A Study on Regulatory Requirement for Development of Cardiac Pacemaker In USA

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Abstract: *Cardiac pacing is an emerging lifesaving procedure that is being widely used in the recent times. Therefore, it is considered vital for the healthcare professionals to be aware of patients' knowledge and experience after the cardiac device implantation and also the impact these implanted devices have on their day-to-day life. This study was conducted with an aim to assess the knowledge and attitude of patients regarding permanent pacemakers (PMs) and their quality of life (QOL) after the permanent PM implantation. A descriptive cross-sectional study design was used in this study. A total of seventy patients were chosen by total enumerative sampling technique among those patients attending the cardiology outpatient department, PM clinic and selected cardiology wards of a tertiary care centre in South India. A significant association between attitude and age was found. Conscious effort must be taken to help patients cope better and experience good QOL through systematic teaching after the PM implantation. This will help patients to function maximally and live life to their best capacities in the family and society.*

Key Words: Attitude, knowledge, permanent pacemaker, quality

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1. INTRODUCTION OF CARDIAC PACEMAKER[1-4]

The true beginning of the concept of a pacemaker began over 200 years ago. In the late 1700s, Luigi Galvani discovered that he could cause contraction of a frog heart simply by passing an electrical current through the heart. This concept was further realized nearly 100 years later with the first successful resuscitation of a child by Gilliam de Boulogne utilizing electricity. He was able to accomplish this by introducing an electrical current to the patient's chest with a return electrode on the leg after a drowning. After this feat, many successful resuscitations were reported, leading to the term "artificial cardiac pacemaker" by Dr. Hyman in 1932.

Pacemakers are adjustable artificial electrical pulse generators, frequently emitting a pulse with a duration between 0.5 and 25 milliseconds with an output of 0.1 to 15 volts, at a frequency up to 300 times per minute. The cardiologist or pacemaker technologist will be able to interrogate and control the pacing rate, the pulse width, and the voltage, whether the device is temporary or permanent. Pacemakers are typically categorized as external or internal. The external variety is almost always placed for temporary stabilization of the patient or to facilitate some type of surgical procedure and the implantable type is usually permanent and often, significantly more complex than the temporary, external variety.

Pacemakers are one type of cardiac implantable electronic devices (known as CIED). The first implantable ICD was developed in 1980, and since that time, it has become more difficult to differentiate between pacemakers and ICDs. This is because every ICD currently implanted has an anti-bradycardia pacing function. It is critical for the patient and any health care provider to understand which device has been implanted to prevent unnecessary ICD therapy. This is most likely to occur with any electromagnetic interference (EMI) and could lead to activation of the device. Most types of CIED use several insulated lead wires with non-insulated tips that are implanted in the heart, either by percutaneous vein insertion or directly by a cardiac surgeon. Cardiac pacemakers are made up of two parts: the pulse generator and the leads or electrodes. The North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) jointly developed a generic pacemaker code, utilized worldwide, that would allow provider and manufacturers to describe the characteristics of the device, and this was last updated in 2002 and is shown below in the Pacemaker Table. The first letter in the code indicated which chamber is paced; the second letter indicates which chamber is being sensed by the device; the third letter indicates if there is a response to sensing; the fourth position indicates whether the device will modulate or change the programmed rate independent of the patient's cardiac activity, the fifth and last letter of the

code indicates additional multisite pacing. The last two letters of the code (in the fourth and fifth position) are rarely used in typical nomenclature. The simplest settings are AAI and VVI. The AAI mode paces and senses in the atrium and each sensed event triggers the generator to fire

within the P wave and the VVI mode paces and senses the ventricle and is suppressed by a sensed ventricular event.

2. REGULATORY FRAMEWORK IN USA

2.1. Applicable Regulation and Guideline[5]

There are two important aspects of long-term care of patients with implantable pacemakers. Clinical follow-up involves complete evaluation of the patient as an individual and is generally the responsibility of the referring physician. Technical follow-up, concerned with pacemaker function and detection of impending pacemaker failure, should be the responsibility of a physician with extensive pacemaker experience. Follow-up surveillance should include:

- A program for pacemaker replacement and a system for its implementation.
- telephone number of the responsible physician. Complete instructions for every patient, preferably written. They should include information about suitable physical and social activities, the frequency and nature of postoperative visits, and a procedure for obtaining medical care in emergency situations. The patient should be given an identification card to carry with him at all times; it should show, as a minimum, the date of implantation and the type of pulse generator and electrode used, and the name, address and
- Regularly scheduled follow-up appointments. The frequency with which a patient receives follow-up examinations will depend upon the type of surveillance system utilized, the complication rate and anticipated longevity of the specific pacemaker used, the age and medical condition of the patient and other variable social and geographic factors. Optimally patients should be seen within one month after discharge from the hospital to detect early problems, at least three times during the first year and approximately every two months thereafter until one approach the anticipated end-of-life of the pacemaker. With standard output units, this will be 24 months and with low output pacemakers, 36 months. Approximately six months before anticipated end of-life, the patient should begin to receive closer surveillance either with monthly visits, weekly trans telephone monitoring, or a suitable combination of both.
- Record of pacemaker function. The important parameters that have been selected for measurement of pacemaker function should be recorded in an easily retrievable form so that all individuals responsible for follow-up have ready access to the information.

