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Evaluation of CIED-related Tricuspid Regurgitation in Single-chamber Leadless Pacing vs. Conventional Pacing

A single-center randomized clinical trial

Final Degree Project

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Figure 14: Leadless cardiac pacemaker implantation steps confirmed by fluoroscopy. AP, anteroposterior; RAO, right anterior oblique; LAO, left anterior oblique. (A) A venogram may optionally be performed; (B) The LCP (leadless cardiac pacemaker) is positioned into the RV (right ventricle) by deflecting the catheter and placed ~0.5–1 cm from the RV apex; (C and D) Protective cover is pulled back to expose the flexible part of the catheter; (E) The pacemaker is undocked from the delivery catheter while a tethered connection is maintained. In case the position is suboptimal, the LCP can be reengaged, unscrewed, and repositioned. (F) The LCP is released by rotating the release knob of the catheter.

Figure 15: Flow chart.

Abbreviations

AF: Atrial Fibrillation.

ASE: American Society of Cardiology.

AV: Atrioventricular.

BMI: Body Mass Index.

CIED: Cardiac Implantable Electronic Device.

CRT: Cardiac Resynchronization Therapy.

CT: Computed Tomography.

CW Doppler: Continuous Wavelength Doppler.

CV: Contractile Vena.

EACVI: European Association of Cardiovascular Imaging.

EHRA: European Heart Rhythm Association.

EKG: Electrocardiogram.

EROA: Effective Regurgitant Orifice Area.

ESC: Europeans Society of Cardiology.

EPS: Electrophysiological Studies.

FAC: Fractional Area Change.

HBP: His Bundle Pacing.

HUJT: Hospital Universitari Dr. Josep Tueta.

ICD: Implantable Cardioverter-Defibrillator.

LBBAP: Left Bundle Branch Area Pacing.

LV: Left Ventricle.

LVEF: Left Ventricle Ejection Fraction.

MPI: Myocardial Performance Index.

MRI: Magnetic Resonance Imaging.

PISA: Proximal Isovelocity Surface Area.

PW Doppler: Pulsed Wave Doppler.

RA: Right Atrium.

RVol: Regurgitant Volume.

RV: Right Ventricle.

RVBD: Right Ventricle Basal Diameter.

RVLS: Right Ventricle Longitudinal Strain.

SA: Sinoatrial.

S': Tricuspid Annular Systolic Velocity.

SND: Sinoatrial Node Disease.

TAPSE: Tricuspid Annular Plane Systolic Excursion.

TR: Tricuspid Regurgitation.

TTE: Transthoracic Echocardiography.

TV: Tricuspid Valve.

Abstract

Background

Conventional transvenous pacemaker leads can interfere with TV leaflets, tendinous cords, and papillary muscles, leading to notable TR. Leadless pacemakers are designed to be implanted without transvenous leads, thus are thought to cause less mechanical disruption to the TV apparatus. However, existing data on the impact of leadless pacemaker implantation on TR is limited and inconsistent.

Objectives

To determine whether leadless pacemakers, compared to conventional transvenous pacemakers, reduce CIED-related TR at 12 months post-implantation.

Methods

A randomized clinical trial is designed to compare CIED-related TR evolution between patients receiving a leadless pacemaker versus a conventional pacemaker at HUJT. TR progression, defined as a worsening of at least one severity grade post-implantation, will be analyzed as the main outcome at 12 months post-implantation. Secondary outcomes will include the assessment of RV function and procedure-related complications.

A total of 172 participants will be enrolled in the study through consecutive non-probabilistic sampling, with an equal distribution between the two groups. Participants will be randomly allocated to either the leadless pacemaker group or the conventional pacemaker group. Patients aged 18 years or older with indications for single-chamber pacing will be included, excluding those with pre-existing significant TR, severe RV or LV impairment, or comorbidities that preclude device implantation.

Results

Leadless pacemaker implantation is expected to result in less TV interference compared to conventional pacemakers, which may lead in a reduced incidence of TR. No significant increase in complications is anticipated.

Key Words

Micra; leadless pacemaker; tricuspid valve; tricuspid regurgitation; AV block; echocardiography; valvular heart disease; TAPSE.

Introduction

Fundamentals of Cardiac Pacing

Physiological Principles of Cardiac Electrical Conduction

The cardiac electrical conduction system is a sophisticated network essential for initiating and coordinating the heartbeat. This system ensures the propagation of electrical impulses that trigger synchronized contractions of the heart chambers, enabling efficient blood circulation. It comprises the sinoatrial (SA) node, atrioventricular (AV) node, His-Purkinje system, and the interplay of ionic channels and gap junctions that facilitate the propagation of action potentials (1).

The SA, located in the right atrium (RA) near the superior vena cava, serves as the natural pacemaker of the heart. It autonomously generates rhythmic electrical impulses, initiating atrial contraction (2,3). The AV node, situated in the Koch's triangle within the RA, acts as a relay point. It introduces a deliberate delay in the electrical conduction, allowing adequate ventricular filling before ventricular contraction. This delay is crucial for maintaining an optimal sequence of cardiac chamber contractions (4).

Communication between the SA and AV nodes occurs through specialized conduction pathways in the atrial myocardium. These pathways efficiently transmit electrical impulses from the SA node to the AV node, coordinating cardiac activity. The anterior tract connects the SA node to the AV node and the left atrium, ensuring synchronized depolarization of both atria. The middle tract (Wenckebach's) transmits impulses to the AV node via the interatrial septum, while the posterior tract (Thorel's) provides an additional route for impulse transmission (5).

The His-Purkinje system is critical for ventricular impulse transmission, ensuring synchronized and efficient heart contractions. It includes the His bundle, which originates at the AV node and extends through the interventricular septum, dividing into the right and left bundle branches. The right bundle branch conducts impulses to the right ventricle (RV), while the left bundle branch splits into anterior and posterior fascicles to coordinate left ventricular contraction. Purkinje fibers, branching from these bundles, distribute impulses across the ventricular myocardium, enabling near-simultaneous depolarization of both ventricles for maximal pumping efficiency. The synchronized contraction of the atria and the ventricles is vital for maintaining an

adequate and efficient blood flow from the heart to the systemic and pulmonary circulation (6).

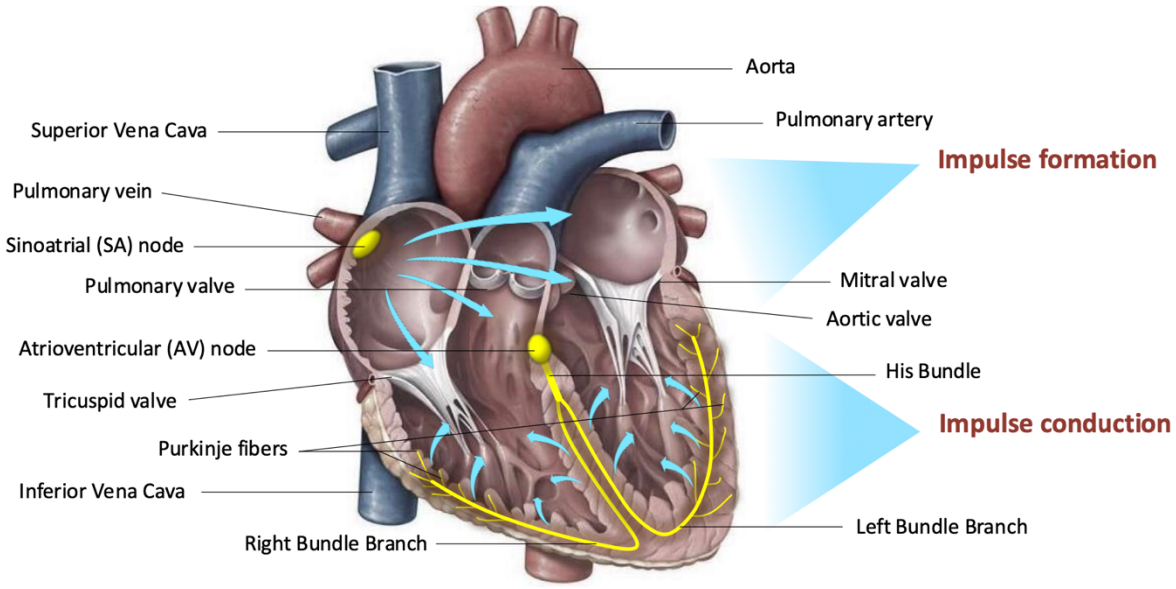

Figure 1: Anatomy of the heart's conduction system, impulse formation and conduction (7).

Cardiac Conduction in Bradyarrhythmia

Cardiac electrical conduction is depicted on an electrocardiogram (EKG) through a series of characteristic waveforms that represent the sequential depolarization and repolarization of the heart's chambers. Standard EKG includes 12 leads, which provide a comprehensive view of the heart's electrical activity from different angles (8,9).

In Sinoatrial Node Disease (SND), the absence of P waves on the EKG signify failed impulse generation or transmission from the SA node to the atria. This often results in irregular or prolonged PP intervals, reflecting pauses in atrial activation.

In Atrioventricular (AV) Blocks, abnormalities in the PR interval translate represent a delay or disruption in the conduction of electrical impulses between atrial depolarization (P wave) and ventricular depolarization (QRS complex). These changes often manifest as a prolonged, progressively lengthening, or completely dissociated PR interval, depending on the degree and type of AV block, reflecting impaired signal transmission through the AV node or surrounding conduction pathways (10).

Definition of Cardiac Pacing

Cardiac pacing is a medical procedure that involves the use of electrical impulses to regulate the heart's rhythm and ensure that it beats at a rate adequate for the patient's

needs. Conventional pacing typically involves the use of a pacemaker to deliver electrical impulses to the RV. Devices have evolved to include more physiologic pacing methods, such as His bundle pacing (HBP) and left bundle branch area pacing (LBBAP), which aim to engage the heart's intrinsic conduction system and preserve ventricular synchrony (11). Temporary pacemakers are used in short-term situations, often in a hospital setting, while permanent pacemakers are implanted for long-term management of chronic heart rhythm disorders (12,13).

The main goal of cardiac pacing is to restore normal heart rhythm at a steady and sufficient rate to meet the body's oxygen and nutrient demands, improving overall heart function and patient quality of life. Additionally, cardiac pacing helps prevent symptoms associated with bradyarrhythmia and conduction disorders, such as syncope, presyncope, exercise intolerance, and even heart failure (10).

Cardiac Pacing for Bradycardia and Conduction Disorders

Sinoatrial Node Dysfunction

Definition: SND, formerly referred to as sick sinus syndrome, encompasses a group of conditions characterized by impaired conduction and propagation of electrical impulses at the SA node. These abnormalities lead to an inadequate atrial rate that fails to meet physiological demands, particularly during stress or physical activity. Although it can occur at any age, it is most commonly observed in older individuals (14). The bradycardia-tachycardia variant is the most prevalent form of SND, primarily caused by age-related degenerative fibrosis of the SA node and atrial myocardium. Bradyarrhythmia in this variant is frequently associated with atrial tachyarrhythmias, such as atrial fibrillation (AF), and may result from sinoatrial blocks causing atrial pauses or from overdrive suppression following an atrial tachyarrhythmia (2).

