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A REVIEW ARTICLE ON CARDIAC PACEMAKER

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DEPARTMENT OF PHARMACUTICAL QUALITY ASSURANCE

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Abstract:-

Despite the many advances that have occurred in the Pacemakers. Here , authors provides the study about type and necessity of installation of pacemakers. Also includes the time or condition of the heart when the Pacemakers should supposed to be installed. Study also involves the materials , methods and components required for pacemakers and reasons of implantation.

Key words :-

Cardiac Pacemakers, arrhythmia ,pacemakers , electrophysiology

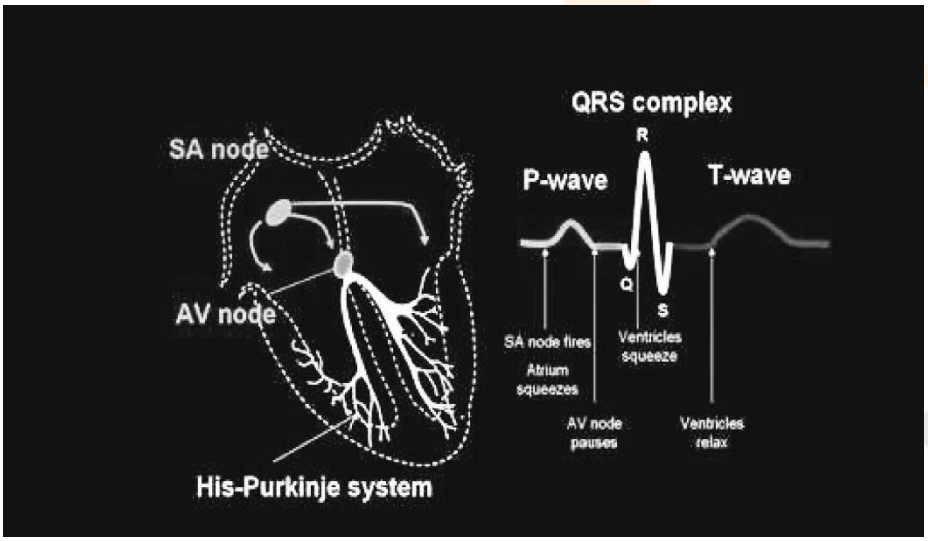
Introduction: -

The heart is an evolutionary success story. During the course of evolution, novel structures And functions have been added to the primitive ancient pump. The network of transcription Factors regulating mammalian embryonic heart development shows a high degree of evolutionary Conservation. Similar signalling pathways controlling muscle growth, patterning, and contractility Have been found in animals as distantly related as humans and drosophila (10–22).Even the most basic heart-like structure shares the common crucial feature of all hearts, the Ability to rhythmically contract and pump fluid through the body. Thus, the heart is the motor of fluid-based transport system for nutrients, metabolites, and oxygen. Even animals with radically Different lifestyles and body plans, such as insects, fish, birds, and terrestrial animals show a striking Conservation in cardiac function . The cardiac pacemaker and conduction system In the mammalian heart can be considered as an important advancement to increase cardiac efficiency. Mammals possess a sophisticated network of pacemaker nodes, specially coupled cardio myocytes. (3).

Electrical System of Heart: Heart's electrical system includes three important parts:

• S-A node (sinoatrial node) — known as the heart's natural pacemaker, the S-A node has Special cells that create the electricity that makes your heart beat.
• A-V node (atrioventricular node) — the A-V node is the bridge between the atria and Ventricles. Electrical signals pass from the atria down to the ventricles through the A-V Node.

• His-Purkinje system — the His-Purkinje system carries the electrical signals throughout The ventricles to make them contract. The parts of the His-Purkinje system include:
§ His Bundle (the start of the system)
§ Right bundle branch
§ Left bundle branch
§ Purkinje fibers (the end of the system)The signal in SA node is generated as the two vena cava fill your heart's right atrium with Blood from other parts of your body. This signal causes the atria to contract. This action pushes Blood through the open valves from the atria into both ventricles. The P wave on the ECG marks The contraction of your heart's atria. The signal arrives at the AV node near the ventricles. It Slows for an instant to allow your heart's right and left ventricles to fill with blood. On an ECG, This interval is represented by the start of the line segment between the P and Q wave. The signal Is released and moves along a pathway called the bundle of His, which is located in the walls of Your heart's ventricles. From the bundle of His, the signal fibers divide into left and right bundle Branches through the Purkinje fibers that connect directly to the cells in the walls of your heart's Left and right ventricles. On the ECG, this is represented by the Q wave. The signal spreads Across the cells of your ventricle walls, and both ventricles contract. On ECG, the R wave marks The contraction of left ventricle and S wave represents the contraction of right ventricle. The Contraction of left ventricle pushes blood into the aortic valve, then to aorta and to all the parts of The body. The contraction of right ventricle pushes the blood into the pulmonary valve, then to Pulmonary arteries and to the lungs. On the ECG, the T wave marks the point at which your Heart's ventricles are relaxing. Now the deoxygenated blood is brought back by the vena cava to The right atrium and again the SA node is ready to generate an electrical impulse. In a normal, healthy heart, each beat begins with a signal from the SA node. This is why The SA node is sometimes called your heart's natural pacemaker. Your pulse, or heart rate, is the Number of signals the SA node produces per minute. Heart's conduction system senses need for Oxygen and responds with the proper heart rate. A problem in your heart's electrical system can Disrupt your heart's normal rhythm. Any kind of abnormal rhythm or heart rate is called An arrhythmia. Any disease of the heart (cardio) and blood vessels (vascular) is Called cardiovascular disease (CVD). Many of these problems have similar names, like heart Failure and heart attack, Bradycardia and tachycardia.(6)