2.2. Regulation that Strikes and right Balance5

A variety of reform options are available to policy makers to strengthen and streamline FDA's approval process and improve oversight and safety of implantable devices. As previously discussed, without endorsing or ranking them, these options include the following:

- Strengthen the premarket approval process for the riskiest implantable devices.
- Strengthen the market clearance process for devices of moderate risk through increased use of the de novo approach.
- Eliminate "grandfathered" market clearance for implantable devices and require testing of devices that were in use prior to 1976.
- Prohibit recalled devices from serving as predicate devices—that is, older devices that have been recalled should not serve as the basis for clearance of newer implantable devices.
- Impose limits on the time that a device can serve as a predicate device.
- Strengthen post market oversight and reporting for implantable devices through the use of more post market surveillance studies, innovative monitoring techniques, and additional funding for these activities.
- Make better use of implantable device patient registries.
- Expand use of unique device identifiers.
- Improve communication with stakeholders.
- Strengthen quality controls by giving FDA authority to conduct premarket inspection of all facilities that make implantable devices.
- Strengthen FDA enforcement activities through improved targeting of recalls and other actions.

Implantable devices can and do save lives. They improve the quality of life for millions of Americans. Sometimes, they fail. When this happens, people can sustain serious injury or death. Careful regulation and oversight are essential to ensure the safety and effectiveness of these devices both before and after they reach the market. Regulatory oversight needs to safeguard patients while still encouraging innovation that makes implants safer, more effective, and more affordable.

3. STATUS OF CARDIAC PACEMAKER

3.1. Status of Nomenclature for Implantable Cardiac Pacemakers6

When there was only one type of pacemaker, no matter what it was called, everyone knew it was a device that discharged at a fixed rate. To obviate any such confusion in this review, we have designed the following nomenclature code to identify the mode of operation of the pulse generator.

Table 1: Three letter Identification Code

1st Letter	2nd letter	3rd letter
Chamber Paced	Chamber Sensed	Mode of Response

V – VENTRICLE	A - ATRIUM
I– INHIBITED	T - TRIGGERED
D - DOUBLE CHAMBER	O - NOT APPLICABLE

First letter: The paced chamber is identified by V for ventricle, A for atrium or D for double both atrium and ventricle.

Second letter: The sensed chamber, if either, is again V for ventricle, A for atrium.

Third letter: The mode of response, if any, is either:

I for inhibited, a pacemaker whose output is blocked by a sensed signal, or

T for triggered a unit whose output is discharged by a sensed signal.

The letter "O" indicates that a specific comment is not applicable.

3.2. Electrodes, Leads and Connectors[6]

By definition, the electrode is the uninsulated portion of a lead, anode or cathode, in direct electrical contact with the body. In unipolar electrode systems only one electrode, the cathode, is in the heart. The other, an "indifferent" electrode remote from the heart, is a large metal plate often the external capsule of the pulse generator. In a bipolar electrode system both electrodes, cathode and anode, lie against or near responsive myocardial tissue. The electrode may take the form of a hemisphere, cylindrical ring, coil, or a screw-in wire.

The most popular electrode materials are platinum iridium and a cobalt-nickel alloy, chosen because of their resistance to corrosion, satisfactory electrical conductivity, compatibility with body tissues, and limited polarization effects. New electrode materials should be compared to these as standards.

The electrode is in continuity with the metallic lead wire from the pulse generator. Sometimes it is merely the bare end of the wire; in most cases, however, it is a separate metallic element joined to the lead wire. This junction must be strong, permanent, and of a similar metal so that corrosion will not occur at the connection. The most common lead wire configuration is the helical coil in which no one point will be subjected to excessive flexion and thus to ultimate fracture. Wires are typically composed of steel, cobalt-nickel alloys or platinum-iridium, with the last somewhat less resistant to flexion fatigue. Despite the sophisticated design, wire fractures continue to occur at a rate of 1% to 2% a year. With the development of long-term power sources efforts will have to be made to develop still better leads. Manufacturers should provide information regarding the electrical resistance of the lead system, its dimensions, materials, electrode surface area, and anticipated threshold of stimulation.

Unipolar electrodes are smaller in diameter than bipolar, have superior R wave sensing, are easier to repair, and may necessitate less surgery during pulse generator replacement. Bipolar electrodes, on the other hand, are less sensitive to interfering signals and in some cases if one lead fractures, may be converted to a unipolar system. Both types are used widely and it is impossible at this time to recommend one over the other.

When pacemakers were first developed, one of the principal considerations was that electrodes should be large enough to prevent corrosion by high current density. It soon became evident that there was unequally strong argument for the use of small electrodes. The threshold of stimulation of the heart is directly related to the effective electrode size; the smaller the electrode surface area the lower the stimulation threshold. Lower stimulation thresholds require less pulse generator output and less current drain from the battery, so battery life can be prolonged by smaller electrodes. Earlier fears that the small electrode system would corrode have not been realized because of the use of reduced current output pulse generators, and because appropriate materials have been found with low corrosion effects. Most manufacturers now provide pacemakers with small area electrodes, and these are to be recommended. Although the electrodes could be made smaller still, it remains to be demonstrated that further gains can be made in increasing the life of conventional batteries. The fear that small electrodes would be associated with a high incidence of perforation has not been borne out by practical experience.

