CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

Advancement in the field of Science, Technology, Engineering and Computer Science has contributed not only to the advancement of the respective fields but also influenced the applied fields. Medicine is one such field which has exploited the benefits to the fullest extent in diagnosing the disease at the earliest stage and the treatment of the ailments either by non interventional method or interventional method such as surgical correction.

1.2 NUCLEAR CARDIOLOGY

Nuclear cardiology is one such field of super specialization in non interventional diagnostic tool in cardiology, where it utilises the developments in more than one field such as radiation technology, computers technology, image processing electronics and crystal growth. Another non interventional method used as a diagnostic tool in cardiology is Echo cardiography combined with colour doppler.

These two diagnostic tools helps the specialists to assess the functional aspects of the heart.

In the case of diagnosis using the Radionuclide it is further divided as (1) Thallium 201 scintigraphy (2) First Pass study and (3) the gated blood pool imaging.
1.2.1 Thallium-201 Myocardial Scintigraphy

This has become a clinically important method for detection and evaluation of both acute and chronic coronary artery disease.

Several radionuclides were developed for the non invasive evaluation of the myocardial blood flow. The commonly adopted clinical method was to inject the radioisotopes intravenously.

The radionuclide was proposed as a potassium analog for scanning in 1970 (Kawana et al 1970).

1.2.1.1 Clinical value of thallium 201

The clinical utility of thallium imaging depends to a great extent on its predictive value.

Thallium imaging is much suited for the evaluation of the cardiac status of the patients who have undergone coronary bypass surgery, patients who have had acute infarction and also to monitor the results of coronary artery angioplasties.

In the case of angioplasty patients the suggested clinical protocol is to image the patients prior to angioplasty and repeat the procedure again three or more days after the angioplasty.

Performance of the procedure before three days after the angioplasty may give false positive results, as there appears a delay in the recovery of the myocardium after the angioplasty.

This study has the ability to diagnose the extent of the coronary artery disease accurately in nearly 90% of the diseased blood vessels.
In 1973 Tl-201 with a longer half life was introduced for myocardial scintigraphy and since then it has been applied extensively in the clinical evaluation of patients with both ischemic and non ischemic cardiac disease (Lebowitz et al 1973).

Thallium is a metallic element with biological properties similar to potassium. The ionic radii of the two elements are close to each other and the distribution of thallus (Tl⁺) following the intravenous administration is primarily intracellular. The myocardial kinetics of thallium following intravenous injection can be divided into two successive but overlapping phases, viz., initial distribution and redistribution.

The radioisotope ²⁰¹Tl decays by electron capture to mercury-201 with K-X-rays of 69-83 KeV (93% abundant) and gamma rays of 167 KeV (10% abundant) and 135 KeV (3% abundant).

The radiation dose delivered to the patient per 37MBq (i.e., 1mCi) has been estimated to be 0.34 mSv to the heart, 0.24 mSv to the total body and the kidney receives the highest dose of 1.2 mSv (Alkins et al 1977). The usual amount of radioactive ²⁰¹Tl injected for myocardial imaging is 55.5 - 74 MBq (i.e., 1.5 - 2 mCi).

1.2.2 First Pass Radionuclide Angiography

The computerised techniques for quantitative nuclear medicine have been applied to functional evaluation of the heart in an expanding and accelerated rate. One such method is first pass radionuclide angiography.

The almost universally used radionuclide for this study is ⁹⁹ᵐTc. This radionuclide has several advantages over other isotopes.
i) It is widely available and can be produced in any laboratory by a portable, low cost generator.

ii) Its principle gamma energy is 140 Kev. It is well suited for the scintillation gamma cameras.

iii) It has a short physical half life of 6 hrs.

iv) It can be chemically labelled to other agents to alter its pharmacokinetic properties.

The short, effective half life in the body enables as much as 740 MBq (ie. 20 mCi) of activity to be administered with a total body radiation absorbed dose which is acceptably as low as 0.26 mSv (Kerciakes et al 1976).

The $^{99m}$Tc radio pharmaceutical injected can be imaged during its initial transit through the central circulation. The first pass determination of Left Ventricular Ejection Fraction (LVEF) may be included as part of acute infarct imaging using the bone-scanning agent pyrophosphate. Similarly labeled red blood cells or albumin, is used for equilibrium radionuclide angiography. It can be monitored during their initial bolus transit through the cardiac chambers, thus providing two methods of calculating LVEF but with one injection of radio pharmaceutical.