Development of the Heart and Its Basic Electric Configuration: A simple heart tube is formed subsequent to the formation of A cardiac crescent by fusion of the 2 heart-forming regions of The lateral plate mesoderm in gastrulation stage mammalian Embryos. Not all cells of the (pre)cardiac mesoderm differentiated immediately. Cells located medially in the cardiac Mesoderm are kept behind and become positioned dorsally And caudally to the arising heart tube. These cells, referred to As second heart field,(23) proliferate rapidly and serve as a Progenitor pool that continuously provides myocardium to Both poles of the heart tube.(24) Before their differentiation to Myocardium and addition to the heart tube, these cells Drastically decrease their proliferation rate.(23,24) Labeling studies have indicated that the cardiac crescent and early heart Tube only

represent the outer curvature (apex) of the left Ventricle and parts of the AVC and atria, whereas the Remainder of the heart derives from cells added later.(23,25 –28 The initial embryonic heart tube myocardium possesses a Phenotype that resembles that of the nodal tissues in displaying automaticity, poor contraction, and slow transmission Of the depolarizing impulse.(29 –31) Sarcomeres and sarcoplasmic reticulum are not well-developed in this primary Myocardium.(29,30,32) Caudal pacemaker activity in this slow conducting heart tube results in sluggish, unidirectional Peristaltic contractions that are reflected in a sinusoidal ECG.During further elongation of the heart tube, the developing Ventricular and atrial chambers acquire a working myocardial Phenotype and rapidly expand by highly increased levels of Proliferation (30)The underlying molecular programs involve up regulation of genes for high conductance Gap junctions that contribute to the rapid transmission of the Electric impulse, of mitochondrial genes associated with the Increase in mitochondrial number and activity, and of genes For sarcomere components.(29,30) Cardiac regions including the sinus venosus, the AVC, Inner curvatures, and the outflow tract do not differentiate Into chamber myocardium, retain low proliferation rates and Will consequently form constrictions.(29, 30)Dominant pacemaker activity remains localized at the intake, the sinus Venosus.The AVC retains its embryonic mode of conduction, which is much slower that that of the newly formed Chambers. Thus, the impulse between the rapidly propagating Atrial and ventricular chambers is effectively delayed.(29,31) Concomitant with chamber formation, the initially peristaltic Contraction mode of the embryonic heart tube is replaced by A pattern of serial and rapid contractions of the atrial and Ventricular compartment(s), and the derived ECG starts to Resemble that of a mature heart . This basic Configuration of alternating slow-conducting and poorly contracting pacemaker components (sinus venosus, AVC, outflows tract) and fast-conducting myocardial components (atria And ventricles) can be found in embryos and adults of all Vertebrates with multi-chambered hearts, including human.(30) Higher vertebrates, such as mammals, will Develop a morphologically distinctive SAN in the sinus Venosus, an AVN within the AVC, and an AV bundle and Ventricular conduction network to efficiently and co-ordinately activate the ventricles. The structural differentiation of These components varies widely between species. They are Hardly present or not discernible in fish, they are very Well-developed in large mammals, and in the mouse they are In-between. Thus, species-specific morphological adaptations
Are likely to have arisen during evolution.(1).

HISTORY OF PACEMAKER :

The first acquisition of knowledge about importance of cardiac pacing and heart pulse with relation to healthy Life of human being was studied long back say approximately 460 BC before (33). Some great ancient Philosopher like Hippocrates and Aristotle showed initial signs for the knowledge of heart pacing as necessity of Life. In China, Wang Shu-he, an ancient philosopher, wrote ten books on the heart and its pulse. The study of Pulse is called shygmology‖ and pulse as shygmos by Greeks scientists. In 1580,Geronimo Mercurially Derived the concept of syncope and illustrated its connection with a slow pulse rate (33). In 1775, first time electrodes were used on the sides of hen‘s chest and defibrillation of heart undertaken by Danish physicist Nickolev Abildgaard. In 1791, electric activity was found in frog muscles and heart by an Italian physician and natural scientist, and his published experimental finding was contribution to modern Cardiac electrophysiology. Action currents of the heart was derived by Rudolph Albert von Kollicker in 1855. In 1982, first time in history of cardiac therapy, a human heart (a 46 year old female ―Catherina Serafin) Was stimulated using electric current and her hate rate was controlled as required (33). In 1889, A English doctor John Mac William, published his experiments in the British Medical Journal (BMJ) Which described the application of electric impulses at rate of 60-70 per minute across the chest that provoke The ventricular contractions with heart rhythm of 60-70 bpm (34). The next step of advancement in recording of cardiac pacing was the invention of extremity bipolar electrode System by F.N. Wilson wherein he introduced the unipolar chest wall electrodes in 1933. In 1942, augmented
(Unipolar amplified) extremity lead was invented by E. Goldberger which completed the formation of 12 lead Electrocardiogram systems (35)