Table 2: Suggested Nomenclature code for Implantable Cardiac Pacemakers

Chamber paced	Chamber sensed	Mode of response	Generic description	Previously used designation
V	O	O	Ventricular pacing; no sensing function	Asynchronous; fixed rate; set rate
A	O	O	Atrial pacing; no sensing function	Atrial fixed rate; atrial asynchronous
D	O	O	Atrioventricular pacing; no sensing function	AV sequential fixed rate
V	V	I	Ventricular pacing and sensing, inhibited mode	Ventricular inhibited; R inhibited ; R blocking ; R suppressed; non-competitive inhibited
V	V	T	Ventricular pacing and sensing; triggered mode	Ventricular triggered; R triggered; R wave stimulated; non-competitive triggered

A	A	I	Atrial pacing and sensing; inhibited mode	Atrial inhibited; P inhibited; P blocking
A	A	T	Atrial pacing and sensing; triggered mode	Atrial triggered; P triggered; P stimulated; P synchronous
V	A	T	Ventricular pacing: atrial sensing, triggered mode	Atrial Synchronous, atrial synchronized, AV synchronous
D	V	I	Atrioventricular pacing, ventricular sensing, inhibited mode	Bifocal sequential demand, AV sequential

The lead system is attached to the pulse generator by a connector or "plug-in." Connection and disconnection are made by physical compression or by various types of screw arrangements and all connectors currently available are physically and electrically secure when properly used. Because corrosion at the connector can occur if dissimilar metals come in contact with each other, materials of the connecting elements should be identical. Manufacturers have not agreed upon a universal connector system but when one pacemaker model is exchanged for another, they will provide adapter kits to accommodate the pulse generator of one model to the lead wire of another; there should also be a description of how to convert a bipolar to a unipolar system.

Problems with both connection and disconnection have occurred. In connecting the pulse generator and the lead wire, lack of adequate proof of a secure contact has led to faulty connection and later disruption of the elements. Freezing of the connection by metallic corrosion, mechanical jamming, and silicone cement at times have made disconnection difficult or impossible. Further work in design of connectors is necessary. The connector should provide positive indication of proper contact, the metallic elements should be protected from tissue fluids, and disconnection should be accomplished by a simple manoeuvre that will not require destruction of any of the components. Although a universal connector for all pacemakers would be a highly desirable feature, this cannot be recommended strongly at this time because it would be restrictive in the development of new designs and devices.

3.3. Pulse Generator[6, 7]

Pulse generators are 100 to 200 gm. discoid or rectangular packages with rounded edges. Weight and size are largely dependent on the power source, which usually consists of a battery of four or five individual mercury zinc cells. The battery and the electronic components are usually potted in epoxy resin which provides protection against component movement and, to some extent, against body fluids. The outer surface of the epoxy pot may be the surface of the pulse generator. Alternately the entire unit may be covered with silicone rubber or by a titanium or stainless steel case. The metallic coverings are designed to provide protection against electromagnetic interference (EMI) and, if hermetically sealed, additional protection against the body environment. Although it has always seemed desirable to encase the pulse generator or at least its circuitry in a hermetically sealed case, this has only recently become practical. All currently available pulse generators are well accepted by the body, and component materials, including the anode of the pacemaker system, are no allergenic, non-toxic, and non-carcinogenic. The ideal implant would be a flat package, with rounded smooth edges, as small as possible and with a specific gravity the same as body tissues.

3.4. Pacemaker Output[6]

At first the electrical output of the pacemaker was established empirically. The upper limit was determined in part by pacemaker size which, in turn, was related to the number of cells in the batteries. The lower limit of output was not known. The moder pulse generator typically contains four or five mercury zinc cells in series or series-parallel configuration. In an attempt to increase longevity and reduce size, the standard pulse generator output has been reduced to a level somewhat closer to the excitation threshold of the heart, leaving acceptable margins for threshold rise after the first few weeks of implantation and for the diminishing voltage toward the end of battery life. The stimulating rate also is voltage dependent. Thus, as the battery wears out and voltage drops, the output of the pacemaker is still sufficient to stimulate the heart, but its rate gradually decreases. A sudden rate change of several beats per minute may be a signal for replacement.

The output pulse varies in configuration and duration from model to model, but in general it is a rectangular "monophasic" waveform 0.5 to 1.7 ms. in duration.

The rate of implantable pacemakers is set by the manufacturer at approximately 70 beats per minute. Some pacemakers have rate adjustment controls. One such control is activated by turning a potentiometer in the pacemaker with a special percutaneous needle. Another delivers bursts of magnetic impulses over the pacemaker which activate an internal decoder that adjusts the rate, or the output, or both, to one of a number of predetermined settings.

Most pulse generators consist of a stimulating circuit and a sensing circuit, both of which draw current from the battery. In the presence of complete heart block, an asynchronous pulse generator (VOO) with only a stimulating circuit may be used. As circuit efficiency of the non-competitive triggered or inhibitory (VVT or VVI) pulse generators increases, the need for an asynchronous (VOO) unit decreases.