Etiology: The etiology of SND can be intrinsic or extrinsic. Intrinsic causes include idiopathic degenerative fibrosis, cardiac remodeling, and SCN5A**,** HCN4**,** and MYH6 mutations (15). Extrinsic causes, such as the effects of medications (e.g. beta-blockers, calcium channel blockers class I and III antiarrhythmics) or metabolic disorders (mainly hypothyroidism and electrolyte imbalances), are often reversible (10).

Symptoms: patients with SND may present symptoms resulting from bradyarrhythmia, with concomitant atrial tachyarrhythmias in the context of bradycardia-tachycardia syndrome.

Symptoms either manifest at rest, following the termination of a tachyarrhythmia (conversion pause or pre-automaticity pause), or during physical activity. These symptoms range from mild fatigue, lightheadedness and dizziness to more severe presentations such as presyncope or syncope. Dyspnea during exercise is frequently associated with chronotropic incompetence. Syncope is a prevalent clinical feature of SND, occurring in approximately 50% of patients who ultimately require pacemaker implantation (16).

Diagnosis: the diagnosis of SND relies on a combination of both clinical history and cardiac rhythm documentation. Given the intermittent and often unpredictable nature of SND, this can be challenging. In addition to a detailed medical history, a standard 12-lead EKG, a 24-hour Holter EKG, and an exercise stress test are typically sufficient. If these tests do not clarify the cause of symptoms, external event recorders or continuous-loop implantable cardiac monitors may be considered. For patients experiencing symptoms more than once a month, an external event recorder worn continuously for up to 30 days is usually adequate. A continuous-loop implantable monitor may be used for patients with infrequent and transient symptoms where standard EKG recordings do not provide diagnostic information (17). Multiple EKG abnormalities can be seen in sinus node dysfunction including:

- ◊ Sinus Bradycardia: heart rate <60 bpm originating from the SA node that cannot meet physiological demands, leading to symptoms like fatigue or syncope.
- ◊ Sinus Arrhythmia (Non-Respiratory): irregular sinus node activity not linked to respiratory patterns, common in elderly patients with degenerative sinus node dysfunction.
- ◊ Bradycardia–Tachycardia Syndrome: alternating episodes of bradyarrhythmia (sinus bradycardia or sinus pauses) and atrial tachyarrhythmia (such as AF), typically due to overdrive suppression of the sinus node following a tachyarrhythmia
- ◊ Sinus Arrest and Pause: temporary cessation of SA node activity, leading to pauses of >3 seconds on EKG, potentially causing syncope if escape rhythms fail. If the duration does not exceed 3 seconds, it will be considered as a sinus pause.
- ◊ SA Exit Block: failure of SA impulses to reach the atrium, causing intermittent pauses (missed P waves on EKG).

◊ Atrial Fibrillation with Slow Ventricular Response: AF with a reduced ventricular rate due to suppressed AV node conduction, resulting in fatigue or dizziness.

Additionally, autonomic blockade using propranolol and atropine can help evaluate the intrinsic function of the sinus node by comparing observed heart rates with predicted values (10).

In uncommon situations where the diagnosis remains unclear after initial non-invasive evaluations, invasive electrophysiological studies (EPS) may be an option. These procedures can include assessing the sinus node recovery time and sinoatrial conduction time. However, due to their limited sensitivity and specificity, these techniques are not frequently utilized in routine clinical practice. EPS is not recommended for asymptomatic individuals with sinus bradycardia, as the procedural risks exceed the potential benefits (18).

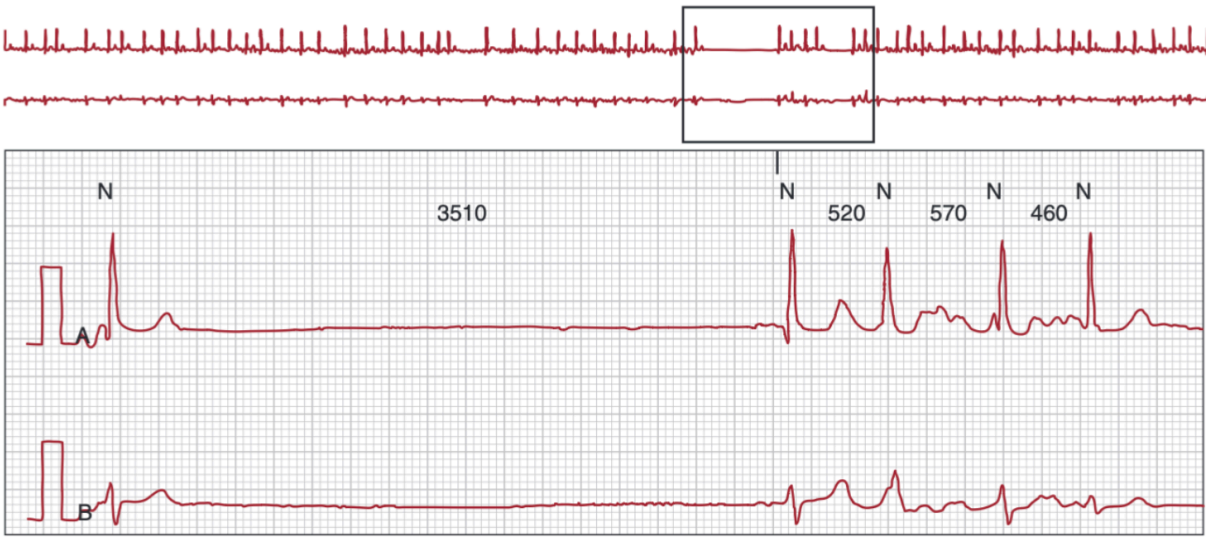

Figure 2: Bradycardia-tachycardia syndrome (17). Atrial fibrillation terminates in the form of a beat and is followed by a pause until the first sinus beat due to a prolonged recovery time of the sinus node.

Treatment: permanent pacemaker implantation is the only effective treatment for symptomatic bradycardia associated to SND (13). In acute situations, temporary treatments such as intravenous atropine (0.5–1 mg IV every 3–5 minutes, up to 3 mg), dopamine (5–20 mcg/kg/min IV), or isoproterenol (20–60 mcg IV bolus, followed by an infusion of 1–20 mcg/min) can be used to manage symptomatic bradycardia. These measures help stabilize the patient until a permanent pacemaker can be implanted (10).

Permanent pacing for SND is only indicated when clinical symptoms directly related to the bradycardia are present. Thus, the decision to proceed with permanent pacemaker

implantation for SND should be based on the presence of symptomatic bradycardia or related symptoms, such as fatigue, dizziness, syncope, or exercise intolerance. Pacing for asymptomatic SND has not demonstrated any impact on long-term prognosis, unlike pacing for atrioventricular block, where intervention is known to significantly improve outcomes (16).

Atrioventricular Block

Definition: AV block is a disorder in the electrical conduction system where impulses are not properly transmitted from the atria to the ventricles. This disrupts the synchronization between atrial and ventricular contractions, potentially compromising the efficiency of the heart's pumping function and, in some cases, affecting adequate blood perfusion (10).

Etiology: AV block can be either congenital or acquired (19).

Congenital AV block, which occurs in approximately 1 in every 15,000 to 20,000 births, can be diagnosed through fetal echocardiography and confirmed postnatally with an EKG. This type of block is often associated with maternal anti-SSA/Ro-SSB/La antibodies that cross the placenta, damaging the fetus's conduction system (20).

Acquired AV block can result from various conditions, including structural heart diseases (e.g. dilated cardiomyopathy, valve disorders or ischemic heart disease), infections (e.g. endocarditis, Lyme disease), autoimmune disorders (e.g. Systemic Lupus Erythematosus, rheumatoid arthritis or Sjögren's syndrome), and side effects of medications (e.g. beta-blockers, calcium channel blockers, digoxin, amiodarone) (19).

The most common causes of acquired AV block in clinical practice are degenerative changes, often associated with aging, chronic hypertension, and diabetes mellitus. These conditions contribute to fibrosis and calcification within the conduction system, particularly in the AV node and His-Purkinje fibers, leading to impaired electrical signal transmission (10).

Classification:

- First-degree AV block: characterized by a prolonged PR interval of >200ms with a 1:1 conduction (for each atrial beat, there is a corresponding ventricular beat), representing a delay rather than an actual block.

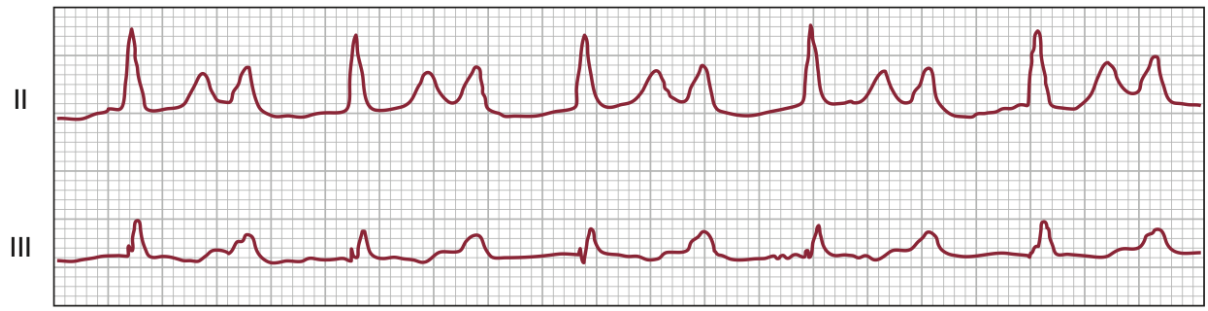

Figure 3: First-degree AV block (17).

◊ Second-degree AV block:

♦ Mobitz Type I (Wenckebach): PR interval progressively lengthens until an atrial impulse fails to conduct to the ventricles. The pattern is usually regularly irregular, where after the dropped beat, the cycle repeats.

