the distribution of extracardiac tracer activity; (2) interpretation of images with respect to the location, size, severity, and reversibility of perfusion defects as well as cardiac chamber sizes, and, especially for Tl-201, presence or absence of increased pulmonary uptake; (3) incorporation of the results of quantitative perfusion analysis; (4) consideration of functional data obtained from the gated images; and (5) consideration of clinical factors that may influence the final interpretation of the study. All of these factors contribute to the production of a final clinical report.

Display:

It is strongly recommended that the reading physician use the computer monitor screen rather than hard copy (e.g., paper or film) to interpret the study. A computer monitor is capable of displaying more variations in gray scale or color, making it easier to discern smaller variations in activity. Moreover, it is not possible to properly view moving images (e.g., raw cine data or gated images) on hard copy. A linear gray-scale translation table is generally preferred to color tables since the gray-scale demonstrates more consistent grades of uptake, but this is also dependent on the familiarity of the individual reader with a given translation[53].

Evaluation of the Images for Technical Sources of Error:

1. Patient motion:

The experienced reader should be familiar with the normal appearance of raw planar images and be able to identify motion artifact. In patients who have had a technetium-based perfusion agent with negligible myocardial redistribution (e.g., Tc-99m sestaMIBI or Tc-99m tetrofosmin), consideration should be made for repeating the image acquisition when significant motion is detected. Alternatives, such as planar imaging or prone positioning may also be considered [54].

2. Attenuation and attenuation correction:

The most common being diaphragmatic in men and the breast in women. Breast attenuation artifact is most problematic when the left breast position varies between the rest and stress images (i.e., ‘‘shifting breast attenuation artifact’’). When the apparent perfusion defect caused by breast attenuation artifact is more severe on the stress images than on the resting images, it is difficult to exclude ischemia. Breast attenuation artifact can be confirmed by repeating the acquisition with the left breast repositioned [55].

3. Initial Image Analysis and Interpretation:

The initial interpretation of the perfusion study should be performed without any clinical information other than the patient’s gender, height and weight. Such an approach minimizes the bias in study interpretation. All relevant clinical data should be reviewed after a preliminary impression is formed.

a) Ventricular dilation:

Before segmental analysis of myocardial perfusion, the reader should note whether or not there is LV enlargement at rest or poststress. Dilation of the LV on both the stress and resting studies usually indicates LV systolic dysfunction, although it may be seen in volume overload

states (e.g., severe mitral or aortic regurgitation) with normal ventricular systolic function. An increased stress-to-rest LV cavity ratio, also referred to as transient cavity dilatation (TCD) or transient ischemic dilation (TID), has been described as a marker for high-risk coronary disease [56]. It is actually apparent, and not true, dilatation of the ventricle with stress, and is most likely caused by diffuse subendocardial ischemia and can be seen in other conditions, such as microvascular disease, that causes diffuse subendocardial ischemia even in the absence of epicardial coronary disease. TID is typically described qualitatively but may also be quantified[57].

b) Lung uptake:

The presence of increased lung uptake after thallium perfusion imaging has been described as an indicator of poor prognosis and should therefore be evaluated in all patients when using this perfusion agent. No clear consensus has emerged as to the significance of lung uptake with technetium-based perfusion agents, although increased lung Tc-99m tracer uptake may provide a clue to the presence of resting LV systolic dysfunction in patients who are not candidates for gated SPECT imaging due to severe arrhythmias [58].

c) Right ventricular uptake:

There are no established quantitative criteria for RV uptake, but in general, the intensity of the RV is approximately 50% of peak LV intensity. RV uptake increases in the presence of RV hypertrophy, most typically because of pulmonary hypertension. The intensity of the RV may also appear relatively increased when LV uptake is globally reduced [59].

d) Perfusion defect location:

The perfusion defects should be characterized by their location as they relate to specific myocardial walls—that is, apical, anterior, inferior, and lateral.

e) Perfusion defect severity and extent:

Defect severity is typically expressed qualitatively as mild, moderate, or severe. Mild defects may be identified by a decrease in counts compared to adjacent activity without the appearance of wall thinning, moderate defects demonstrate wall thinning, and severe defects are those that approach background activity. Defect extent may be qualitatively described as small, medium, or large. In semiquantitative terms, small represents less than 10%, medium represents 10-20%, and large represents greater than or equal to 20% of the LV. Alternatively,

defect extent may also be estimated as a fraction such as the ‘‘basal one half’’ or ‘‘apical one-third’’ of a particular wall or as extending from the base to the apex. Defects whose severity and extent do not change between stress and rest images are categorized as ‘‘fixed’’ or ‘‘nonreversible.’’ American Society of Nuclear Cardiology has considered several models for segmentation of the perfusion images and has previously recommended either a 17- or 20-segment model for semiquantitative visual analysis. In order to facilitate consistency of nomenclature with other imaging modalities, the 17-segment model is preferred and the 20-segment model should no longer be used [(60)]. The use of a scoring system provides a reproducible semiquantitative assessment of defect severity and extent. A consistent approach to defect severity and extent are clinically important because both variables contain independent prognostic information. Points are assigned to each segment according to the perceived count density of the segment. In addition to individual scores, it has been recommended that summed scores be calculated. The summed stress scores equals the sum of the stress scores of all the segments and the summed rest score equals the sum of the resting scores (or redistribution scores) of all the segments. The summed difference score equals the difference between the summed stress and the summed resting (redistribution) scores and is a measure of perfusion defect reversibility reflecting inducible ischemia. In particular, the summed stress score has been shown to have significant prognostic power, although the resting perfusion data provide incremental prognostic information as well[(61)].

f) Reversibility:

Reversibility of perfusion defects may be categorized qualitatively as partial or complete, the latter being present when the activity in the defect returns to a level comparable to surrounding normal myocardium. The semiquantitative scoring system may be used to define reversibility as a >2 grade improvement or improvement to a score of 1. Reversibility on a quantitative polar or on 3D displays will depend on the particular software routine in use and the normal reference databases used in the program. Areas of reversibility are typically described by pixels that improve to< 2.5 SDs from the normal reference redistribution or resting database [(62)].

Myocardial nomenclature and segmentations:

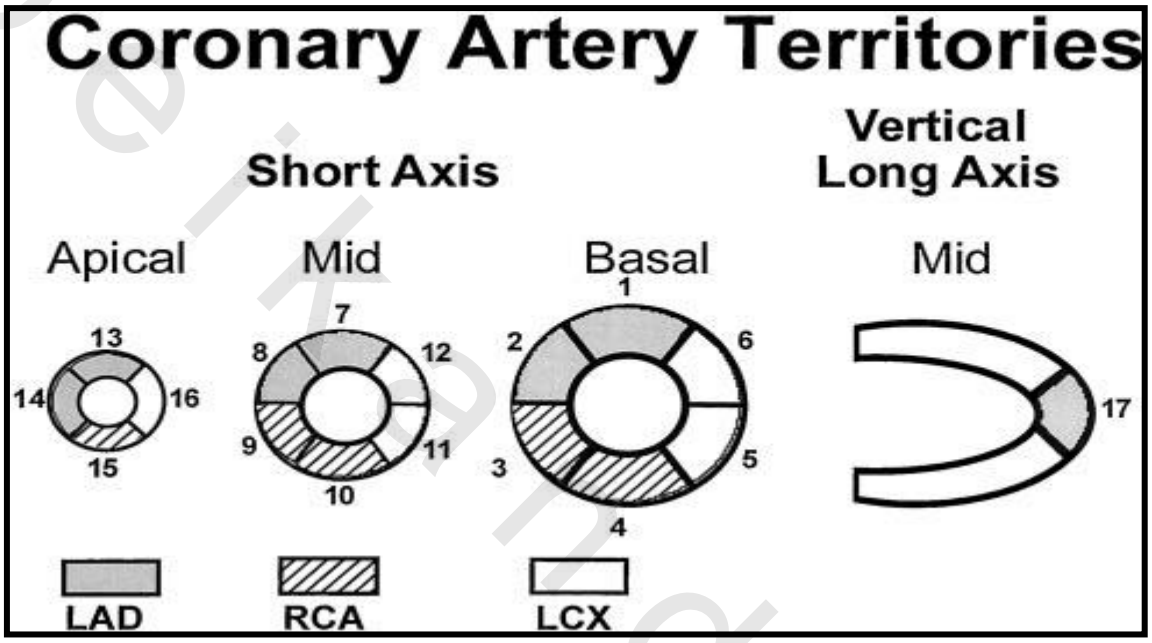

Figure 4: Left ventricular wall segmentation and assignment of vascular territories[63].