The success of first-pass method depends to a great extent on the injection technique. The radiopharmaceutical with high concentration of the activity in a small volume is used as a bolus and is followed by a large volume of about 20 ml of saline as flush solution to wash off the veins from radioactivity.

The bolus of activity is followed by the detecting system till the bolus completes one cycle in the blood circulation and the data collected every second is stored as a series of separate frame of image. These images are used later for analysis. This method will take enormous amount of computer hard disk space.
In the case of first pass studies the activity is concentrated in a small volume to give a true bolus. The entire bolus will fall within the Field of View (FOV) of the gamma camera, the count rate will be very high, so care should be taken to ensure that it does not exceed the count rate capability of the gamma camera. Few centres use multi-crystal gamma camera with its superior count rate capability. During acquisition both analog and digital images are acquired. The digital images allow quantitative parameters to be computed.

### 1.2.2.1 Clinical value

Even though the LVEF is more easily measured by the gated blood pool imaging study, the first pass technique is useful either for a rapid measurement of ejection fraction or Right Ventricular Ejection Fraction (RVEF) is necessary.

For example, it has been used to assess right ventricular performance during stress in patients with coronary artery disease (CAD).

This technique has a wide application in congenital heart disease, particularly in the quantitative assessment of the left to right shunting and also in patients with valvular heart diseases.

### 1.2.3 Gated Blood Pool Imaging

The multiple gated blood pool equilibrium scintigraphy has become widely utilized for the clinical assessment of regional and global left ventricular function both at rest and during exercise. This technique can also be used for the Right Ventricular Ejection Fraction (RVEF) and also the segmental wall motion abnormalities.
1.2.3.1 Technical considerations

The performance of the radionuclide ventriculography requires

a) A scintillation camera with a collimated detector to record, the distribution of radio active tracer in the chest.
b) A radio pharmaceutical that remains in the cardiovascular compartment.
c) A gating device synchronized to physiologic functions to time the scintigraphic events with respect to the cardiac cycle.
d) A protocol for imaging which determines the variety of patient positioning to give useful diagnostic information such as the calculation of ejection fraction and the assessment of regional wall motion.
e) A bicycle ergometer with adjustable load to evaluate the ventricular function under stress.
f) A computer to collect, store and process the data.

1.2.3.2 Gamma camera

The imaging system commonly used for the gated blood pool study is an Anger type of gamma camera.

The best images are obtained from the standard field of view stationary or mobile cameras which have 37 or more photomultiplier tubes and 1/4 inch thick and 28 inch diameter thallium activated sodium iodide crystal.

The use of 1/4 inch crystal gamma camera gives better spatial resolution, which is the most important feature for the assessment of the regional wall motion, compared to 1/2 inch thick crystal gamma camera with a small loss in count sensitivity of 15% (Chapman et al 1979).
The other features like short dead time, pulse pile up rejection and buffered derandomizer circuits have increased the higher count rate capability of the new Anger type gamma camera system thus reducing acquisition times.

An additional method to get higher count rate from the cardiac compartments is the use of cardiac shielding. This device consists of a lead mask placed over the collimator to stop gamma rays which are emitted from non cardiac regions before they reach the scintillation crystal, thus allowing a higher percentage of gamma rays from heart to be detected and counted per unit time.

The choice of the collimator used for gated blood pool study is parallel-hole collimator, because it is non distorting and is inherently uniform in detecting counts from the field of view. The type of parallel-hole collimator depends upon the study to be performed, for example, when rapid imaging is required as in the case of exercise MUGA, a very high sensitive large hole collimator is used, when brief imaging period is not required, a small hole, high resolution and low sensitive parallel hole collimator will be the most suitable option.

For blood pool scintigraphy a special type of parallel hole collimator the slant-hole collimator, can also be used. In this type of collimator, the array of parallel holes are oriented 15-30 degrees away from the perpendicular axis of the crystal. While this collimator is in place, the detector may be placed flatly against the chest of the patient and the head of the camera is tilted and oriented in the caudal direction. The 45° Left Anterior Oblique (LAO) view results in better separation of the atria from the ventricle without the loss in count sensitivity that would be associated with caudal angulation of the entire detector.
1.2.3.3 Radio pharmaceuticals

The most commonly used radio pharmaceuticals for the multiple gated equilibrium blood pool scintigraphy are $^{99m}$Tc human serum albumin, $^{99m}$Tc RBC labelled, *in vitro* and *in vivo* labelled Sn-PYP+ $^{99m}$Tc-Pertechnetate.