With available equipment pulse generator life can be prolonged by the use of:

- Small surface area electrodes
- Variable output (voltage, current and pulse duration) pulse generators, adjustable to the level required to pace the heart.
- Asynchronous (VOO) pulse generators where suitable
- Reduced output pulse generators for replacement of old units

- Replacement of pulse generators just before exhaustion rather than at an elective predetermined interval.

4. NONCLINICAL TESTING[8]

The following series is intended to identify issues that need to be addressed to qualify a "new" pacemaker lead and to identify some of the non-clinical tests which may be used to support a pacemaker lead submission. Sponsors should examine this listing to determine testing appropriate for their device. Since new lead designs may experience failure modes not previously seen, this guidance document may not reflect the complete battery of non-clinical testing necessary to qualify all pacing leads/designs. It's the responsibility of the lead manufacturer to define a comprehensive testing methodology for a particular lead design.

4.1. Biocompatibility

Biocompatibility evaluation depends, in part, on the full characterization of all sterilized device materials in contact with tissue and/or body fluids. In order to accurately identify these materials, the material specifications from the manufacturer, qualitative and quantitative information concerning all constituent materials used in the manufacturing of the lead should be provided. All protocols, test results and identification of control materials should be provided in order that an independent evaluation of the study conclusions can be made. Protocols do not need to be submitted if standard methods are utilized (e.g., USP methods) and complete references for the methods are provided.

Biocompatibility testing may not be necessary if a material has a long history of use in currently marketed pacemaker leads. If there is sufficient knowledge about the biocompatibility/toxicity of every constituent of the lead, then it need not be subjected to further biocompatibility tests. It is incumbent upon the device submitter to provide sufficient evidence to establish that further biocompatibility testing is not necessary. A sponsor may submit information and data available in publications or from other legitimate sources which show that the material is non-toxic in tests identical to or equivalent to the biological tests listed below. Any changes in formulation, manufacturing or processing between the tested and submitted products which might affect biocompatibility should be identified.

The effects of sterilization on device materials and potential leachable, as well as toxic by-products resulting from sterilization should be considered when conducting biocompatibility tests. Therefore, testing should be conducted on the sterilized final product and any leachable material from the sterilized final product. The exact chemical analysis of device extracts may be omitted if the extracts are subject to toxicity testing. But, as stated above, the qualitative and quantitative description of all constituent materials in the device before extraction should be provided and the material specifications for the device should be comprehensive.

4.2. Animal Studies

The purpose of animal studies is to assess the structural integrity, biostability, electrical performance, biocompatibility, handling characteristics and/or mechanical performance of the fully assembled lead. Animal studies should be designed to closely approximate the intended use of the device in humans. Electrical data should consist of measurement of the following parameters:

- R and P wave amplitudes at implant and at appropriate intervals following implant
- Voltage stimulation threshold at a 0.5 ms pulse width at implant and at appropriate intervals following implant.
- Strength duration (pulse width versus stimulation threshold)
- Pacing impedance at implant and at appropriate intervals following implant.

4.3. Bench Testing

Electrical and mechanical tests should be conducted on components, subassemblies and/or finished leads, as appropriate. All tests should be performed on leads fabricated by representative manufacturing processes and subjected to the final validated sterilization procedures intended for the device. If test samples are subjected to either no sterilization or other sterilization procedures, the rationale for the procedure used should be supplied.

An adequate number of samples should be tested. If sample devices of different lead models are tested, it should be clearly indicated which models were used for each test.

Testing of leads or subassemblies should be performed after sterilization. Testing should include, but not necessarily be limited to the following, as appropriate:

1. Verify the electrical continuity of each conduction path by measuring the DC resistance.
2. Measure leakage current during voltage application (before drying, after soaking).
3. Determine the strength of each bond, joint, etc, in the lead (lower 95 percent confidence bound) as well as the composite lead strength. Leads should be subjected to a tensile test which simulates the stress it may experience during the implant procedure as well as after implant. Before pull testing, the lead should be soaked in saline for 10 days to simulate any effects of body fluids on the lead body.
4. For leads that are hermetically sealed at the distal end, verify that the lead is leak-proof when immersed in isotonic saline at 37°C under physiological pressure for a minimum period of ten days.
5. Document the corrosion resistance of all conductors and electrode materials in the condition of the finished lead. Address current pulsing when appropriate.
6. Evaluate the performance of the sty let intended to be used during lead placement. Measure the sty let insertion and removal forces.
7. Fatigue resistance of the conductor(s) should be verified. Intact leads should be used for this testing. Loading conditions that are utilized should be able to be extrapolated to worst-case physiological conditions, for example, stresses and ranges of motions etc. Different areas of the lead are subjected to different stresses; this

factor should be taken into consideration in the design of an appropriate test protocol. Test methods designed to accelerate fatigue of conductors should be shown to be able to produce characteristic fracture morphologies that may have been documented previously in vivo.