First Artificial Pacemaker: The credit of development of first pacemaker goes to two doctors: Mark Lidwill from Australia and Albert Hyman from America but they work independently unknown and distant to each other. In 1926, Mark C Lidwill Who was working in Royal Prince Alfred Hospital of Sydney used the two pole electrodes in which one was Applied to a skin pad soaked in saline solution and other was a needle that is pinned into the appropriate cardiac Chamber. He used the ac supply to run this portable device later on known as the pacemaker. The rate of pacing Of this device was 80 to 120 pulses per minute with input supply voltage variation from 1.5 to 120 volts.In the early 20th century, Albert Hyman designed the first experimental heart pacemaker which was spring Wound hand cranked motor named as artificial Pacemaker‘ . The generator of this pacemaker was Capable of providing pulses for 6 minutes without rewinding . In this pacemaker, the supply current is Provided by the magneto-generator (A) to interrupter disc on surface contact when a spring motor (D) is Powered by hand crank (F) rotation. The interrupter disc is rotated by rotations of spring motor at desired speed Set by part E and H. The magnetic pieces B′ and B″ are used to provide necessary flux to magneto generator. The periodic pacing is provided by electrode needle (L) at 30, 60 or 120 bpm, generated by interrupted disc and Regulated by the impulse controller (G). At condition of any hindrance in generation of stimulus a neon bulb is Glowed.(9).

Classification of pacemakers:-

- **Based on placement of pulse generator:**

External pacemaker (Temporary): These types of pacemakers are used to treat the critical condition Of bradyarrhytmia (Second or third degree atrioventricular block (AVB) or severe symptomatic bradycardia in Emergency situation of patients who are thermodynamically unstable. In this type of pacemaker, the pace Generator is placed outside the body and pacing electrodes are introduced inside the heart using proper protocols .(9).

Implantable Pacemaker (Permanent): According to definition of implantable internal pacemaker, an Internal pacemaker is one in which electrodes are placed into heart; and the electronic circuitry and power Supply are implanted within the body . Implantable permanent pacemakers may function continuously To contract the heart or on demand of heart when natural pacemaker fails to stimulate the heart with or without Physiological need of body which depends on selection of pacemaker among fixed rate, demand type or rate Responsive pacemaker. First implantable pacemaker was invented by Wilson Great batch in 1958 while he was Working on circuitry of oscillator to record of heart sound and mistakenly he put the wrong value register and it Started to give electric pulse in regular intervals. Later this circuit was improved and used with the corrosion free Lithium battery as first implanted pacemaker (9)

Implanted cardiac defibrillators (ICD): Pacemaker is a device used to treat the bradycardia that is The situation when heart rate is too slow (less than 60 bpm) [24]. However, with known, sustained ventricular Tachycardia or fibrillation type of arrhythmia where pacemaker are not useful implanted cardiac defibrillators Particularly known as ICD is used . An ICD is battery powered device having two leads which implanted in Pocket under collarbone. The electrode lead is introduced through blood veins into heart chamber that transmit The electric impulse from pulse generator to heart in case of life-threatening ventricular tachycardia and prevent To sudden death of patient due to heart attack . Current generation device is available with functioning Capability of both pacemaker and ICD.(9).

- **Based on need of pacing**

Fixed-rate pacemaker (Asynchronous pacemaker): As per definition of fixed rate pacemaker, it is The device which delivers electric stimulus at a constant frequency/rate regardless of heart‘s rhythm . It is Also called asynchronous pacemaker due to non-synchronization with any atrial or ventricle activities and Provide impulses at fixed rate. This type of pacemaker does not use sensing element to pick up the heart rhythm. Their pacing rate is generally set 60-70 beats per second in adults and 80-100 beats in children. Their pulse Generator circuitry is simple in construction because of non-requirement of feedback path but due to continuous

Operation, battery power drainage is high. Other disadvantage of this type of pacemaker is emergence of Competition between natural pacing of heart and device pacing due to interference by any spontaneous electric Activity occurring within the heart and it also increase the risk of atrial fibrillation and perforating the Thin heart wall. Fixed rate pacemaker provides three types of pacing modes AOO for atrial pacing, VOO for Ventricle pacing and DOO for dual pacing(9).

Variable rate pacemaker: In this type of pacemaker pacing rate can be varied according to either Setting of the specific pacing mode or activity of body. This type of pacemaker equipped with the sensor which Detects the heart pulse and feedback to actuator of pulse generator. The variable rate pacemaker can be further Categorized in two types one is demand type pacemaker or synchronous pacemaker and second is rate Responsive pacemaker. (9)