The radionuclide employed is $^{99m}$Tc with a physical half life of 6 hours and which decays by isomeric transition to technetium 99, emitting gamma rays of 140 KeV. The radiopharmaceutical that first received the widespread use for gated equilibrium blood pool imaging was $^{99m}$Tc tagged to human serum albumin (Dworkin et al 1971).

The radiation dose to patient resulting from the administration of the usual dose 370-1110 MBq (i.e., 10-30 mCi) for an adult patient will be very small compared to diagnostic contrast ventriculography, which is associated with exposures of 4 to 100 cGy/minute to the skin, and an exit dose of 0.3 to 12 cGy per minute (Penfil et al 1968).

When technetium 99m albumin has been used, tracer loss to extravascular compartments has been found to be significant, 40 percent loss at the end of the first hour after injection (Hegge et al 1978) leading to a lower count rate per MBq injected and poorer target to background count ratio than is achieved by more ideal intravascular agents, this limitation is very important for long duration studies.

In the absence of bleeding the RBCs' remain intravascular. So the RBC labelled cells are ideal for blood pool imaging. The absorbed radiation dose to the patient is almost similar to $^{99m}$Tc-albumin. The *in vitro* method employs a tin (Sn) containing kit to which 8 cc of patients blood is added followed by incubation at room temperature for 15 minutes.
This method normally has 95% labelling efficiency and permits adequate labelling prior to injection.

The *in vivo* method is the most commonly used method in routine blood pool scintigraphy for reasons of simple procedure, convenience and availability.

This simple technique involves the injection of non radioactive stannous pyrophosphate or DTPA (Diethylene Triamine Penta Acetic acid). These are commercially available. After the injection 30 minutes *in vivo* incubation is allowed and this results in the formation of red blood cell complex. Then Technetium-99m in the pertechnetate form is injected intravenously. *In vivo* combination of the technetium-99m and the stannous red blood cell complex occurs now.

Though this *in vivo* method is quite reliable, at times results in less than ideal tagging. Unlike the *in vitro* method, the labelling adequacy of *in vivo* method can not be determined prior to injection.

*In vitro* labelling of RBC's appears to be superior to *in vivo* labelling. The former has higher intravascular retention of radioactivity i.e., more than 95% for *in vitro* and more than 75% for *in vivo* (Hegge et al 1978).

However, both the red cell tracers are excellent blood pool radiopharmaceuticals.

Another radioactive tracer considered for blood pool scintigraphy was Indium 113m. Unfortunately this radionuclide has a gamma emission with very high energy of 393 KeV to be used with low energy, high resolution collimators.
The loss in resolution that occurs from the use of high energy collimators makes this radiopharmaceutical less suitable for clinical use.

1.2.3.4 Physiologic synchronizer

In the Gated blood pool imaging, the scintigraphic data from continuous successive cardiac cycles are added to form a statistically significant and reliable image.

To derive information regarding ventricular function, the data must be divided temporally to correspond to the different parts of the cardiac cycle.

This temporal division of the data is achieved through the use of a physiologic synchronizer or gating device. The patients ECG is usually employed as a trigger for the gating device.

There can be either dual gating or multiple gating. In the case of dual gating only two portions of the cardiac cycle alone is recorded. Where as in the case of multiple gating the gating is more than two it may be 16, 24 or 32 depending upon our requirement.

In our case the multiple gating of 24 was used in almost all the cases except in the case of stress MUGA (Multigated acquisition) study. The simplest method is to record images of the entire cardiac cycle, with this method the cardiac cycle is divided into sufficient number of segments to make it likely that the end diastole will be accurately represented in one segment of the recorded data.

The optimal frame rate results from a tradeoff between temporal resolution and adequate counts per frame. In a given imaging time the
higher the number of frames lower will be the counts per frame and lower the frame rate, higher will be the counts per image.

So in order to obtain a statistically significant, reliable and good quality high resolution image the whole process has to continue for 200-600 cardiac cycle to complete so that the total counts per frame may reach 1-2 lakh counts.