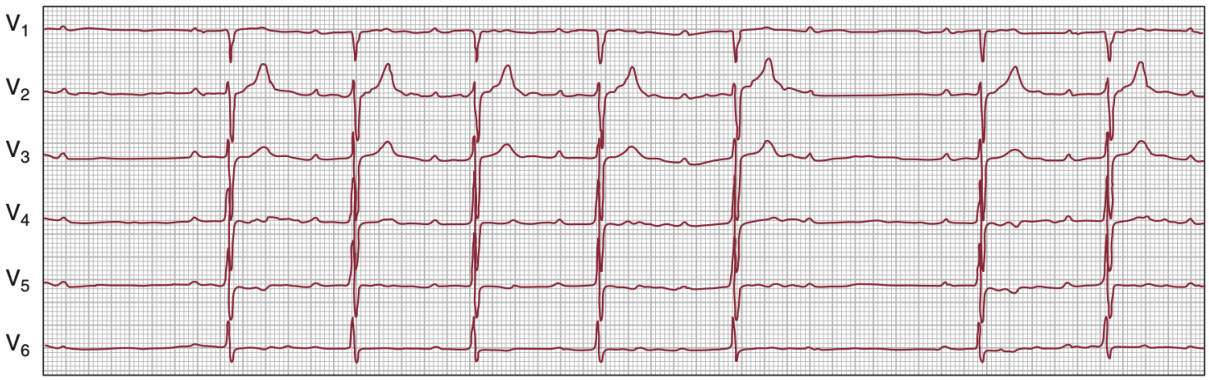

Figure 4: Mobitz type I (Wenckebach) AV block (17).

♦ Mobitz Type II: PR interval remains constant for all conducted beats, but occasionally, the atrial impulse is completely blocked, resulting in a dropped QRS complex without any prior change in the PR interval. These dropped beats are associated with a wide QRS complex.

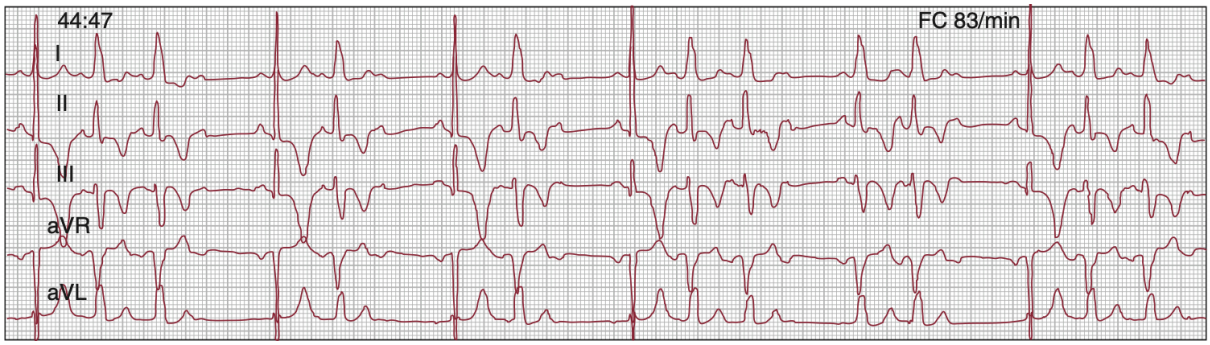

Figure 5: Mobitz type II AV block (17).

◊ Third-degree AV block (complete block): total failure of conduction between the atria and ventricles, resulting in a complete dissociation between atrial and

ventricular activity. The atria still generates P waves, but they are not transmitted to the ventricles, which generate their own escape rhythm, typically from the AV node or ventricular tissue.

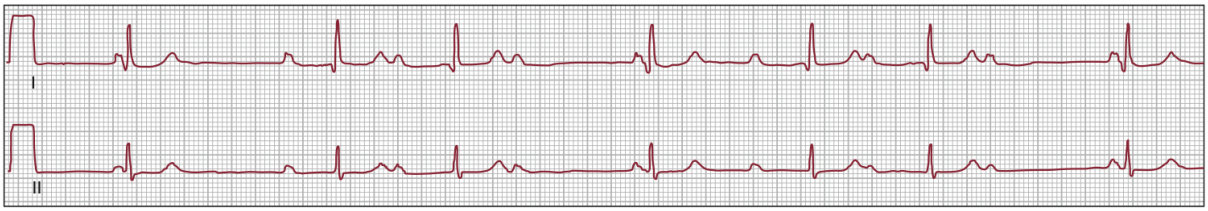

Figure 6: Third-degree AV block (17).

High-grade or advanced AV block occurs when two consecutive P waves are not conducted, often due to intra or infra-Hisian block (10).

AV block can also be classified as transient or permanent. Transient blocks are often reversible and caused by factors such as Lyme disease, acute ischemia, or vagal tone, while permanent blocks are linked to structural abnormalities of the conduction system and will not resolve spontaneously (10,13,21).

Symptoms: symptoms vary depending on the degree of AV block, ventricular frequency, and rate of occurrence (10).

- ◊ First-degree AV block: often asymptomatic. Fatigue or exercise intolerance can occur when the PR interval is prolonged (>300ms), leading to loss of atrioventricular synchrony, reduced cardiac output, and increased pulmonary pressure.
- ◊ Second-degree AV block: Mobitz I can be asymptomatic in healthy individuals. Some patients may experience fatigue, dizziness or exertional intolerance. Mobitz II block is more likely to cause symptoms, including syncope, due to the unpredictable nature of the blocked beats and potential for progression to complete heart block.
- ◊ Third-degree AV block: the complete dissociation between atrial and ventricular contractions leads to severe bradycardia, syncope, fatigue, and heart failure symptoms.

Diagnosis: the diagnosis of AV block can usually be established through non-invasive methods. When the recording is long enough, an EKG typically provides the necessary information to characterize the type and localize the level of the block. In patients with intermittent AV block, Holter EKG monitoring and exercise testing are important to

correlate symptoms with the rhythm (17). These abnormalities are reflected in changes to the PR interval and the pattern of atrial and ventricular activity, indicating a delay or block in the transmission of electrical impulses through the AV node (10).

In specific population, advanced imaging and monitoring techniques may be required for diagnosing AV block. For fetal cases with, echocardiography remains the primary modality, helping to identify mechanical or hemodynamic events that serve as markers for atrial and ventricular depolarization (10).

Screening is done when persistent fetal bradycardia or arrythmia are detected, positive maternal anti-SSA/Ro-SSB/La antibodies or clinical Systemic Lupus Erythematosus or Sjögren's syndrome (22).

The site of the block (nodal, intra-Hisian and infra-Hisian) is clinically important and can be determined through EPS if it's not evident from the EKG and clinical context (10).

Treatment: the management of AV block is based on its degree and the underlying cause. Recommendations are based on the need to prevent sudden cardiac death, manage symptomatic bradycardia, and improve quality of life (16).

- ◊ Third-degree AV Block: pacing is indicated for all patients regardless of symptoms due to the high risk of severe bradycardia, hemodynamic instability, and sudden cardiac death.
- ◊ Advanced Second-degree AV Block: includes high-grade blocks with two or more consecutive non-conducted P waves, warranting implantation even in asymptomatic patients due to the high risk of progression. High-grade block or new bundle-branch block following anterior myocardial infarction also requires pacing progression to complete block (23).
- ◊ Second-degree AV Block: for Mobitz II, pacemaker implantation is recommended even in asymptomatic cases due to the significant risk of progression to complete heart block and the presence of unreliable escape rhythms. For Mobitz I, it is only indicated if symptomatic or if associated with a wide QRS complex, suggesting an infranodal location.
- ◊ First-degree AV Block: pacing is usually not indicated unless the PR interval is extremely prolonged (>300ms) and symptoms such as fatigue or exercise intolerance are present.

- ◊ Congenital Complete AV Block: pacemaker implantation is indicated for symptomatic patients and asymptomatic cases with profound bradycardia, left ventricular dysfunction, or conduction abnormalities like a wide QRS or prolonged QT interval (20).
- ◊ AV Block in Neuromuscular Disorders: associated with progressive conduction disease (such as myotonic dystrophy or Kearns-Sayre syndrome). These cases have a high risk of sudden cardiac death and require pacing (24,25).
- ◊ Vagal-mediated AV block is a paroxysmal form of AV block associated with a slowing of the sinus rhythm. This type of block is generally considered benign and does not typically require pacemaker implantation in asymptomatic patients.

Single-chamber Pacing

Single-chamber ventricular pacing involves the implantation of a pacemaker with a single lead positioned in the right ventricle, passing through the tricuspid valve. Main indications for single-chamber pacing include:

For SND, single-chamber VVI(R) pacing is appropriate in patients with persistent dysfunction and significant comorbidities, with or without chronotropic incompetence, or in paroxysmal dysfunction with significant comorbidities or any reason to avoid a dual-chamber system (e.g. increased procedural risks, lead-related complications or limited venous access). Frail patients may benefit from VVI pacing due to its lower procedural risk compared to DDD pacing, as keeping AV synchrony may not justify additional risks.

In the context of AV block, VVI(R) is used in patients with persistent AV block and SND, along with reasons to avoid dual-chamber pacing, as well as for persistent blocks with AF, since atrial sensing is unnecessary, and avoids the higher complication rates. For persistent AV block without SND, VDD is a feasible option when DDD is not achievable. If significant comorbidities are present, VVI pacing can be a safe alternative. For paroxysmal AV block, VVI and VDD can also be used. When associated with AF, VVI + rate hysteresis is an effective alternative. Patients with advanced age or significant comorbidities may also benefit from single-chamber pacing, as the procedural risks of dual-chamber pacing may outweigh the potential advantages (16).

In patients with these characteristics, leadless pacemakers represent a suitable therapeutic option, as their pacing modes are well-aligned with the clinical needs and limitations of this population.