The nomenclature of short, vertical long and horizontal long axes has been used for the cardiac planes generated by SPECT, PET, cardiac CT, and CMR. The heart is segmented to 17 segments for assessment of myocardium and ventricular cavity (figure 4). Left ventricle should be divided into equal thirds perpendicular to the long axis of the heart. This will generate 3 circular basal, mid-cavity, and apical short axis slices of the left ventricle. Myocardial segments should be named and localized with reference to both the long axes of the ventricle and the 360° circumferential locations on the short-axis views. The names basal, mid-cavity, and apical identify the location on the long axis of the left ventricle. The circumferential locations in the basal and mid-cavity are anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral. By using this system, for example: segments 1 and 7 identify the locations of the anterior wall at the base and mid-cavity.

Segments 1, 2, 7, 8, 13, 14, and 17 are assigned to the left anterior descending coronary artery distribution. Segments 3, 4, 9, 10, and 15 are assigned to the right coronary artery when it is dominant. Segments 5, 6, 11, 12, and 16 generally are assigned to the left circumflex artery. The greatest variability in myocardial blood supply occurs at the apical cap, segment 17, which can be supplied by any of the 3 arteries [63].

Blood supply of the heart:

The heart receives blood from left coronary arteries (LCA) and right coronary arteries (RCA). (Figure 5)

1. Left coronary artery:

The left coronary artery arises from the left aortic sinus (at an acute angle from the aorta) as a single short main artery (left mainstem). The LCA bifurcates to form the left anterior descending artery (LAD) and left circumflex (LCx). The LAD anastomoses with the posterior descending artery (PDA) a branch of the right coronary artery (RCA). The LAD supplies the interventricular septum (anterior two-thirds), the apex, and the anterior aspects of the right and left ventricle and right and left bundle branches. The LCx has a major branch, the left marginal artery. In around 10–15% of the population, the LCx anastomoses with the RCA to give rise to the PDA. In general, the LCx supplies the posterior aspect of the left atrium and superior portion of the left ventricle [64].