8. Connectors intended to be used for joining pulse generators and leads should withstand the mechanical forces that might occur after implantation. Generally, most lead connectors are designed to comply with ISO 5841-3 (IS-1). This standard outlines the appropriate testing for lead connectors. If the connector is labelled as "IS-1" compatible, it should meet all ISO 5841-3 testing and dimensional requirements.

9. Evaluate the performance of the anchoring sleeve packaged with the lead. Testing should assure that the lead will be held securely in place and not damage the lead body when the anchoring sleeve is sutured according to the Instructions for Use.

10. Measure the pressure exerted by lead tip and express in units of pressure.

5. CLINICAL TESTING8

If the design of the lead is novel enough or new indications/claims are being sought for the lead, a clinical trial may be needed. Examples where clinical data may be appropriate include:

- Incorporation of an electrode that has not been approved for use on another lead body.
- Changes to a marketed lead which might alter the handling characteristics.
- Change in indication from atrial to ventricular pacing.

The success of a clinical trial is based on the overall coordination of three steps: the design of the study; the conduct of the study; and the analysis of the results. Each step of the initial overall study plan should be executed and carefully considered by the sponsor. The clinical study should be ultimately capable of demonstrating the effectiveness and safety of the device in terms of:

- Prescribed, recommended, suggested and other conditions of use in the labelling or advertising.
- Probable benefit to health weighed against any probable injury or illness.
- Reliability of the device (see 21 CFR 860.7(b))
- Intended patient population.

5.1. Clinical Study Design

A detailed protocol for a clinical trial should include:

1. A well-defined, clear question (hypothesis) or set of questions that are to be answered about the lead by the clinical study.

2. A statement of the study type, i.e., randomized, case control, concurrent control etc. In all cases, the data intended to be used as a control should be identified and comparability discussed with respect to critical study variables including indications, outcome variables, definitions, baseline characteristics, inclusion/exclusion criteria.

3. A sample size of all study groups calculated to demonstrate that a sufficient number of patients will be enrolled to adequately address the study hypotheses. Sample size is primarily a function of the pre-determined level of significance and the power of the study to detect a treatment effect of a predetermined magnitude. As a general rule should not be greater than 0.05 and b should not be greater than 0.20. Any deviation from this range of values should be clearly justified. The greater the difference to be detected between treatment and control groups in the study, the lower the number of subjects needed, provided the a and b remain unchanged. It is imperative that the sponsor seek the assistance of a statistician familiar with clinical trial methodology in order to develop the protocol and determine the appropriate number of subjects to be enrolled in the study.

4. A specification of the outcome variables or clinically relevant endpoints that will be measured to support the study hypotheses. The measure of each primary endpoint should be objective and concisely defined.

5. A description of the means to eliminate selection bias should be included in the protocol. Sequential screening of all potential subjects for the study, with a record of the patients not enrolled and the reason for non-enrollment is one way of avoiding selection bias.

6. A specification of all baseline and follow-up assessments consistent with the study objectives. Follow-up assessments should include the allowable time window.

5.2. Study endpoints

Endpoints commonly used for the evaluation of permanent pacing leads include the following:

1. Effectiveness

- Battery longevity
- Pacing impedances
- Voltage stimulation threshold
- Sensing characteristics

2. Safety

Lead related adverse events (observations and complications). The following should be addressed regarding complications and observations:

- Observations are lead-related adverse events which are corrected by non-invasive measures, e.g., reprogramming.
- Complications are lead-related adverse events that are corrected using invasive measures to correct or which result in the loss of a significant device function, e.g., lead dislodgment; and
- deaths, all deaths and lead-related deaths

5.3. Criteria for Lead – Related Complication and Failures

WHEN: The following condition occurs:

- Insulation Breach
- Dislodgement
- Pacing impedance less than 200 ohms (describe how impedance was measured)
- Loss of capture
- Perforation
- Conductor failure
- Extra cardiac Stimulation
- Pacing impedance greater than 3000 ohms or beyond the measuring capabilities of the device (describe how impedance was measured)
- Over sensing
- Loss of sensing/Under sensing AND: The condition was not:
- Corrected by reprogramming of the pulse generator (except for reprogramming of mode or polarity)
- Caused by a pulse generator malfunction.

THEN: The occurrence should be reported along with the following interventions/interactions in which the lead was:

- Abandoned Surgically
- Abandoned Electrically
- Modified Surgically
- Modified Electrically
- Tolerated (based on medical judgment)
- Removed/Explanted (full of partial)