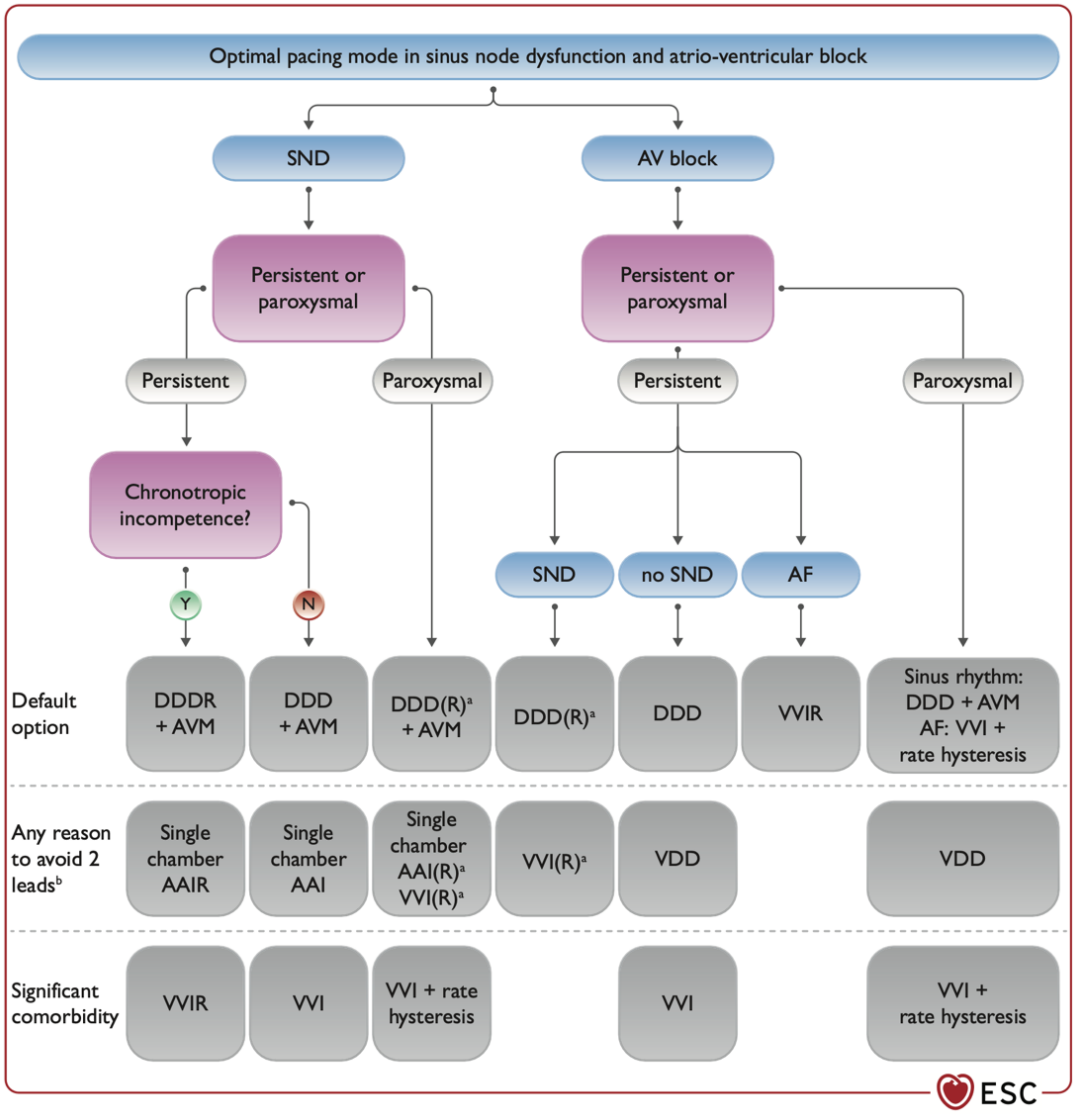

Figure 7: Optimal pacing mode and algorithm selection in sinus node dysfunction and atrioventricular block (16). AF, atrial fibrillation; AV, atrioventricular; AVM, atrioventricular management [i.e. AV delay programming (avoiding values >230 ms) or specific algorithms to avoid/reduce unnecessary ventricular pacing]; CRT, cardiac resynchronization therapy; SND, sinus node dysfunction. [a] (R) indicates that the programming of such a pacing mode is preferred only in the case of chronotropic incompetence. [b] Reasons to avoid two leads include young age and limited venous access. Note: in patients who are candidates for a VVI/VDD pacemaker, a leadless pacemaker may be considered.

Conventional Pacemakers

Design and Function

A conventional transvenous pacemaker consists of two main components: a pulse generator and one or more leads. The pulse generator is a compact, battery-powered device implanted subcutaneously, usually in the infraclavicular region. It houses the battery and electronic circuitry required to produce electrical impulses. The leads are insulated wires that are inserted transvenously into the heart chambers. Their role is to transmit electrical impulses from the pulse generator to the myocardium, thereby

ensuring the heart maintains an appropriate rate and rhythm in response to physiological needs.

Conventional pacemakers offer various programmable parameters, such as pacing modes, rate control, pulse width, output amplitude, sensing thresholds, and refractory periods, to optimize functionality and meet patient-specific needs. Dual-chamber pacemakers provide additional features like adjustable AV delay and algorithms for atrial arrhythmia management, improving chamber synchronization and hemodynamic performance (12).

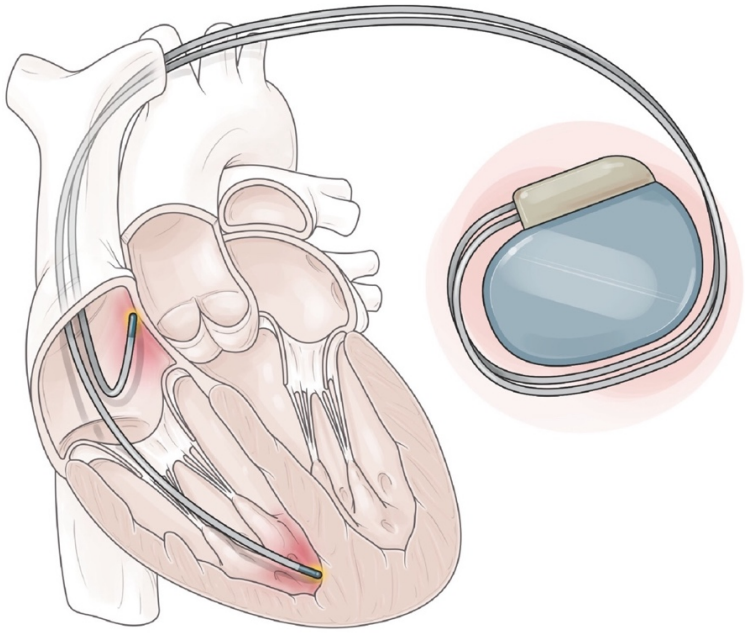

Figure 8: Conventional dual-chamber pacemaker leads positioned in the RA and RV (26).

Implantation Procedure

Standard pacemaker implantation is detailed in *ANNEX 1*. According to the European Heart Rhythm Association (EHRA) consensus statement and practical guide on optimal implantation technique (27):

Preoperative preparation for pacemaker implantation involves confirming the indication, evaluating medical history, and performing tests such as EKG and transthoracic echocardiography. The sterile operative environment requires trained personnel, and local anesthesia is used, with deep sedation or general anesthesia for complex cases.

Venous access is typically through cephalic, axillary, or subclavian veins, with fluoroscopy aiding in safe placement. A chest incision is made to create a pocket for the device, followed by lead placement in the right ventricle and/or atrium. Leads are

secured to prevent dislodgement, and the generator is positioned and tested. Postoperative care includes chest X-rays, EKG, and device checks, with follow-up appointments and remote monitoring to ensure proper function. For generator replacement, preoperative imaging is crucial to assess lead condition and compatibility with new hardware.

This procedure emphasizes minimizing complications, such as infection, hematoma, or lead issues, and tailoring the device settings to the patient's clinical requirements.

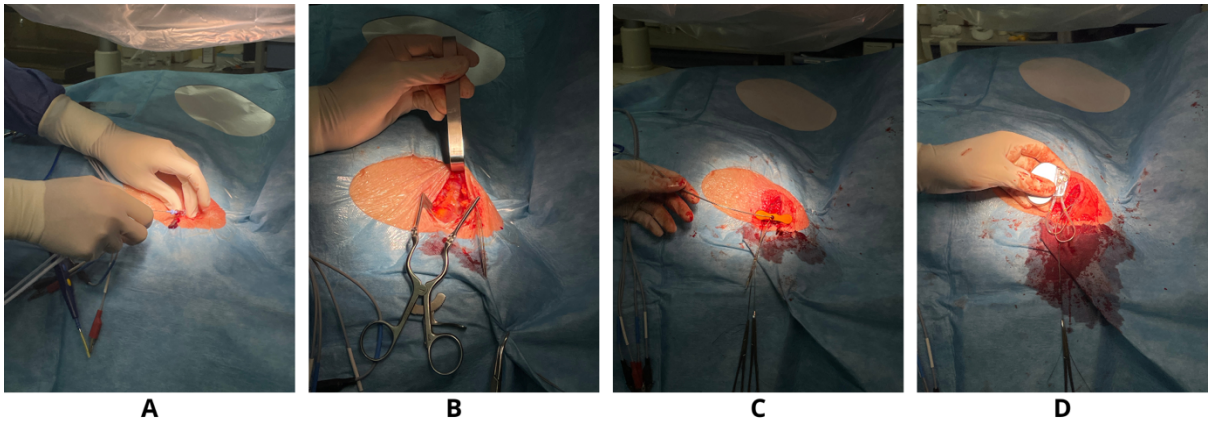

Figure 9: Conventional pacemaker implantation technique (by author). (A) Axillary venous access; (B) Subcutaneous pocket dissection; (C) Lead positioning and testing; (D) Generator and lead connection and placement in pocket.

Potential Complications

Despite their sophistication, conventional pacemakers have inherent limitations. Procedure-related death is rare (0-0.1%), with perioperative mortality mainly due to comorbidities like heart failure.

The EHRA has established a consensus to classify the most common complications related to pacemaker implantation (27).

Perforation, pericarditis and tamponade: lead perforation occurs in 0.09% to 1.5% of cases and can cause pericarditis, pericardial effusion, tamponade, pleural effusion, or lung perforation. It can present acutely (<24 hours) or sub-acutely (<1 month) but can also occur years later. Symptoms include vagal symptoms, chest pain, high capture thresholds, and diaphragmatic capture.

Tamponade, indicated by hemodynamic instability and a non-moving cardiac silhouette on fluoroscopy, requires confirmation by echocardiography and treatment with pericardiocentesis.

Mild pericardial effusion (<10 mm) occurs in 8.3% of patients post-implantation, typically asymptomatic. Moderate and large effusions may require monitoring or pericardiocentesis, especially if there is hemodynamic compromise or recurrence.

Arrhythmias during implantation: audible pulse signals from continuous EKG monitoring help identify arrhythmias during the procedure. Complete AV block can occur due to trauma to the right bundle branch when positioning the right ventricular lead, especially in patients with left bundle branch block. Backup pacing and transcutaneous pacing should be ready as a precaution. It typically resolves within minutes but may persist for hours in some cases. Pre-positioned defibrillation pads are recommended to avoid disruption of the sterile field in case emergency defibrillation or pacing is required.

Pneumothorax during implantation: it occurs in 0.4% to 2.8% of cases, depending on the venous access used (being extra-thoracic safer than intra-thoracic). Risk factors for pneumothorax include age >80, female sex, low BMI, chronic obstructive pulmonary disease, and subclavian vein puncture increase the risk. Cephalic vein cutdown or axillary vein puncture are preferred to reduce this complication.

Suspect pneumothorax if air is aspirated during needle insertion. Fluoroscopy may also reveal large pneumothorax. A routine chest X-ray is recommended within 24 hours for all patients. If suspected, perform an immediate chest X-ray, and repeat after several hours or the next day. A CT scan may be needed if X-ray is inconclusive. Small apical pneumothorax may resolve with conservative management. However, in most cases a chest tube is required.

Pocket hematoma: the incidence of pocket hematoma ranges from 0.2% to 16.0%, depending on the definition and factors like anticoagulation. It increases the risk of infection by approximately nine times. Conservative management is preferred due to the 15-fold increased infection risk with reintervention. Surgical revision is necessary if there is wound dehiscence, skin erosion, severe pain, or arm swelling. Needle aspiration is contraindicated as it can cause incomplete evacuation and infection.