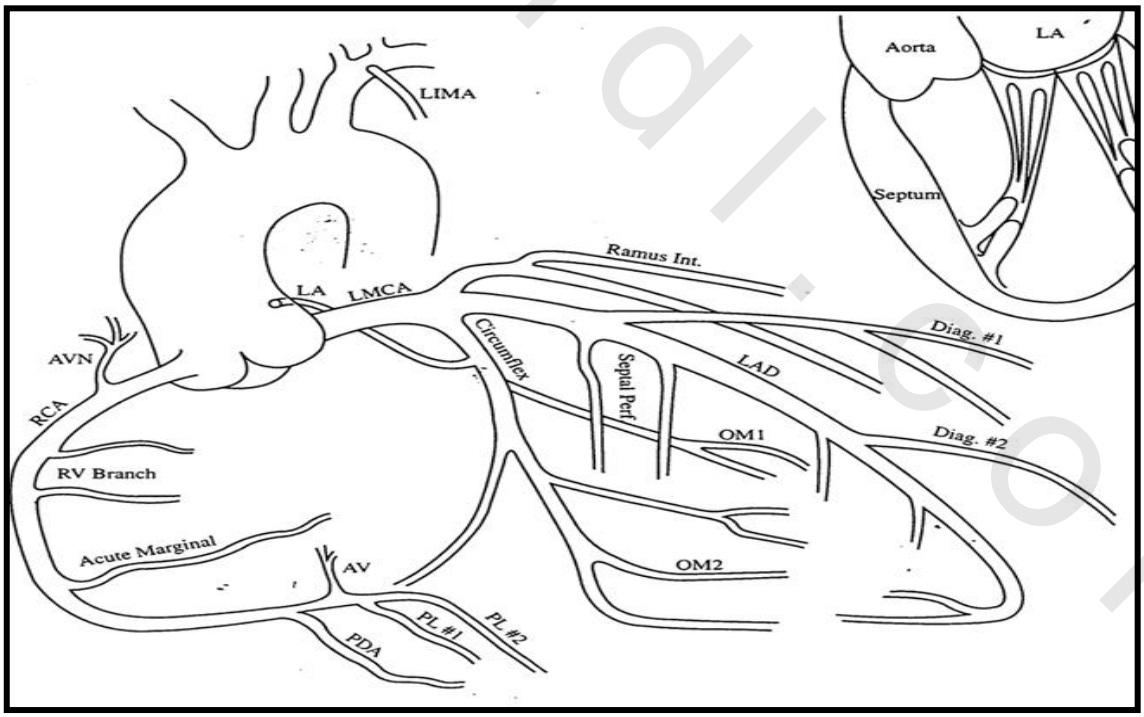

Figure 5: Blood supply of the heart [63].

2. Right coronary artery:

The RCA arises from the right aortic sinus and has major branches such as:

a) PDA (supplying the posterior third of the interventricular septum and AV node).

b) Nodal artery (supplying the right atrium and the SA node).

c) Right marginal artery (supplying a portion of the right ventricle, the inferior left ventricular wall, and the PDA).

In the majority (80–90%) of cases, the RCA supplies the atrioventricular node (AV node) [(65)].

In general, the RCA is dominant in 60–65% of cases because it gives off a PDA branch (balanced coronary circulation). In about 10–15% of cases, the LCx gives rise to the PDA (left predominant circulation) [(66)].

Technetium Tc99m:

Technetium is produced by process called elution. The 99Mo-99mTc generator is the most commonly used radionuclide generator system in nuclear medicine. The generator consists of 99Mo absorbed onto an alumina column. 99Mo decays by beta emission to 99mTc with a half-life of 67 hours. To minimize radiation exposure from the emitted beta particles and gamma radiation, the alumina column is shielded, typically by depleted uranium. The 99mTc can be removed from the column, as sodium pertechnetate (Na99mTc04) by drawing a solution of sodium chloride through the column. This process is known as elution or 'milking' of the generator [(67)].

Technetium Tc99m–labeled myocardial perfusion tracers were introduced in the clinical arena in the 1990s. ^{99m}Tc emits 140 keV of photon energy and has a physical half-life of 6 hours. Despite the excellent myocardial extraction and flow kinetic properties of thallium, its energy spectrum of 80 keV is suboptimal for conventional gamma cameras (ideal photopeak in the 140-keV range). In addition, thallium's long physical half-life (73 hours) limits the amount of thallium that may be administered to stay within acceptable radiation exposure parameters. Thus, ^{99m}Tc-labeled tracers improve on these two limitations of thallium. Although three ^{99m}Tc-labeled tracers (sestaMIBI, teboroxime, and tetrofosmin) have received U.S. Food and Drug Administration (FDA) approval for detection of CAD, only sestaMIBI and tetrofosmin are available for clinical use at present [(68)].

Tc^{99} m to be used as indicator of coronary blood flow, it must be labeled by another compound either sestaMIBI or tetrofosmin that selectively concentrates in the myocardium [(69)].

SestaMIBI is a lipophilic monovalent cation with a trade name of cardiolite. SestaMIBI will not be extracted by non-viable myocardium and in plasma, less than 1% is protein bound. Hyperpolarized state of plasma membrane and mitochondrial potentials increases the uptake and retention of 99mTc-sestamibi. The first pass extraction fraction for 99mTc-sestamibi is approximately 65%, which is lower than that for thallium. Only about 1–2% of the injected dose localizes to the myocardium at rest. However, this lower extraction fraction is overcome by injecting a larger dose, which in turn results in a higher count rate. The uptake in myocardium is proportional to blood flow in the physiologic flow range. However, at higher flow rates there is a plateau in extraction [(70)].