The multigated blood pool scintigraphy can immediately display the images after acquisition in a continuous cine loop, in a movie format without any flicker. This will facilitate to diagnose the segmental wall motion abnormalities.

This can also be used to draw activity against time curves from multiple gated data, providing further information regarding the systolic and diastolic phases of the cardiac cycle as normalised ejection and filling velocities.

1.2.3.5 The clinical utility of this study

The most common clinical indication for this study is to assess ventricular functional parameters, specifically ejection fraction.

The gated blood pool study is very sensitive for detecting abnormality in ventricular contractability as well as providing reproducible, useful and accurate parameters of ventricular function. On the other hand the study is not indicative of the cause of the abnormality if any, for example the ventricular dysfunction may be due to inadequate blood flow, lack of muscle mass or abnormalities in the myocardium.

In the field of oncology, the use of cardiotoxic drugs has brought the performance of the gated blood pool study to a clinical forefront.
Chemotherapy with cardiotoxic drugs such as doxorubicin, often leads to congestive heart failure.

It has been reported that with resting ejection fraction less than 45% incidence of chronic cardio toxicity rapidly escalates. The presence of a normal resting ejection fraction but an abnormal exercise value reflects probably more advanced cardio toxicity.

The clinical indication for looking at right ventricular function are patients with primary hypertension and right sided infarction.

The calculation of right ventricular stroke volume may also be helpful in assessing whether shunting or valvular regurgitation is present or not as stroke volumes for both ventricles in a normal heart are similar.

1.3 DOPPLER ECHO CARDIOGRAPHY

The Left Ventricular functional assessment was also done using the Doppler scan and "B" mode Echo cardiography.

The ejection fraction and also the regional wall motion abnormality was seen for the patients using the "B" mode ultrasound machine combined with doppler.

1.3.1 "B" Mode Ultrasound

Though the other modes of ultrasound imaging techniques gives useful information but they are only in limited areas.

The "B" mode ultrasound plays a very large role as a diagnostic tool.
The "B" mode produces a picture of a slice of tissue. The sound beam acts like a surgical blade. It images sagittal section when it cuts through the length of the body and images a transverse or cross section when drawn from side to side.

1.3.2 Doppler Technique

The Doppler effect is a change in the perceived frequency of sound emitted by a moving source. The effect was first observed and described by Christian Johanan Doppler in 1843. It is the frequency shift caused by a moving source, observed by a static receiver.

The magnitude of the Doppler shift is given in the following formulas.

\[
\gamma_o = \frac{v}{v+s} \gamma_c \quad (1.1)
\]

In the direction of the movement of sound source

\[
\gamma_o = \frac{v}{v-s} \gamma_c \quad (1.2)
\]

In the opposite direction of source movement.

where

- \( \gamma_c \) = frequency of sound source
- \( \gamma_o \) = observed frequency of sound
- \( v \) = velocity of sound-340 m/s
- \( s \) = velocity of sound source

The wave length change is caused by the source motion changing the spacing between crests.
In contrast to pulsed sonography in which the intensity of returning echoes is greatest when the ultrasound beam is perpendicular to a reflecting surface, the Doppler shift is greatest when the beam strikes a vessel at a small angle.

The smaller the angle between the sound beam and the flow direction \( \theta \), the greater the vector of motion toward the transducer and greater the Doppler shift.

\[
\frac{2\gamma s}{v} \cos \theta \quad \text{(1.3)}
\]

\( \Delta \gamma \) = Frequency change (Doppler shift Hz)
\( \gamma \) = Frequency of initial beam
\( s \) = Velocity of blood (m/s)
\( v \) = Velocity of sound (1540 m/s)
\( \theta \) = Angle between sound beam and direction of blood flow

To control the location and volume of a pulsed Doppler beam, it is useful and necessary for the operator to know where the sensitive volume is located within the patient. This is done by coupling the Doppler ultrasound system with real time ultrasound imaging.

Different transducers operating at various frequencies are used to perform the imaging and Doppler parts of the examination (5 MHz for imaging and 3 MHz for Doppler).

Before the imaging and Doppler study is done, assessment of the resolution of the imaging system is to be done. So the system was subjected to a series of tests. A quality assurance phantom was fabricated exclusively for this purpose and all the tests were carried out.