Prevention of hematoma involves optimal perioperative management of anticoagulation and antiplatelet drugs, along with good surgical technique and hemostasis. Hemostatic sutures can be placed at venous entry sites, and compression techniques, like sandbags or tapes, can help prevent hematoma. The use of suction drains is controversial due to infection risks, and there is limited evidence supporting hemostatic agents.

Lead displacement: lead displacement occurs in 1.2–3.3% of implantations, with a higher incidence for atrial leads compared to right ventricular leads. Active fixation leads tend to have fewer dislodgements than passive leads. Diagnosis is typically confirmed by chest X-ray after abnormal electrical testing, though micro-dislodgements may not be visible. Revision is usually required, but if the lead function is unaffected and there are no adverse effects like arrhythmias or lead chatter, repositioning may be unnecessary. If repositioning is needed, it is often deferred for a few weeks to minimize pain and infection risk.

Others: inadvertent arterial puncture can be identified by pulsatile flow or bright red blood and treated with compression or surgical revision. Air embolism, potentially lethal, can be prevented by blocking the sheath and introducing the lead during a breath-hold, with fluoroscopy showing air in the RV. Pneumopericardium from lead perforation may require CT for diagnosis and resolves with pneumothorax drainage. Acute deep vein thrombosis may occur after implantation, resolving with heparin and oral anticoagulation.

Tricuspid Regurgitation in Cardiac Pacing

Etiopathogenesis

Right ventricular pacing is implicated in the development and progression of tricuspid regurgitation (TR) due to several factors. The mechanisms of lead-related TR can be classified into three categories: implantation-related, pacing-related, and device-related (28).

- **Implantation-related:** leads can interfere with the tricuspid valve (TV) apparatus by impinging on or adhering to the valve leaflets, affecting the subvalvular apparatus, or even causing perforation or laceration of the leaflets. The angle at which leads are placed and the number of leads can influence the risk of developing TR. Certain lead placement locations, such as apical, have been found to more commonly cause impingement of the posterior leaflet. 3D echocardiography has been helpful in guiding placement to avoid leaflet impingement.
- **Device-related:** in addition, the presence of the lead can cause fibrosis and scarring of the TV apparatus, which can restrict leaflet motion and contribute to regurgitation. Lead extraction can also lead to leaflet avulsion. Endocarditis can

result in leaflet perforation, destruction, or formation of vegetations that impair valve function. Infected leads and the presence of vegetations can also cause mechanical interference with the TV, exacerbating TR by further impairing leaflet coaptation.

◊ **Pacing-related:** pacing-induced electrical desynchrony can contribute to TR by causing asynchronous contraction of the RV, which negatively impacts valvular function.

Other factors like permanent AF, pulmonary hypertension, right ventricular dilation, and previous cardiac surgery contribute to the worsening of TR and must be carefully managed to prevent further complications (28). Risk factors for developing lead-related TR include older age, female sex, lead location (apical pacing has shown more TV interference (29)), number of leads, preexisting ventricular dilation, AF and previous cardiac surgery (30,31).

Timing of TR progression can vary depending on its underlying mechanism. Acute changes in TR may occur soon after implantation, due to mechanical leaflet restriction or injury. However, exacerbation of TR typically occurs between 1 and 12 months after implantation, with heart failure and hospitalizations often occurring after 12 months (28).

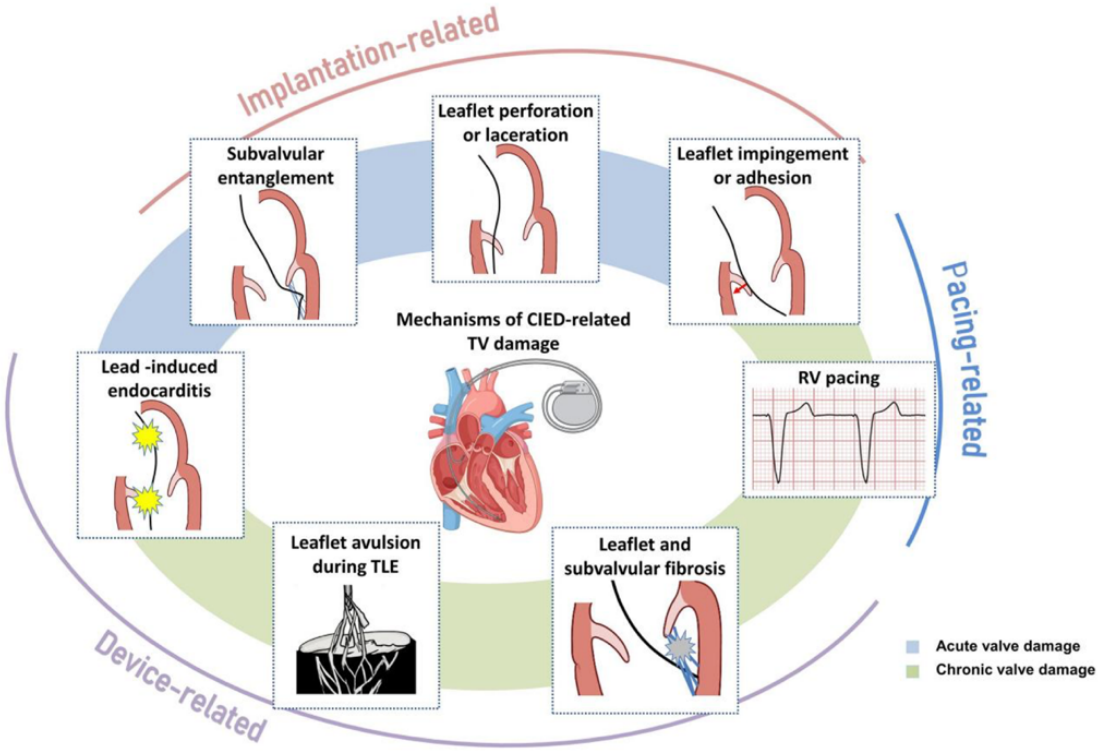

Figure 10: Mechanisms of cardiac implantable electronic device-related tricuspid regurgitation (28). CIED, cardiac implantable electronic device; RV, right ventricle; TLE, transvenous lead extraction; TV, tricuspid valve.

Epidemiology

TV disease, primarily TR is the most common right-sided valvular heart condition. Physiological trace to mild TR is often normal. For years, moderate or severe TR was considered benign and under-treated, however, recent studies have shown that moderate and severe TR are independent predictors of mortality, especially in patients with significant left-sided valve disease and left ventricular dysfunction (32).

Clinically significant TR is more prevalent in women and increases with age. Overall, TR prevalence is 0.55%, with 0.47% in men and 0.59% in women. Given the aging population, the burden of TR is expected to rise globally. Primary or organic TR accounts for 10% of cases, with causes like Ebstein's anomaly, rheumatic disease, and trauma. Secondary or functional TR is more common and linked to conditions like pulmonary hypertension and heart failure (33).

The prevalence of moderate to severe TR following Cardiovascular Implantable Electronic Device (CIED) implantation has been reported. A meta-analysis with 8,144 patients reported a 25.1% incidence of at least one grade worsening of TR after the implantation (34). Another meta-analysis of 66,590 participants also found that 24% experienced at least one grade worsening of TR after device implantation (35). A study with 458 patients reported a 20% incidence of moderate to severe TR during a median follow-up of 2.1 years (36).

Regarding leadless pacemakers, a single-center observational study, including 69 patients who received Micra™ device between May 2016 and May 2021, showed 6 patients (9%) had new significant TR during a 11.4 month follow-up, and 7 patients (10%) experienced TR improvement. Systematic review of 7 studies found no significant change in TR severity before and after leadless pacemaker implantation (37).

Beurskens et al (38) compared echocardiographic changes before and after implantation of leadless pacemakers and dual-chamber DDD. An unexpected 43% showed TR progression after leadless pacemaker implantation, similar to DDD pacemaker patients.

Limited and conflicting evidence from small, non-randomized studies underscores the need for a detailed analysis of factors associated with TR progression in leadless pacing.

Clinical Manifestations

Symptoms of TR include fatigue, peripheral edema, ascites, and hepatic congestion, indicating elevated systemic venous pressures due to impaired forward flow. Elevated central venous pressure is often seen as jugular venous distension and a positive hepatojugular reflux, reflecting increased pressure on the RA and venous system. Dyspnea on exertion also results from increased volume load on the RA and ventricle, reducing cardiac efficiency during physical activity (39).

Diagnosis

The diagnosis of TR by echocardiography is performed through diverse imaging techniques and hemodynamic parameters. A comprehensive evaluation includes 2D and 3D echocardiography, along with color Doppler, continuous wave Doppler (CW), and pulsed wave Doppler (PW), to accurately assess the severity and pathophysiology of TR (40,41):

- ◊ **Central Jet:** evaluates the extent of the regurgitant jet in the RA using color Doppler imaging. A larger jet area typically correlates with more severe tricuspid regurgitation. This measurement is usually obtained in apical four-chamber or subcostal views and provides a quick, visual estimate of the severity of the regurgitation.
- ◊ **Contractile Vena (CV) width:** measures the narrowest diameter of the regurgitant jet, just beyond the tricuspid valve, in the apical four-chamber or parasternal RV inflow views.
- ◊ **Contractile Vena (CV) area in 3D:** utilizes three-dimensional echocardiography to measure the CV area, providing a more accurate assessment than 2D CV methods.
- ◊ **Proximal Isovelocity Surface Area (PISA) radius:** the radius of the hemispherical flow surface proximal to the regurgitant orifice. Using Doppler imaging, this method provides an indirect quantification of regurgitation severity, as a larger PISA radius suggests more significant regurgitation. Measurements are typically taken during mid-systole.
- ◊ **Effective Regurgitant Orifice Area (EROA):** calculates the area of the orifice through which regurgitation occurs. This parameter is derived using Doppler principles and the PISA method. It is one of the most reliable quantitative metrics to assess the severity of tricuspid regurgitation.

- ◊ **Regurgitant Volume (RVol):** measures the volume of blood returning to the RA per heartbeat. It is calculated by combining the EROA with the velocity-time integral (VTI) of the regurgitant jet. Expressed in milliliters per beat, it provides a direct estimate of the regurgitant burden on the heart.
- ◊ **CW Doppler velocity waveform and density:** to analyze the shape and density of the CW Doppler velocity waveform. Dense, triangular waveforms often indicate more severe regurgitation, while the waveform shape can give additional insights into the pressure gradients and flow characteristics across the tricuspid valve.
- ◊ **Hepatic vein flow:** with abdominal Doppler imaging to detect changes in blood flow patterns within the hepatic veins. The presence of systolic flow reversal during systole, is a strong indicator of severe tricuspid regurgitation and reflects the impact of regurgitation on systemic venous return.