Myocardial clearance of 99mTc-sestamibi is slow and the agent does not redistribute like 201Tl. The main route of excretion is hepatobiliary (approximately 33%) with a half-life of approximately 30 minutes. This high hepatic concentration may result in liver-dominant SPECT images with compromised cardiac resolution; so fatty meal used to speed hepato-biliary clearance of the Tc^{99} m sestaMIBI and, additional fluids will help gastrointestinal motility moves activity away from the heart. However, there can be very intense activity in the colon many hours later, especially in patients with a high splenic flexure, which would also affect myocardial imaging, considering that during exercise, splanchnic blood flow lessens, resulting in less splanchnic uptake than at rest. Therefore, imaging is best done after a brief waiting period to allow for some liver and biliary clearance but before significant accumulation can occur in the transverse colon. Typically, imaging is begun 30 minutes after peak injection and 45 to 60 minutes after rest one. The organs at risk are the gallbladder and kidneys. Although the breast takes up 99mTc-sestamibi, there is only minimal transfer to breast milk and cessation of breast-feeding is not essential [(71)].

Gamma camera:

The standard camera used in nuclear cardiology studies, a gamma camera, captures the gamma ray photons and converts the information into digital data representing the magnitude of uptake and the location of the emission. The photoemissions collide along their flight path with a detector crystal. There, the gamma photons are absorbed and converted

into visible light events (a scintillation event). Emitted gamma rays are selected for capture and quantitation by a collimator attached to the face of the camera-detector system. Most often, parallel hole collimators are used so that only photon emissions coursing perpendicular to the camera head and parallel to the collimation holes are accepted (Figure 6) [72].

This arrangement allows better appropriate localization of the source of the emitted gamma rays. Photomultiplier tubes, the final major component in the gamma camera, sense the light-scintillation events and convert the events into an electrical signal to be further processed. The final result of SPECT imaging is the creation of multiple tomograms, or slices, of the organ of interest, composing a digital display representing radiotracer distribution throughout the organ. With SPECT myocardial perfusion imaging (MPI), the display represents the distribution of perfusion throughout the myocardium [73].