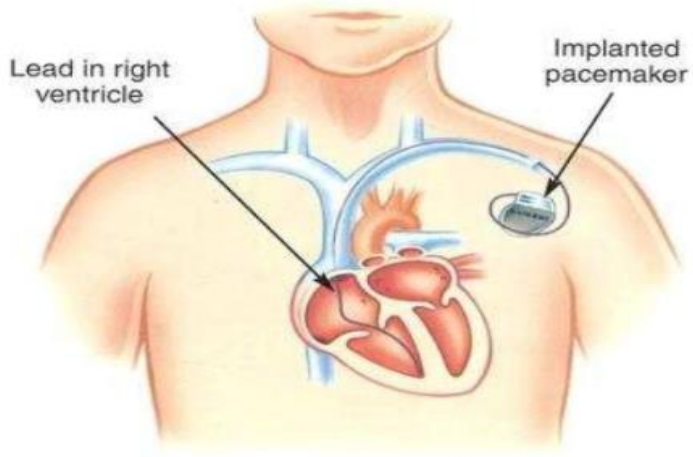
Demand pacemaker (Synchronous): This type of pacemaker provides electrical stimulation to the Heart when it senses indication of inadequate spontaneous pacing of natural pacemaker of heart due to any Arrhythmic severity. It‘s also known as triggered circuit . Most of the time this type of pacemaker‘s pulse Generator remains in standby mode in condition of accurate functioning of heart that is sensed by the sensors Integrated in feedback path of the circuit. If sensor detects any absence of heart pulse, it activates the actuator of Pulse generator and an electrical impulse is transmitted to heart chamber through the electrodes. (9)

Rate Responsive Pacemaker: Rate responsive or rate adaptive pacemaker provides the pacing rate as Per hemodynamic need of heart. During exercise or any physiological activity, there is requirement of increased Heart rate to provide the high volume of cardiac output to fulfill the metabolic need of body . It‘s integrated With some physiology activity sensor which continuously monitors and paced the heart analogous to variation in Activity of body. The selection of algorithm and sensor principle determines the hemodynamic efficiency of the Rate adaptive pacemaker . Actually it provides effective pacing due to assessment of hemodynamic Performance of heart and establishment of a physiological correlation between inotropic and chronotropic Cardiac function . Inotropic cardiac function is related to heart contraction and chronotropic cardiac function Affects the heart rate. There are various physiological parameters which affect the variation of heart rate so Efficiency of rate adaptive pacemaker depends on number of sensor, different parameters being considered, Sensing technology and adaptive algorithms. The list of few physiological variables and their corresponding Sensors . The basic block diagram of rate responsive pacemaker .(9)

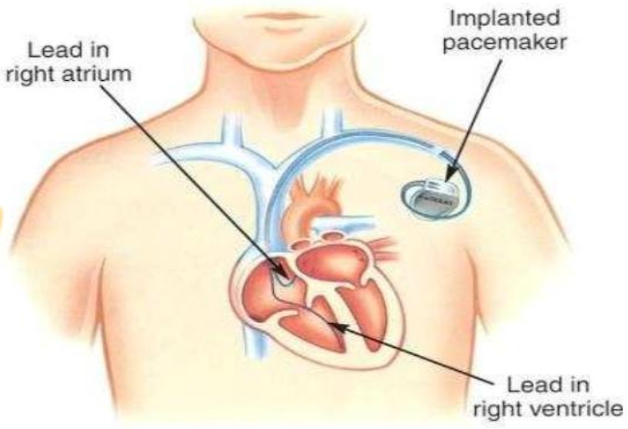
- **Based on stimulation of chamber or number of leads**

The pacemaker device may be categorized on the basis of number of chambers of heart to which pacing is Provided and number of electrode lead also depends on and generally equal to the number of chamber for which Electrical stimulation is available. There are three types of pacemaker available depending on the number of Stimulated chamber or number of lead basis:

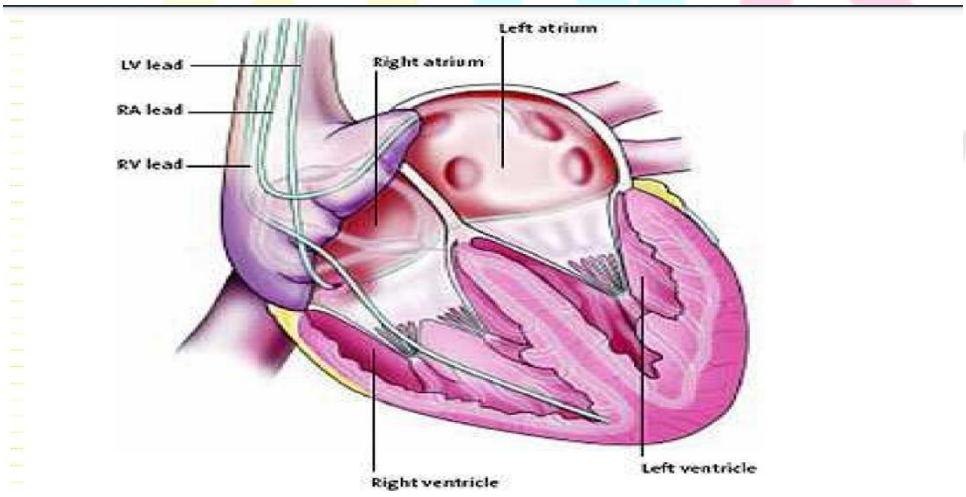
Single chamber/ One lead pacemaker: This type of pacemaker Has one lead that connects the pulse generator to one Chamber of your heart. For most people, we use the Single-chamber pacemaker to control heartbeat Pacing by connecting the lead to your right ventricle (lower heart chamber).In dual-chamber pacemakers, electrodes are inserted Into both the right atrium and right ventricle . The circuitry is designed to allow for a physiologic delay (normal synchrony) between atrial And ventricular stimulation. This AV delay (interval Between the atrial and ventricular pacemaker stimuli) Is analogous to the PR interval under physiologic Conditions. Ventricular single-lead pacemakers (with the lead Positioned in the right ventricle) are primarily used to Generate a reliable heartbeat in patients with chronic Atrial fibrillation with an excessively slow ventricular Response. The atrial fibrillation precludes Effective atrial stimulation such that there is no Reason to insert an atrial lead. (7).