6. THE EVOLUTION OF PACEMAKERS[9-20]

6.1. Excitation and Conduction System[9-13]

The heart is composed of atrial and ventricle muscles that make up the myocardium and specialized fibres that can be subdivided into excitation and conduction fibres. Once electrical activation is initiated contraction of the muscle follows. An orderly sequence of activation of the cardiac muscle in a regularly timed manner is critical for the optimal functioning of the heart. The excitation and conduction system responsible for the control of the regular pumping of the heart is presented in Figure 1. It consists of the intermodal tracks, the bundle if HIS, Sino atrial Node (SA), Bachmann's bundle, bundle branches, the Atria Ventricular (AV) node, Purkinje Fibres. Cardiac cells are able to depolarize at a rate specific for the cell type. The intrinsic rate of AV-nodal cells is about 50 beats per minute (bpm), whereas Purkinje fibres depolarize at a rate of no more than 40 bpm. During normal sinus rhythm, the heart is controlled by the SA node having the highest intrinsic rate of 60–100 bpm depending on the hemodynamic demand. The right atrial intermodal tracks and Bachmann's bundle conduct the SA-nodal activation throughout the atria, initiating a coordinated contraction of the atrial walls. The impulse reaches the AV node, which is the only electrical connection between atria and ventricles. The AV node introduces an effective delay, allowing the contraction of the atria to complete before ventricular contraction is initiated. Due to this delay, an optimal ventricular filling is achieved. Subsequently, the electrical impulse is conducted at a high velocity by the His- Purkinje system comprising the bundle of His, Purkinje fibres and bundle branches. Once the bundle of His is activated, the impulse splits into the right bundle branch, which leads to the right ventricle and the left bundle branch serving the left ventricle. Both bundle branches terminate in Purkinje fibres so The Purkinje fibres are responsible for spreading the excitation throughout the two ventricles, enabling a coordinated and massive contraction.

6.2. Cardiac Signals[9, 16]

Surface Electrocardiogram

The electrocardiogram (ECG) is a recording from the body surface of the electrical activity generated by the heart. In 1899, the ECG was originally observed by Waller. In 1903, Einthoven introduced electrophysiological concepts still in use today, including the labelling of the waves characterizing the ECG. He assigned the letters P through U to the waves avoiding conflicts with other physiologic waves studied at that time Figure 2 depicts a typical ECG signal.

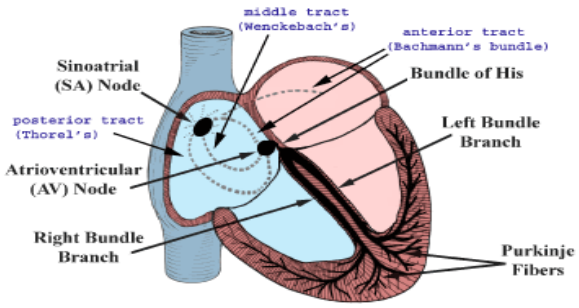

Fig - 1: The cardiac conduction system

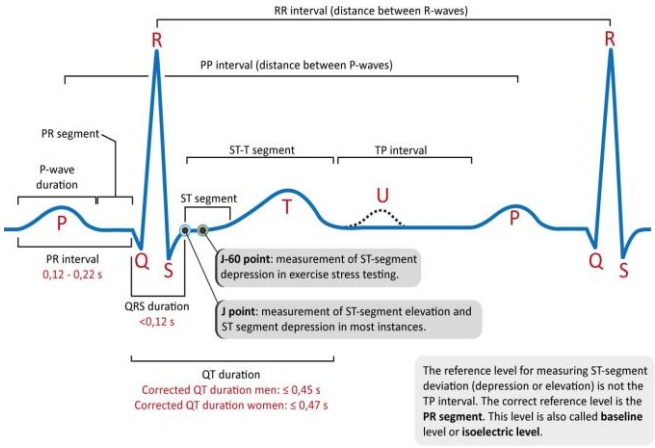

Fig - 2: Typical electrocardiogram

6.3. The History and Development of Cardiac Pacing

Artificial Pacemakers[9, 18]

An artificial pacemaker is a device that delivers a controlled, rhythmic electric stimulus to the heart muscle in order to maintain an effective cardiac rhythm for long periods of time.

ensuring effective hemodynamic performance. The indication for implanting a permanent pacemaker and selection of the appropriate mode of operation are mainly based on the type of cardiac disease involved such as failure of impulse formation (sick-sinus syndrome) and/or impulse conduction (AV-block).

Functionally, a pacemaker comprises at least three parts: an electrical pulse generator, a power source (battery), and an electrode (lead) system.

Different types of output pulses (e.g., monophasic, and biphasic) can be used to stimulate the heart. The output stimulus provided by the pulse generator is the amount of electrical charge transferred during the stimulus. For effective pacing, the output pulse should have an appropriate width and sufficient energy to depolarize the myocardial cells close to the electrode. Generally, a pacemaker can provide a stimulus in both chambers of the heart. During AV block, ventricular pacing is required because the seat of disease is in the AV node or His-Purkinje system. However, in case of a sick sinus syndrome, the choice of pacemaker will be one that will stimulate the right atrium.

A pacemaker utilizes the energy stored in batteries to stimulate the heart. Pacing is the most significant drain on the pulse generator power source. The battery capacity is commonly measured in units of charge (ampere hours). Many factors will affect the longevity of the battery, including primary device settings like pulse amplitude and duration and pacing rate. An ideal pulse generator battery should have a high energy density, low self-discharge rate, and sufficient energy reserve between early signs of depletion and full depletion to allow for safe replacement of the device.