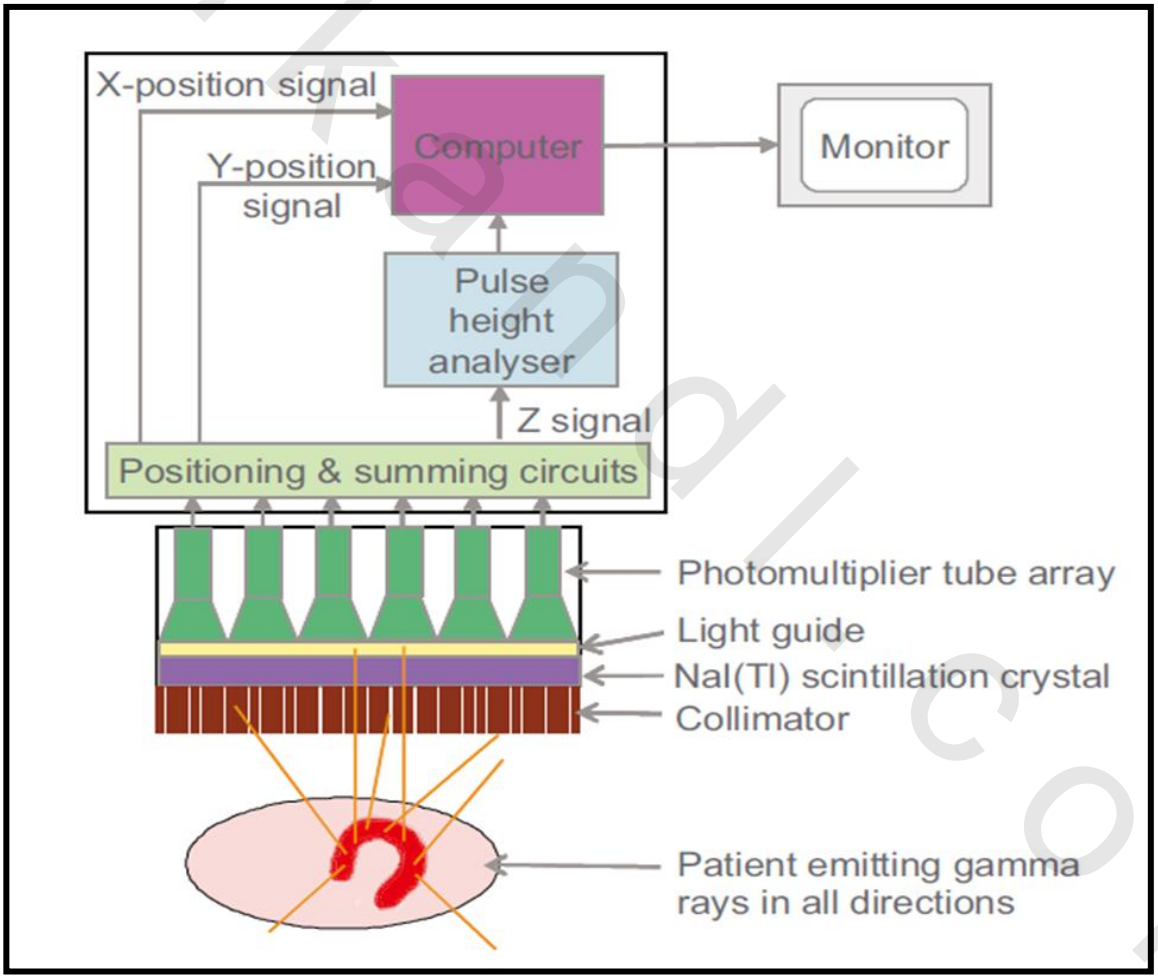

Figure 6: Schematic diagram of Gamma camera [72].

Structure of gamma camera:

The gamma camera consists of a large, relatively thin (9–25 mm) sodium iodide scintillation crystal that is doped with a small amount

(~0.7%) of thallium to form NaI(Tl). Gama rays emitted in all direction and some of these gamma rays pass through the collimator and enter the gamma camera detector where they strike the NaI(Tl) scintillation crystal and are converted to flashes of light . The light photons are then viewed by all of the photomultiplier tubes (PMTs), the amount of light detected by the array of PMTs is transformed into three electronic signals (called X, Y and Z). The X and Y signals represent the location of where the gamma ray hit the crystal. The Z signal represents the gamma ray energy deposited in the crystal. Gamma rays passed through a pulse height analyzer to determine if it is within the range of values expected for the specific radiopharmaceutical used. Gamma rays represented by dots in the monitor of the Gamma camera. Thousands of gamma rays are detected, and so thousands of dots appear on the monitor to eventually create an image [(74)].

Collimators:

Important part of Gamma camera what is called collimator. This important part consists of a lead plate with thousands (30 000 to 60 000) of tiny holes (0.8 to 1.5 mm diameter) through it. The lead walls between the holes are called septa. Each hole accepts gamma rays from only a limited angle, and those gamma rays not travelling in the preferred direction are absorbed by the lead septa and never reach the detector. This means that a large proportion of emitted gamma rays do not contribute to the imaging process [(75)].

Two principal parameters describing collimator performance are resolution and sensitivity. Unfortunately it is not possible to optimize both sensitivity and resolution simultaneously. For example if the hole size of collimator is wide the sensitivity (the proportion of gamma rays incident on the collimator that actually pass through to the detector) increased and the resolution deteriorate, but if the hole length increased the sensitivity is decreased and the resolution improved. So the collimator is manufactured by specific parameters for specific functions. The septal thickness is determined by the energy of the gamma ray to be imaged, and is chosen to prevent gamma rays from crossing from one hole to the next. High resolution collimators with thin (short) septa and small holes are used for 99mTc high resolution cardiac imaging, whereas for 201Tl scans, due to the low energy of the 201Tl gamma rays, a low energy general purpose collimator is more appropriate [(76)].

According to the position of the collimator there are 2 types: parallel collimator and converging collimator. The parallel one is the most widely used collimator. Converging collimators have a field of view

that magnify the object within the field of view but there is also some image distortion due to the fact that different planes of the object are at different distances from the collimator [77].

The spatial resolution of the image is comprised of intrinsic resolution (resolution of detector alone) and the collimator resolution. The intrinsic resolution is determined by the thickness of the scintillation crystal. As crystal thickness increases, the spatial resolution deteriorates but detection efficiency increases. In order to overcome the long time of the test, gamma cameras with multiple detectors are often used. Cameras with two or even three detectors allow two or three angular projections to be acquired simultaneously. This allows the image to be acquired in half or one-third of the time required for a single detector camera [78]