Functional cardiac CT and MRI play key roles in assessing lead-related TR. CT with high temporal resolution helps identify the mechanism of TR, assess lead–leaflet interaction, and evaluate tricuspid annulus and vascular access routes, aiding in planning for transcatheter interventions or transvenous lead extraction. MRI, safe for both conditional and non-conditional devices, is used to evaluate ventricular size, function, myocardial fibrosis, and TR severity, especially when echocardiographic assessment is inconclusive. Both imaging modalities help in the planning of interventions and anticipating complications, although artifacts from the pacing device may complicate the analysis (28). Besides, they are more invasive and expensive, making them less accessible for routine monitoring.

Stages

A. **At Risk of TR:** includes patients with risk factors for developing TR, such as the presence of a CIED lead, without current evidence of TR. Echocardiography shows normal tricuspid valve hemodynamics.
B. **Progressive TR:** include patients with mild to moderate TR with no hemodynamic nor clinical consequences. Central jet <50% of the RA, VC width <0.7 cm, EROA <0.40 cm^2, and RVol <45 ml.
C. **Asymptomatic Severe TR:** the hemodynamic consequences include RA and RV dilation, elevated atrial pressure with a "c-V" wave, and increased venous pressure, but without clinical symptoms. Central jet ≥50% of the RA, VC width

≥0.7 cm, EROA ≥0.40 cm^2, RVol ≥45 mL, dense continuous wave Doppler signal with a triangular shape, and systolic flow reversal in the hepatic veins.

D. **Symptomatic Severe TR:** exhibits the same valve hemodynamics and consequences as C-stage TR but with clinical symptoms including exertional dyspnea, fatigue, ascites, and edema (39).

Stage	Definition	Valve Hemodynamics	Hemodynamic Consequences	Clinical Symptoms and Presentation
B	Progressive TR	■ Central jet <50% RA ■ Vena contracta width <0.7 cm ■ ERO <0.40 cm^2 ■ Regurgitant volume <45 mL	■ None	■ None
C	Asymptomatic severe TR	■ Central jet ≥50% RA ■ Vena contracta width ≥0.7 cm ■ ERO ≥0.40 cm^2 ■ Regurgitant volume ≥45 mL ■ Dense continuous wave signal with triangular shape ■ Hepatic vein systolic flow reversal	■ Dilated RV and RA ■ Elevated RA with "c-V" wave	■ Elevated venous pressure ■ No symptoms
D	Symptomatic severe TR	■ Central jet ≥50% RA ■ Vena contracta width ≥0.7 cm ■ ERO ≥0.40 cm^2 ■ Regurgitant volume ≥45 mL ■ Dense continuous wave signal with triangular shape ■ Hepatic vein systolic flow reversal	■ Dilated RV and RA ■ Elevated RA with "c-V" wave	■ Elevated venous pressure ■ Dyspnea on exertion, fatigue, ascites, edema

Figure 11: Stages and diagnosis of tricuspid regurgitation (39). c-V wave indicates systolic positive wave; ERO, effective regurgitant orifice; RA, right atrial; RV, right ventricular; and TR, tricuspid regurgitation.

Treatment

Every patient with conventional pacing devices are at higher risk for TR and require regular echocardiographic monitoring. Early referral to an expert center is crucial for treatment. Surgery and transcatheter therapies can help prevent irreversible damage and improve quality of life and prognosis (28).

The treatment of CIED-related TR follows an algorithm based on the severity of regurgitation and the patient's clinical condition. Initial evaluation should include thorough echocardiography to assess the regurgitation severity and electrode interaction with the TV. It is recommended to consider surgical intervention in patients with symptomatic severe tricuspid insufficiency before significant right ventricular dysfunction or end-organ damage develops (39,42).

Medical management: in mild to moderate cases, medical management with loop diuretics is effective for controlling symptoms of systemic venous congestion. Loop diuretics, such as furosemide, are typically the first-line treatment due to their potent diuretic effect. Aldosterone antagonists (spironolactone or eplerenone) also manage

fluid retention and improve outcomes. In cases of refractory edema, thiazide diuretics can be added as a second-line treatment (39).

Although diuretics help manage right heart failure symptoms, they cannot reverse disease progression. Current guidelines recommend that, in the absence of severe right ventricular dysfunction or pulmonary hypertension, these treatments should not delay referral for surgery or transcatheter interventions (28).

Transvenous lead extraction: there are no specific guidelines on its use for significant TR, a risk–benefit analysis by an interdisciplinary Heart Team is essential to assess whether lead extraction could improve or worsen TR, considering the risks of lead jailing and potential valve damage. TR mechanism must be carefully evaluated using echocardiography to confirm a lead-related cause. Studies show limited success, with only a minority of patients experiencing TR improvement, and complications such as acute TR worsening may occur (28).

Surgical management: if electrode extraction is not feasible or does not sufficiently mitigate TR, valve repair or replacement may be indicated. Repair strategies include annuloplasty and leaflet reconstruction, while valve replacement involve either a biological or mechanical prosthesis. Although isolated tricuspid valve surgery has been associated with high early mortality rates, recent evidence focusing on pre-operative optimization and patient selection has led to improved outcomes, especially when surgery is performed early. If the lead interferes with valve function, repositioning or removal may be necessary. For complex cases, coronary sinus pacing may be considered to avoid issues with trans-prosthetic leads (28).

Transcatheter interventions: in patients with high surgical risk, transcatheter interventions, such as edge-to-edge repair, annuloplasty or transcatheter valve replacement, are emerging as viable alternatives (28).

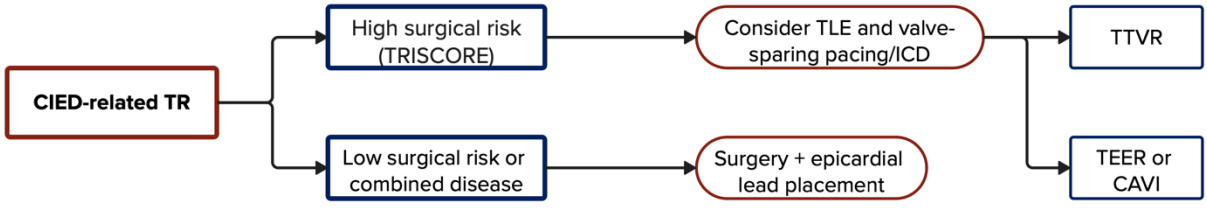

Figure 12: Treatment algorithm of CIED-related TR (adaptation from (28)). CAVI, caval valve implantation; ICD, implantable cardioverter defibrillator; TEER, transcatheter edge-to-edge repair; TLE, transvenous lead extraction; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve replacement.

Leadless Pacemakers

Design and Function

Leadless pacemakers are self-contained devices designed to provide single-chamber pacing without the need for transvenous leads or a subcutaneous pocket. They integrate the pulse generator and pacing electrodes into a single compact unit, and use fixation mechanisms like a helical screw or self-expanding nitinol tines to securely anchor into the ventricular wall (43). These devices are designed to provide VVI stimulation in patients requiring single-chamber pacing.

Clinical studies have demonstrated their efficacy, showing high implantation success rates while meeting required pacing and sensing thresholds (44).

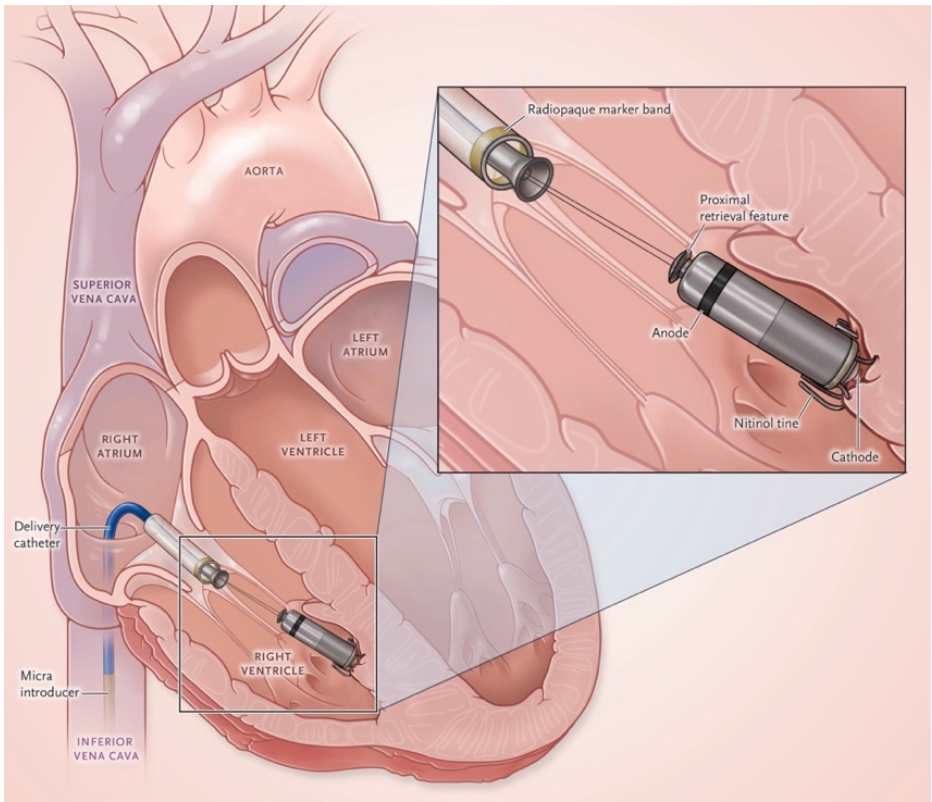

Figure 13: Micra™ transcatheter leadless pacemaker positioned in the right ventricle (45).

Furthermore, leadless pacemakers reduce complications associated with traditional systems, such as infections and lead dislodgment, by removing the need for transvenous leads and subcutaneous pockets. This makes them a safer and more efficient alternative for eligible patients (46).

Performance of leadless pacemakers has been evaluated for both Medtronic® and Abbott® devices. These devices have undergone clinical trials demonstrating their

efficacy and safety, with high success rates for implantation and reliable pacing and sensing thresholds (45).

Second-generation leadless pacing technology, like Micra™ AV2, incorporates AV synchronization through the detection of atrial contractions via an accelerometer. Operating in VDD mode, it facilitates AV synchrony in patients with complete AV block and intrinsic sinus rhythm. Synchrony is achieved by an algorithm that identifies mechanical atrial signals, enhancing patient quality of life and reducing the occurrence of pacemaker syndrome. This advancement addresses the limitations of earlier models, providing a more physiologically appropriate pacing solution and improving clinical outcomes for patients with AV conduction disturbances (47).

Dual-chamber leadless stimulation, such as Aveir™ DR system, consists of two separate devices implanted in the right atrium and right ventricle, and has shown promising results in maintaining AV synchrony and providing dual-chamber (DDD) pacing. Thus, it offers a more natural heart rhythm regulation and helps prevent issues like AF and ventricular desynchrony that can arise with single-chamber pacemakers (48).