Dual chamber / Two lead pacemaker: In this type of pacemaker pacing wire is placed in two Chamber, one in atrium and second in ventricle. This type of pacemaker tries to resemble the natural heart Rhythm by pacing atrium and ventricle in proper coordination.



Biventricular / Three lead pacemaker: This type of pacemaker has three lead system and functioning Of this pacemaker is also called the cardiac resynchronization therapy (CRT). CRT is used in the patients who Are suffering from ventricle desynchronise, a condition in which the left and right ventricles do not contract simultaneously.(36).



Biological pacemakers

In spite of constant enhancements in gadget advances, _Electronic pacemakers actually have limits and Complications55,72-75. A few circumstances warrant

Non-gadget choices. Patients with equipment related Diseases who require a pacemaker have a Contraindication to re-implantation before successful Antibiosis is laid out. In something like one occasion (inborn heart block), hazardous bradycardia can't be Treated by electronic pacemakers. This condition Brings about fetal passing or stillbirth in ~80% of cases And would require in utero pacing76,77, which isn't
Yet doable. Subsequently, natural pacemakers are Being created to give a helpful option in contrast to Electronic gadgets. Conduction framework problems are at present
Treated with electronic pacemakers. Electronic Pacemaker advancements proceed to develop, and Most recent age gadgets are more modest, have longer Battery term, and further developed usefulness Contrasted and past gadgets. Later on, we will Presumably see further upgrades in electronic gadgets: Moderate scaling down; double chamber, leadless Pacing; and further developed sensor advances to all
The more likely acclimate to metabolic and physiological necessities. Different electronic Pacemakers are right now accessible to treat explicit Patient populaces, (for example, single-chamber or Leadless gadgets in constant AF or biventricular Pacemakers in HF with wide QRS complex), and Gadget advancements will most likely have further
Enhancements custom-made to specific patient Requirements. If effectively tried in specialty Populaces (for instance, patients with gadget related Diseases), organic pacemakers could give a remedial Option in contrast to gadgets later on administration Of patients with conduction framework problems.(7).
Necessity of a pacemaker: Heart has a natural pacemaker (SA node) which may not work at times. Generally heart Beats between 60 and 100 times a minute. Heart beat fewer than 60 times a minute is Bradycardia. Pacemaker comes into existence when a person is suffering from Bradycardia. As a Result, your heart may not pump enough blood to meet your body's needs, and you may feel tired Or dizzy. Normally, the SA node automatically maintains a heart rate adequate for your body's Needs – for example, heart rate decreases during sleep and increases during exercise to match Your body's need for oxygen. But there are conditions which cause heart to pump slowly. They Are:
§ Sinus Bradycardia: The signals coming from the SA node may be too slow.
§ Sick Sinus Syndrome: The signals coming from SA node may alter between being Too fast and too slow.
§ Sinus pause or Sinus arrest: The signals coming from SA node may occasionally Stop.
§ Heart Block: The signals from may form normally in the sinus node but fail to Transmit from the upper to the lower chambers. All the above conditions cause the heart to pump too slowly. This can cause symptoms such as Dizziness or fainting. Pacemakers are usually recommended in these situations. Artificial pacing Helps to restore the heart rhythm towards normal improving the heart's ability to circulate blood Through the body. (6).

BATTERY TECHNOLOGY

Batteries used in Implantable cardiac pacemaker require high level of safety, reliability and longevity (37). Technological advancement in leads/electrodes along with microelectronics reduces energy requirement by two Orders and sharply reduces internal current drain which leads to decrease in size and increase in functionality, Reliability and longevity (38). A cardiac pacemaker uses half of its battery power for cardiac simulation and Other half for monitoring and data logging.
During 1958-1959 rechargeable (secondary batteries) nickel-cadmium batteries were used in pacemaker Implants in human beings. They were inductively recharged by the transmission of energy to the implanted Receiver. The cell voltage was 1.25 V and the capacity was 190 mAh. The major problems were two fold; the First being too short life time and the second was to place the responsibility for recharging in the hands of Patients, which is not a good medical practice. It was well known that primary or non-rechargeable batteries Would give longer lifetime compared to secondary batteries, and patient anxiety regarding frequent recharging.