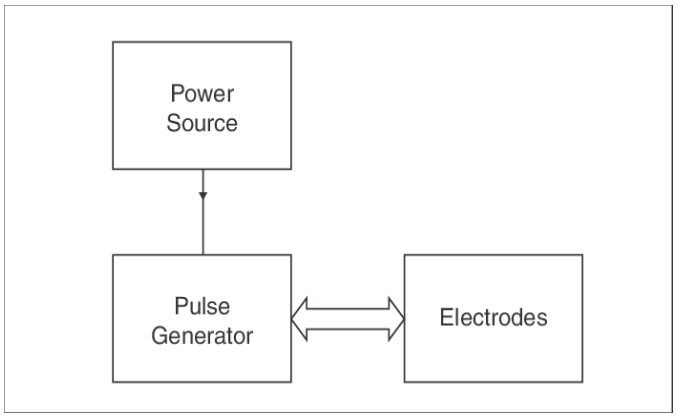

Fig - 3: Basic pacemaker functional block diagram

6.4. Hyman's Pacemaker[9]

In the early 20th century, many experiments such as drug therapy and electrical cardiac pacing had been conducted for recovery from cardiac arrest. Initial methods employed in electrically stimulating the heart were performed by applying a current that would cause contraction of the muscle tissue of the heart. Albert S. Hyman stated that the introduced electric impulse serves no other purpose than to provide a controllable irritable point from which a wave of excitation may arise normally and sweep over the heart along its accustomed pathways.

6.5. Demand Pacemaker[9, 19]

These pacemakers, called asynchronous or fixed-rate pacemakers compete with the natural heart activity and can sometimes even induce arrhythmias or Ventricular Fibrillation (VF). By adding a sensing amplifier to the asynchronous pacemaker in order to detect intrinsic heart activity and thus avoid this competition, one obtains a demand pacemaker, and it provides electrical heart-stimulating impulses only in the absence of natural heartbeats. The other advantage of the demand pacemaker compared to the fixed rate system is that now the battery life of the system is prolonged because it is only activated when pacing stimuli are needed.

6.6. Dual-Chamber Pacemaker[9, 22]

A dual-chamber pacemaker typically requires two pacing leads: one placed in the right atrium and the other placed in the right ventricle. A dual-chamber pacemaker monitors (senses) electrical activity in the atrium and/or the ventricle to see if pacing is needed. When pacing is needed, the pacing pulses of the atrium and/or ventricle are timed so that they mimic the heart's natural way of pumping. Dual-chamber pacemakers were introduced in the 1970s. One of the first descriptions of a dual-chamber pacemaker was given by Berkovits in 1971 and Berkovits announced a bifocal (AV sequential) pacer that sensed only in the ventricle but paced both chambers. In the presence of atrial standstill or sinus-node syndrome plus AV block, the bifocal pacemaker could deliver a stimulus to the atrium and then, after an appropriate interval, to the ventricle. In accordance with the principles of the demand pacemaker design, a sense amplifier is provided to detect intrinsic ventricular activity. The timing control circuits determine both atrial and ventricular time-out stimulating period. However, the atrial-stimulating impulse is generated first and after a predetermined time interval (200 Ms), the ventricular-stimulating impulse is generated. Three electrodes are provided: a neutral electrode, an electrode for atrial stimulation and an electrode for ventricular pacing and sensing. The Field-Effect Transistor (FET) Switch (S FET) is inserted in the feedback path of the ventricular electrode in order to avoid erroneous detection because of the atrial contraction. The S FET is normally conducting. The negative pulse generated at the atrial electrode is transmitted through the diode Da, charging the capacitor Ca, and turning off the switch. When the atrial stimulating terminates, Ca discharges through resistor Ra and turns on the switch again. In this manner, the sense amplifier is disabled during each atrial stimulation and for a short interval thereafter.

7. IMPLANTABLE PACEMAKERS TESTING GUIDELINES[21]

This guideline describes a general framework for design verification testing of a safe and effective implantable cardiac pulse generator. The tests are designed to

reasonably assure safe and effective functioning of the pacemaker in the patient, according to written specifications of performance, and its survival under expected environmental conditions in the body and during storage, shipping, and handling.

This guideline is intended to apply to bradycardia pacemakers which are to be commercially marketed and are manufactured using standard production techniques and methods. It may not apply to devices which are used in limited research applications.

The testing is that referred to in the premarket approval regulation 21 CFR Part 814 and must be reported as described in 21 CFR Part 814 articles 814.20(b) (3) (v) and 814.2020(b) (6). The testing requirements include any and a1 l additional requirements imposed or referred to in the "Good Manufacturing Practice for Medical Devices: General" Regulation (21 CFR Part 820). This guideline represents practices which have been developed over several years and are generally understood by the pacemaker industry.

The tests are grouped into (A) in vitro component tests,(B) in vitro device tests(C)animal tests, (D)biocompatibility tests,(E)clinical investigation and (F) Manufacturing. An appendix provides a sample protocol for preclinical pacemaker testing.

7.1. In vitro component tests:

Component parts shall be tested for design verification by the pulse generator manufacturer of its supplier according to written specifications of performance and testing (such as Military Standard=. or their equivalent).

The component parts referred to shall include, but not be limited to:

Hybrid Integrated Circuit and/or Chip Carrier
Battery
Connector
Other components where necessary to assure reliable operation.