Indications

Single-chamber leadless pacemakers are suitable for patients requiring single-chamber ventricular pacing (VVI) or ventricular pacing with atrial sensing (VDD). They are recommended for patients with obstruction of the venous route used for standard pacemaker implantation (e.g. bilateral venous thoracic outlet syndrome or chronic superior vena cava obstruction), issues with the pocket placement (such as in cachexia or dementia), or increased infection risk (e.g. patients on dialysis or history of CIED infection).

Dual-chamber leadless pacemakers operate in DDD stimulation mode, broadening their indication to symptomatic bradycardia caused by SND or high-degree AV block where preserving AV synchrony provides significant clinical benefits.

Contraindications mainly include active systemic infection, known allergy to the materials, presence of an occluded Inferior Vena Cava (IVC) or IVC filters, severe iliac or femoral venous anatomical abnormalities that might preclude RV device positioning, high risk of device dislodgement (severe ventricular dilation or hypertrophy and other ventricular anatomical abnormalities) and life expectancy less than 1 year (16,49,50).

Implantation Procedure

Standard implantation technique is detailed in *ANNEX 2*. Leadless pacemaker implantation is a minimally invasive procedure. Unlike traditional pacemakers, leadless devices are directly implanted into the myocardium of the right ventricle.

The procedure is performed by accessing the femoral vein under local anesthesia with an introducer sheath and advancing a delivery catheter through the IVC into the RV, eliminating the need for subcutaneous pockets. The pacemaker is positioned and secured using specific fixation mechanisms. Electrical parameters, including thresholds and sensing, are tested to confirm proper function. Once verified, the delivery system is removed, and the access site is closed to ensure hemostasis (51). Septal implantation generally results in lower complication rates and similar long-term electrical performance. Non-septal (apical) sites may provide better immediate electrical parameters, though these benefits diminish over time. The choice of implantation site depends on the patient's anatomy and the need for optimal electrical performance (52).

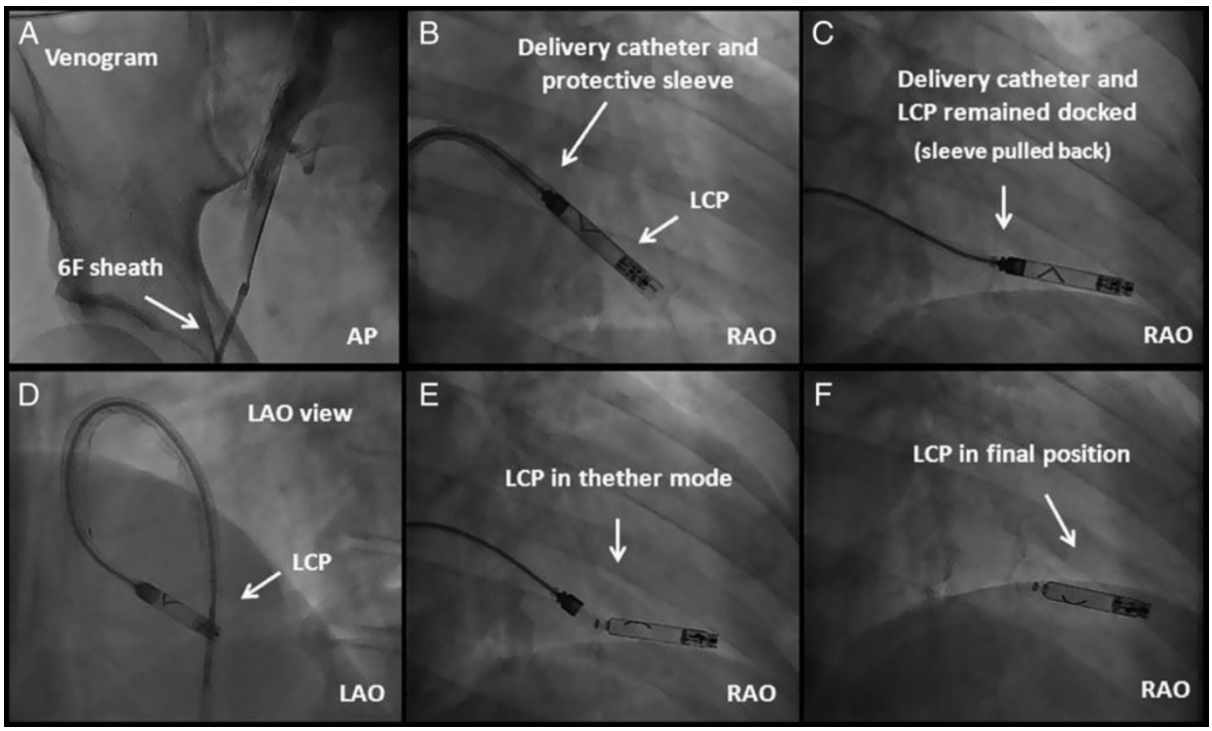

Figure 14: Leadless cardiac pacemaker implantation steps confirmed by fluoroscopy (47). AP, anteroposterior; RAO, right anterior oblique; LAO, left anterior oblique. (A) A venogram may optionally be performed; (B) The LCP (leadless cardiac pacemaker) is positioned into the RV (right ventricle) by deflecting the catheter and placed ~0.5–1 cm from the RV apex; (C and D) Protective cover is pulled back to expose the flexible part of the catheter; (E) The pacemaker is undocked from the delivery catheter while a tethered connection is maintained. In case the position is suboptimal, the LCP can be reengaged, unscrewed, and repositioned. (F) The LCP is released by rotating the release knob of the catheter.

Potential Complications

Overall complication rate is low, highlighting the safety and effectiveness of these devices in clinical practice. Leadless pacemakers have a low infection risk due to the absence of infection-prone components like subdermal pockets and leads. However, early operator experience revealed a higher rate of peri-operative complications, including perforation, tamponade, vascular issues, arrhythmias, and death. Adequate training, accreditation, and well-equipped facilities with on-site cardiac surgery are crucial for safe leadless pacemaker implantation (16).

Perforation, Pericarditis and Tamponade: cardiac perforation can lead to tamponade, a serious complication requiring emergency intervention. The incidence is low but significant, with reported rates up to 1.3%. Symptoms include hypotension, tachycardia, jugular venous distention, and muffled heart sounds (Beck's triad). Cardiac perforation during leadless pacemaker implantation is more likely to require intervention than perforation by a transvenous lead. Treatment involves pericardiocentesis, and in severe cases, surgical intervention (53).

Device Displacement: although rare, device displacement can occur, potentially requiring removal and reimplantation of the pacemaker. The incidence of displacement is approximately 0.13%. This issue is typically addressed by careful implantation techniques and, if necessary, corrective interventions to ensure proper positioning of the device (54).

Vascular Complications: implantation requires a 27 French introducer sheath. Femoral access site complications, including hematomas and pseudoaneurysms, occur in around 2.3% of cases. Conservative measures like compression or aspiration are indicated for hematomas. Pseudoaneurysms may require further intervention, such as embolization or surgical repair (55).

Infection: less common with leadless pacemakers compared to traditional pacemakers, due to the absence of transvenous leads and subcutaneous pockets. Infections are reported at very low rates, around 0.13%. Management typically includes antibiotic therapy, and in severe cases, device removal and replacement may be necessary (54).

Elevated Pacing Threshold: symptoms include failure to capture, which may present as a slow or irregular heart rate. Device replacement may be required due to elevated pacing thresholds, occurring in approximately 1.3% of patients (44).

Justification

The implantation of CIEDs risen significantly, with over 3.8 pacemakers, 2.2 ICDs, and 1.8 CRT devices implanted annually per million in Europe (28).

Conventional transvenous pacemakers have long been the standard treatment for patients with advanced atrioventricular block or symptomatic sinus node dysfunction. However, this approach is associated with both short-term and long-term complications, all of which contribute to increased morbidity and the need for reinterventions (10,56–58).

Leadless pacing removes the need for transvenous leads and subcutaneous pockets, significantly reducing related complications. Comparative studies show that patients with leadless pacemakers have 32% fewer chronic complications and 41% fewer reinterventions than those with traditional transvenous pacemakers. They also report a lower hospitalization rates, with infection rates under 0.2%, and stable electrical function parameters (59). Additionally, leadless pacemakers improve patients' quality of life, with lower device-related discomfort and physical restrictions (60).

Despite these benefits, concerns remain regarding the impact of leadless pacemakers on tricuspid regurgitation. Conventional ventricular pacing has long been associated with TR due to mechanical interference between leads and the valvular apparatus, and pacing-induced ventricular remodeling. Still, the impact of leadless pacemakers on tricuspid regurgitation remains unclear (28).

Early studies on leadless pacemakers suggest that the absence of pacing leads may reduce the mechanical interference with the tricuspid valve, potentially lowering the risk of valve disease. Yet, publications have reported comparable or even unexpected increases of TR in patients receiving leadless pacemakers, presumably linked to interference with subvalvular apparatus (38,61).

CIED-related TR is increasingly being recognized as a significant clinical issue, linked to higher heart failure and mortality risks. Meta-analysis highlight that TR is a key prognostic factor linked to higher mortality and worse clinical outcomes, including organ damage like liver and kidney failure, which significantly impact survival (39,62). Inconsistent data from small, non-randomized observational studies underscore the need for a comprehensive analysis of TR worsening after leadless pacemaker implantation.

Hypothesis and Objectives

Hypothesis

Main Hypothesis

Leadless pacemakers reduce CIED-related TR compared to conventional pacemakers in patients requiring single-chamber pacing.

Secondary Hypothesis

- ◊ Leadless pacemakers minimize deterioration of RV function compared to conventional pacemakers.
- ◊ Leadless pacemaker implantation leads to fewer device-related complications compared to conventional pacemaker implantation.

Objectives

Main Objective

To determine whether the implantation of leadless pacemakers, compared to conventional transvenous pacemakers, is associated with a reduced worsening of CIED-related TR at 12 months.

Secondary Objectives

To assess if leadless pacemaker implantation, compared to conventional pacemaker implantation, is associated with other secondary outcomes:

- ◊ Minimized deterioration of RV function.
- ◊ Reduction in acute and chronic device-related complications, including pneumothorax, pericarditis, perforation, hematoma, lead or device dislodgement, infection or others (e.g. deep vein thrombosis, pneumopericardium, device erosion, etc.).

Methodology

Study Design

This single-center, prospective, randomized clinical trial will compare clinical outcomes of leadless and conventional pacemakers, assessing CIED-related TR, RV function parameters and complications at a 12 month post-implantation endpoint.

Study Population

Study population will include patients with symptomatic bradycardia and indication for single-chamber cardiac pacing. We will enroll patients who meet class I or II guideline-based indications for right ventricular single-chamber pacing (10). Recruitment will take place at HUJT, with a comprehensive screening process to ensure participants meet the inclusion and exclusion criteria.