Second type of batteries that were used for implanted cardiac pacemaker were ―mercury-zinc‖ batteries [55]. The zinc-mercury oxide batteries came with the potential advantages of a high energy density and the discharge Characteristics of maintaining a constant closed-circuit potential difference when operated within the prescribed Current densities. Depending on the electrode design, these batteries had a long life span (up to 3 years). These Batteries, however, had the disadvantage of evolving hydrogen in case residual anode (zinc oxide) was left after Cathode depletion. Also, electrolyte leak from the battery destroyed the adjacent circuit elements and prevented Hermetic sealing. With all these handicaps and the appearance of better power sources, these batteries appeared In 1960s and were done away after being used for about one and a half decade (39) Next types of batteries in line were ―biological batteries (40)based on using power from human body itself but It failed experimentally for practical use. The basic principle in these batteries was to convert the body heat in to
Electrical energy for this purpose a large no of thermoelectric generators are built into an implantable chip. These generators exploit the well-known thermoelectric effect in which a small voltage is generated when the Junctions between two dissimilar materials are kept at different temperatures, since it was seen too difficult to Generate 100 uW at 3 V using a temperature difference of 1 degree Celsius, and hence this led the failure of this Technology (40).

MATERIALS AND METHODS :

All studies were performed using protocols approved by the Columbia University Institutional Animal Care and Use Committee.

Viral/Genetic Preparation

An adenoviral construct of murine HCN2 (mHCN2;Genbank AJ225122) driven by the CMV promoter was prepared (Qu et al., 2003), purified through plaque assay, amplified to a large stock, and harvested and titrated after CsCl banding. The identical procedure was used to construct an adenoviral vector of enhanced GFP (AdGFP), whose sequence was taken from its original vector pIRES2-EGFP (Clontech, Palo Alto, CA) at BamHI and NotI sites and subcloned into the shuttle vector pDC516.Final titters were AdHCN2, 3.4 1011 ffu/mL; AdGFP, 1.4 1012 ffu/mL; 2–3 1010 ffu of each virus was injected per experiment.

Dissociation of Myocytes and Studies of HCN Current Purkinje myocytes were dissociated by modifying a previously published procedure (Boyden et al., 1989). Isolated cells were transferred to a stage-mounted chamber of an inverted epifluorescence microscope to identify GFP-expressing cells. To measure pacemaker currents, cells were super fused with 35°C Tyrode solution containing (in mmol/L): NaCl, 140; NaOH, 2.3; MgCl2, 1; KCl, 5.4; CaCl2,1.0; MnCl2, 2; BaCl2, 4; HEPES, 5; glucose, 10; pH 7.4. Pipette solution contained (in mmol/L) aspartic acid, 130; KOH, 146; NaCl, 10; CaCl2, 2; EGTA-KOH, 5; Mg-ATP, 2; HEPES-KOH, 10; pH 7.2. To record pacemaker current, cells were held at 55 mV and stepped to 55 to 125 mV for 6 sec, followed by an 8-sec step to 115 mV to measure tail current. Human Mesenchymal Stem Cell Maintenance and Transfection

hMSCs (Poietics hMSC, mesenchymal stem cells, human bone marrow) were purchased from Clonetics/Bio Whittaker (Walkersville, MD) and cultured in MSC growing medium (Poietics MSCGM; Bio Whittaker) at 37°C in a humidified atmosphere of 5% CO2. Cells were used from passages 2– 4. A full-length murine HCN2 cDNA was subcloned into a pIRES2-EGFP vector (BD Biosciences Clontech, Palo Alto, CA). Cells were transfected by electroporation using the Amaxa Bio systems Malefactors (Amaxa, Cologne, Germany) technology (Hamm et al., 2002).Transfection efficiency was 30 – 45%. Study of membrane currents in hMSCs was via the techniques described above.(4)

COMPONENTS OF THE PACEMAKING AND CONDUCTION SYSTEM HAVE CONSERVED FUNCTIONS

While subject to neuronal modulations, the intrinsic rhythm of the Heart of higher vertebrates is determined within the tissues of the cardiac pacemaker — the sinoatrial (SA) node. The SA node is situated At the inflow port of the cardiac Pump, or more formally, at the Boundary of the superior caval vein And the right atrium.

Following initiations of a cardiac action potential (AP) within the node, activation is Propagated through the muscular Tissues of the atria, eventually focussing into the atrioventricular (AV) node. As its name implies, the AV node is located at the junction of The atria and ventricles, and functions' as part of a mechanism for Generating a momentary delay in The propagation of AP. The principal
Role of this AV delay generator is to Separate (and to some extent insulates) the activation of the atrial Chambers from that of the ventricle's. Following exit from the AV Node, AP rapidly propagates along The His bundle and its distal Branches, finally activating the Ventricular chambers via a highly Ramified network of Purkinje fibers. Together, this fast conduction system of His-Purkinje tissues forms The last of the main elements of the PCS.(2)

Reasons to implant:-

Regular reasons for implantation are bradyarrhytmia, including several conditions, such as: symptomatic sinus bradycardia, second and third-degree AV block and sick sinus
Syndrome. In these Conditions, the slowed heart rate reduces heart outflow and Decreases oxygen supply to vital organs. Hence, symptoms of Weakness, fatigue, shortness of breath, confusion, loss of Consciousness and heart failure are observed. Since the 1990s, pacemakers are prescribed in other
Conditions, including cardiomyopathy, CHF, atrial fibrillation and tachyarrhythmia's (8).