7.2. In vitro finished Device Testing:

The following testing shall be performed:

Electrical Characterization

This testing shall be designed to verify the proper functioning of the pulse generator within specified tolerances in the human body during the device's expected operational life. All parameters such as rate, pulse width, sensitivity, and timing cycles and periods; and all features such as intra-cardiac, electro-grams, remote measurements, hysteresis, rate fall-back, and elective replacement indicators, must be characterized for functioning under expected temperatures (30C^{o} to 40C^{o}), loads (300 ohms to 2000 ohms), and battery voltage's Beginning of. Life (BOL) to End of Service (EOS). The device shall be programmed to each (node and feature and to the lowest, nominal, and highest values of programmed parameters. Analysis of the effect of worst-case combinations of load, temperature and battery voltage must be made.

Environmental

The pulse generator shall be subjected to a sequence of mechanical and environmental tests to assure that the device will meet its labelled specification after being subjected to condition that exceed those normally have seen in handling, shipping, storage or clinical use. Test shall include:

Temperature storage or cycling
Mechanical Vibration
Mechanical Shock

Interference

The pacemaker shall be evaluated for effects on its functioning and/or programming by external sources of interference. Sources of interference can be from the general environment, in this clinical setting, occupational environment or from the human anatomy. The following sources of interference shall be evaluated for all devices as appropriate to the specific device design:

Conducted and Radiated Electromagnetic interference.
Electrosurgical Units
Defibrillators

Reliability

The device must be tested and analysed from a reliability standpoint. Testing of the device or, where appropriate, its component, must include accelerated life testing which will demonstrate the excepted real time longevity performance and failure rate of the device.

Programmer

Programmers built for verification testing shall be representative of marketable products and subjected to functional, environmental, interference, software, and reliability testing. This testing must be designed to assure its operation according to written specification in conjunction with any and all of its intended pulse conditions; under specified, expected environmental condition; and its survival in use as well as in storage, shipping and handling.

Animal Testing

Animal Testing should be performed where appropriate to verify functions, features, or other characteristics of the device.

Biocompatibility Testing

For a material which has been tested and used previously in direct blood contacting devices, a sponsor may submit information available in publications or other legitimate sources which show that the material is nontoxic in tests identical or equivalent to those listed below. All new materials in the non-hermetic portion of the pulse generator must pass the tests below to insure safety for use in permanent implant.

The required toxicity tests for implantable device are listed as follows:

1. United States Pharmacopeia
2. (U.S.P.) XXI (Class V) Biological Tests for plastics and U.S.P. XXI Intramuscular implant tests and U.S.P. XXI pyrogen test.
3. Sensitization Assay:

4. Estimate the potential for sensitization of a material by using a test such as the guinea pig maximization test.
5. Cytotoxicity Test:
6. Determine the lysis of cells, the inhibition of growth, and other toxic effects on cells caused by material and extracts from the materials using cell culture techniques.
7. Haemolysis:
8. Determine the degree of red cell lysis and the separation of haemoglobin caused by materials in-vitro. Describe the test methodology.
9. Clinical Investigation
10. Objectives
11. The objective of the study must be defined such that the study will constitute a demonstration of reasonable assurance of the safety and efficacy for the device. The study must establish a list of indications and contraindications and, if any, warnings, and precautions for the use of the device. Generally, pacemakers must show pacing and sensing capabilities with modes, parameters, features, and logical combinations of these shown to be safe and effective within the meaning of the Federal. Food, Drug and Cosmetic Act, as amended, 1980.

Patient Selection

Patients should be selected. For the clinical studies who can be expected to benefit from the device's capabilities and whose conditions can demonstrate its effectiveness. The patient should be psychologically stable, cooperative and available for follow-up and have a reasonable life expectancy so that a proper clinical evaluation of the device might be conducted.

Investigators

Investigators for pacemaker studies shold be selected who are qualified by training or experience in cardiovascular disease at a minimum. In the case of devices with special features, trained physicians with special skills should be specified in a representative sample of the investigators.

Manufacturing

A descriptian of the testing during the manufacturing process must be included in the PMh Application in the section required by 21 CFR 814.20(b)4(v). This testing should complement the design verification testing to ensure that each manufactured unit will operate within the specifications of the design with respect to tolerances, environmental considerations, and interfaces. Summary descriptions of the following tests should be included:

Tests

Component

Screen

Burn-in

Assembly

Final Product

Special QC

8. POST-MARKET SURVEILLANCE8

One of the provisions of the Safe Medical Devices Act of 1990 (SMDA) provided for Discretionary Post-Market Surveillance (DPS) studies. The FDA has decided to use this provision to require the submission of additional data about the safety and effectiveness of permanent implanted cardiac pacemaker electrodes. FDA has determined that the legal entity who has received clearance to market through-submission of the premarket notification (510(k)) or premarket approval (PMA) application for a particular lead will have primary responsibility for conducting post-market surveillance of that lead. All others who are involved in the distribution of these devices will be responsible for ensuring that any data or information in their possession is made available to the sponsor of a DPS protocol.

9. CONCLUSIONS

Permanent pacemaker implantation is a very vital part of Cardiology and Cardiac surgery. It is a safe procedure with low complication rates. There is a gradual increase in the number of cases performed annually in Accra, with a slight male preponderance. Most patients are elderly, with complete heart block as the commonest indication. It is lifesaving, improves the quality of life and enhances survival.

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