Implantation procedure:-The pacemaker is implanted subcutaneously during a simple Procedure, lasting between 1–2 hours. The procedure may be Performed in the electrophysiology (EP) lab under local anaesthesia. During the procedure, one or two electrodes are Inserted, under transplantation, through a central (subicula Or cephaly) vein directly into the right ventricle and/or Atrium. After the electrode is located and fixed with the heart Muscle, the pacemaker is located under the skin and starts Operating independently. After the procedure, the patient may notice a slight Swelling around the implantation area and a small (5–
10 cm) scar. A few (1–2%) patients develop major complications such as pneumothorax, infection, haematoma and Blood-loss. One day after implantation is completed, patients are provided with general instructions and vital information concerning life with a pacemaker and they are free to return home. Return to a normal healthy condition (recovery) lasts up to two month, during which most patients regain active lives . (8)

Conclusion:-

Based on the conclusions drawn from these articles, it is evident that the heart's evolution and function represent a remarkable success story in biological history. Throughout evolution, from basic structures to complex systems like the SA node, AV node, and His-Purkinje system, the heart has adapted to efficiently pump blood and maintain rhythmic contractions across diverse species. This evolutionary journey underscores the conservation of essential cardiac functions across mammals and even distant relatives like insects and birds.

Moreover, the development of pacemakers, from historical origins to modern implantable devices, highlights significant advancements in treating cardiac rhythm disorders such as bradycardia and arrhythmias. The integration of genetic research and technological innovations continues to refine cardiac therapies, promising further improvements in patient outcomes.

Overall, these findings emphasize the heart's pivotal role as a vital organ across species, the continual progress in cardiac medicine, and the promising future of cardiovascular care through ongoing research and development.

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References:-

1. Vincent M. Christoffels, Gertien J. Smits, Andreas Kispert, Antoon F. M. Moorman "Development of the Pacemaker Tissues of the Heart" Circulation Research February 5, 2010

2. Robert G. Gourdie*, Brett S. Harris, Jaqueline Bond, Charles Justus, Kenneth W. Hewett, Terrence X. O'Brien, Robert P. Thompson, and David Sedmera "Development of the Cardiac Pace making and Conduction System" Birth Defects Research (Part C) 69:46–57 (2003)
3. Silja Burkhart 1, Vincent van Eif 2, Laurence Garric 1, Vincent M. Christoffels 2 and Jeroen Bakkers ,Review On the Evolution of the Cardiac Pacemaker, Journal of Cardiovascular Development and Disease
4. MICHAEL R. ROSEN,1–3* RICHARD B. ROBINSON,1 PETER BRINK,3 AND IRA S. COHEN1,3 "Recreating the Biological Pacemaker" THE ANATOMICAL RECORD PART A 280A:1046 –1052 (2004)
5. Jihong Qu, PhD*; Alexei N. Plotnikov, MD*; Peter Danilo, Jr, PhD; Iryna Shlapakova, MD; Ira S. Cohen, MD, PhD; Richard B. Robinson, PhD; Michael R. Rosen, MD "Expression and Function of a Biological Pacemaker in Canine Heart" http://ahajournals.org by on June 28, 2024
6. KRISHNA KIRAN KURCHETI , "UNDERSTANDING AND IMPLEMENTING DIFFERENT MODES OF PACEMAKER"
7. Jitendra Sunte , "A Pacemaker Solutions to Heart Rhythm" International Journal of Scientific Research in Mechanical and Materials Engineering ,© 2022 IJSRMME | ISSN : 2457-0435
8. Michal Rassin, Lia Zilcha and Dalia Gross , " 'A pacemaker in my heart' – classification of questions asked by Pacemaker patients as a basis for intervention" Journal of clinical nursing.
9. Atul Kumar Sharma1, Raghuvendra Pratap Tripathi2 , Dinesh Bhatia1,Sudip Paul1 , Nitin Sahai1, T. K. Sinha1 "The Evolution and Advancement of Pacemaker Technology "International Journal of Computational Engineering Research (IJCER) , ISSN (e): 2250 – 3005 || Volume, 08 || Issue, 7|| July – 2018 ||
10. Bishopric, N.H. Evolution of the heart from bacteria to man. Ann. N. Y. Acad. Sci. 2005, 1047, 13– [CrossRef] [PubMed]
11. Boogerd, C.J.; Moorman, A.F.; Barnett, P. Protein interactions at the heart of cardiac chamber formation. Ann. Anat. 2009, 191, 505–517. [CrossRef] [PubMed]
12. Burggren, W.W.; Pinder, A.W. Ontogeny of cardiovascular and respiratory physiology in lower vertebrates. Annu. Rev. Physiol. 1991, 53, 107–135. [CrossRef] [PubMed]
13. Cripps, R.M.; Olson, E.N. Control of cardiac development by an evolutionarily conserved transcriptional Network. Dev. Biol. 2002, 246, 14–28. [CrossRef] [PubMed]
14. Fishman, M.C.; Olson, E.N. Parsing the heart: Genetic modules for organ assembly. Cell 1997, 91, 153–156.[CrossRef]
15. Hertel, W.; Pass, G. An evolutionary treatment of the morphology and physiology of circulatory organs in Insects. Comp. Biochem. Physiol. A Mol. Integr. Physiol. 2002, 133, 555–575. [CrossRef]
16. Meijler, F.L.; Meijler, T.D. Archetype, adaptation and the mammalian heart. Neth. Heart J. 2011, 19, 142–148. [CrossRef] [PubMed]
17. Moorman, A.F.; Christoffels, V.M. Cardiac chamber formation: Development, genes, and evolution. Physiol. Rev. 2003, 83, 1223–1267. [CrossRef] [PubMed]
18. Olson, E.N. Gene regulatory networks in the evolution and development of the heart. Science 2006, 313, 1922–1927. [CrossRef] [PubMed]
19. Satou, Y.; Satoh, N. Gene regulatory networks for the development and evolution of the chordate heart. Genes Dev. 2006, 20, 2634–2638. [CrossRef] [PubMed]
20. Simoes-Costa, M.S.; Vasconcelos, M.; Sampaio, A.C.; Cravo, R.M.; Linhares, V.L.; Hochgreb, T.; Yan, C.Y.; Davidson, B.; Xavier-Neto, J. The evolutionary origin of cardiac chambers. Dev. Biol. 2005, 277, 1–15[CrossRef] [PubMed]
21. Solc, D. The heart and heart conducting system in the kingdom of animals: A comparative approach to it's Evolution. Exp. Clin. Cardiol. 2007, 12, 113–118. [PubMed]
22. Xavier-Neto, J.; Davidson, B.; Simoes-Costa, M.S.; Castro, R.A.; Castillo, H.A.; Sampaio, A.C. Evolutionary Origins of Hearts. In Heart Development and Regeneration; Rosenthal, N., Harvey, R.P., Eds.; Elsevier: London,UK, 2010; pp. 3–46.

23. Buckingham M, Meilhac S, Zaffran S. Building the mammalian heart From two sources of myocardial cells. Nat Rev Genet. 2005;6:826 – 837.
24. Van den Berg G, Abu-Issa R, de Boer BA, Hutson MR, de Boer PA,
25. Soufan AT, Ruijter JM, Kirby ML, van den Hoff MJ, Moorman AF. A Caudal proliferating growth center contributes to both poles of the Forming heart tube. Circ Res. 2009;104:179 –188.
26. De la Cruz MV, Markwald RR. Living Morphogenesis of the Heart . 1st ed. Boston, Mass: Birkha¨user; 1998.
27. Davis DL, Edwards AV, Juraszek AL, Phelps A, Wessels A, Burch JB.A GATA-6 gene heart-region-specific enhancer provides a novel means To mark and probe a discrete component of the mouse cardiac conduction system. Mech Dev. 2001;108:105–119.
28. Aanhaanen WT, Brons JF, Dominguez JN, Rana MS, Norden J, Airik R, Wakker V, de Gier-de Vries C, Brown NA, Kispert A, Moorman AF, Christoffels VM. The Tbx2 primary myocardium of the atrioventricular canal forms the atrioventricular node and the base of the left Ventricle. Circ Res. 2009;104:1267–1274
29. De Haan RL. Differentiation of the atrioventricular conducting system of The heart. Circulation. 1961;24:458 – 470.20.
30. Moorman AFM, Christoffels VM. Cardiac chamber formation: development, genes and evolution. Physiol Rev. 2003;83:1223–1267.
31. De Jong F, Opthof T, Wilde AA, Janse MJ, Charles R, Lamers WH,Moorman AF. Persisting zones of slow impulse conduction inDeveloping chicken hearts. Circ Res. 1992;71:240 –250.
32. Canale ED, Campbell GR, Smolich JJ, Campbell JH. Cardiac Muscle ,Berlin, Germany: Springer Verlag; 1986
33. O. Aquilina, “”A brief history of cardiac pacing”,” Images Paediatric Cardiolology, vol. 27, pp. 17-81, 2006
34.]. M. JA, “”Electrical stimulation of the heart in man”,” British Medical Journal, vol. 1, no. 1468, pp. 348-50, 1889.
35. . McWilliam, John A. “Electrical stimulation of the heart in man.” British Medical Journal 1.1468 (1889): 348.
36. Ganjehei, Leila, Mehdi Razavi, and Ali Massumi. “Cardiac resynchronization therapy: a decade of experience and the dilemma of Nonresponders.” Texas Heart Institute Journal 38.4 (2011): 358.
37. Steinhaus, Bruce, Albert Dawson, and Richard Lu. “Minute volume rate-responsive pacemaker using dual unipolar leads.” U.S. Patent No. 5,562,712. 8 Oct. 1996.
38. . Markowitz, H. Toby, and Michael F. Hess. “Pacemaker with vasovagal syncope detection and therapy.” U.S. Patent No. 5,501,701. 26 Mar. 1996.
39. S. Ruben, “Zinc-Mercuric Dioxysulfate Dry Cell.,” Journal of The Electrochemical Society, , vol. 106, no. 2, pp. Pp.77-78., 1959. .
40. Bhatia, Dinesh, Sweeti Bairagi, Sanat Goel, and Manoj Jangra “Pacemakers charging using body energy.” Journal of Pharmacy and Bioallied Sciences 2.1 (2010)