Inclusion Criteria

- ◊ Patients aged ≥18 years with class I or II indication for single-chamber pacemaker implantation.
- ◊ Individuals capable of understanding and providing informed consent for the study protocol.
- ◊ Patients with an expected life expectancy of more than 12 months.

Exclusion Criteria

- ◊ Previous severe (stage C or D) TV disease.
- ◊ Evidence of severe RV and/or LV dysfunction.
- ◊ Mechanical TV, implanted IVC filter or LV assist device.
- ◊ Existing prior pacemaker, abandoned leads, ICD or CRT device.
- ◊ Venous access unable to accommodate the introducer sheath or implant the device on the RV.
- ◊ Known allergy to Nitinol alloy or other required components.
- ◊ Pregnant or breastfeeding women.

Withdrawal Criteria

- ◊ Unanticipated adverse effects or severe complications related to the procedure.
- ◊ Inability to comply with study follow-up requirements.

Sample Selection

Sample selection will be done through consecutive non-probabilistic sampling. Eligible patients will be selected based on inclusion and exclusion criteria, and then randomly assigned to the leadless or conventional pacemaker groups.

Participants will receive an informative document *(ANNEX 3)* outlining the study details. An informed consent form *(ANNEX 4)* must be signed in order participate. Participants will have the right to withdraw their consent at any point during the study *(ANNEX 5)*.

Sample Size

Sample size was estimated using GRANMO software, based on the prevalence of at least one grade worsening of TR following conventional pacemaker implantation being 25.1% (34), and an estimated 9% after leadless pacemaker implantation (37).

Accepting an alpha risk of 0.05 and a power of 0.8 in a two-tailed test, a total of **86 subjects** per group is required to detect a statistically significant difference in the progression of TR. This calculation results in **172 participants** overall, accounting for an anticipated 5% dropout rate.

Study Variables

Independent Variable

The independent variable of this study will be the implantation of a **Leadless Pacemaker** or **Conventional Pacemaker.** It is described as a qualitative dichotomous variable.

Dependent Variables

Further details regarding dependent variables are provided in the Data Collection section.

Main variable: **Tricuspid Regurgitation (TR)** after the implantation of the pacing device, evaluated via transthoracic echocardiography (TTE) at 12 months post-implantation, and expressed as a qualitative dichotomous variable defined as “Yes” or “No”.

It will be described as a **worsening of at least one grade of severity** after the implantation of the pacing device.

- ◊ **"Yes"** indicates the presence of TR worsening by at least one grade.
- ◊ **"No"** indicates no worsening of TR severity or no evidence of TR based on the same criteria.

Secondary study variables include:

- ◊ **Right Ventricle (RV) Function:** a multiparametric echocardiographic evaluation of RV function will include the following measurements:
  - ♦ **Tricuspid Annular Plane Systolic Excursion (TAPSE):** will be measured using M-mode echocardiography. Represents vertical displacement of the tricuspid annulus during systole.
  - ♦ **Fractional Area Change (FAC):** measures RV systolic function. It will be calculated as the percentage difference between the end-diastolic and end-systolic areas.
  - ♦ **Right Ventricle Basal Diameter (RVBD):** will be measured at end-diastole in the apical four-chamber view at the tricuspid valve annulus level.
  - ♦ **Tricuspid Annular Systolic Velocity (S'):** quantifies the velocity of the tricuspid annulus during systole using tissue Doppler imaging.
  - ♦ **Myocardial Performance Index (MPI or Tei index):** will be assessed via pulsed and tissue Doppler. Combines the isovolumetric contraction and relaxation times with the ejection time to assess global right ventricular function.
  - ♦ **Free-wall Right Ventricle Longitudinal Strain (RVLS):** the degree of longitudinal shortening of the right ventricular myocardium during systole will be measured through speckle-tracking echocardiography.
- ◊ **Complications:** based on clinical criteria, laboratory tests and other complementary imaging techniques, assumed complications will comprehend:
  - ♦ Pneumothorax.
  - ♦ Pericarditis.
  - ♦ Perforation.
  - ♦ Hematoma.
  - ♦ Lead or device dislodgement.
  - ♦ Infection.
  - ♦ Others (e.g. deep vein thrombosis, pneumopericardium, device erosion, etc.).
  - ♦ No complications.

	VARIABLE		TYPE	VALUES
INDEPENDENT VARIABLE	**Pacemaker**		Qualitative Dichotomous	Leadless/Conventional
DEPENDENT VARIABLES	**MAIN VARIABLE**			
	TR		Qualitative Dichotomous	Yes/No
	SECONDARY VARIABLES			
	RV function	**TAPSE**	Quantitative Continuous	mm
		FAC	Quantitative Continuous	%
		RVBD	Quantitative Continuous	mm
		S'	Quantitative Continuous	cm/s
		MPI	Quantitative Continuous	Unitless
		RVLS	Quantitative Continuous	%
	Complications		Qualitative Nominal	Pneumothorax Pericarditis Perforation Hematoma Lead or device dislodgement Infection Others No complications

Table 1: Summary of independent and dependent study variables.

Controlled variables

- **Age:** a quantitative continuous variable measured in years, based on the patient's date of birth. Age is a critical determinant of survival and procedural risks, with advanced age being linked to higher mortality and complications.
- **Sex:** a qualitative dichotomous variable categorized as male or female. Sex differences influence survival outcomes, with women often showing better long-term survival despite older age at implantation.
- **Comorbidities:** a set of qualitative nominal variables including coronary artery disease, diabetes, heart failure, hypertension, chronic renal disease, atrial fibrillation and valvular disease. These conditions are strong predictors of both procedural complications and mortality.
- **Indication:** a qualitative nominal variable categorized based on clinical diagnoses. Class I or II indications for single-chamber pacing will be considered.
- **Implantation Site:** septal vs apical implantation is a qualitative dichotomous variable. This distinction is clinically significant because septal pacing has been shown to improve outcomes such as LVEF and exercise capacity compared to apical pacing.
- **Baseline TR:** will be categorized as none, mild or moderate, since severe TR constitutes an exclusion criterion. Refers to the functional and structural condition of the tricuspid valve, assessed through echocardiographic imaging before the intervention. It will be analyzed with the same compound approach as the main variable.
- **Baseline RV Function:** expressed as a multiparametric variable with set of continuous quantitative measurements, including the same echocardiographic parameters used to evaluate the secondary outcome of RV function (TAPSE, FAC, RVBD, S', MPI and RVLS). Severe RV dysfunction will be considered an exclusion criterion.
- **Right Ventricular Pacing Burden:** a quantitative continuous variable, expressed as the percentage of RVPB. High percentages correlate with adverse outcomes such as reduced left ventricular function and increased heart failure risk.

VARIABLE	TYPE	VALUES
Age	Quantitative Continuous	Numerical (years)
Sex	Qualitative Dichotomous	Male/Female
Comorbidities	Qualitative Nominal	Coronary artery disease Diabetes Heart failure Hypertension Chronic renal disease Atrial fibrillation Valvular disease
Indication	Qualitative Nominal	SND AV block
Implantation site	Qualitative Nominal	Septal/Apical
Baseline TR	Qualitative Ordinal	None/Mild/Moderate
Baseline RV function		
TAPSE	Quantitative Continuous	mm
FAC	Quantitative Continuous	%
RVBD	Quantitative Continuous	mm
S'	Quantitative Continuous	cm/s
MPI	Quantitative Continuous	Unitless
RVLS	Quantitative Continuous	%
RVPB	Quantitative Continuous	%

Table 2: Summary of controlled study variables.

Intervention

This project will be conducted in the Cardiology Service and Arrhythmia Unit of the Hospital Universitari Dr. Josep Trueta in Girona. The Arrhythmia Unit will be responsible for selecting pacemaker candidates according to the latest guidelines from the European Society of Cardiology (16).

Patients with an indication for VVI/VDD single-chamber pacing, whether urgent or elective, will first be given a participant information sheet. After agreeing to the study protocol, they will undergo a standardized transthoracic echocardiogram (TTE) performed by a cardiologist from the Advanced Cardiac Imaging Unit. The images will be systematically analyzed by two cardiologists from the same unit. Once the inclusion criteria are confirmed, patients will sign an informed consent form.

Randomization will be conducted in a 1:1 ratio to one of the treatments using Sealed Envelope. Computerized randomization will be used to identify and balance any potential confounders, thereby avoiding potential bias.

- ◊ **Group 1:** Leadless Pacemaker (Micra™ VR2 and Micra™ AV2 by Medtronic®).
- ◊ **Group 2:** Conventional Pacemaker (devices from Abbott®, Biotronic®, Boston Scientific®, Medtronic® and Microport® will be implanted).

Both interventions will be performed by electrophysiologists from the Arrhythmia Unit who have undergone standard training recommended by the manufacturer. The implantations will be performed under fluoroscopic guidance following standard techniques.

After discharge, device follow-ups will be carried out according to the protocol. Post-24h and 2-week follow-up will help monitor pacemaker thresholds and other required electrical parameters. Short-term complications will be evaluated and treated.

At 12 months post-implantation, a standardized TTE will be performed following the same pre-implantation protocol. Any worsening of TR will be documented, as well as RV function parameters and complications. For patients where intrinsic cardiac rhythm can be achieved without pacing, a pacing-free TTE will help to obtain parameters unaffected by the pacing itself. The team will also collaborate in completing the database. Furthermore, they will lead the dissemination of results through the preparation and presentation of communications at conferences and the drafting of written publications.

Data Collection

Data for this study will be obtained through a combination of clinical history, physical examination, TTE and other relevant diagnostic tests. All patient information will be systematically recorded in the database as the study progresses. A structured data collection process will be conducted to gather both baseline and follow-up information and relevant clinical details.

To ensure participant confidentiality, all collected data will be assigned unique identification numbers instead of personal identifiers. Data collection will be carried out using a standardized data collection sheet *(ANNEX 6)*.

Tricuspid Regurgitation Evaluation

TR will be evaluated as a compound variable, defined as a **worsening of at least one grade of severity**, as classified according to the 2021 ESC/EACTS Guidelines for the management of valvular heart disease (63) and Guidelines for the Evaluation of Valvular Regurgitation After Percutaneous Valve Repair or Replacement (64).

The assessment of TR will focus on identifying and grading the severity of regurgitation using an integrative approach via TTE. The procedure will adhere to standardized guidelines set by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) to ensure consistent and reliable measurements. High-resolution echocardiography equipment with 2D imaging, M-mode echocardiography, Doppler modalities (including color, pulsed-wave, continuous-wave, and tissue Doppler), and speckle-tracking capabilities will be used. Apical 4-chamber view will mainly be used. RV inflow, parasternal long- and short-axis views may complement the assessment depending on image quality and Doppler beam alignment with the regurgitant jet.

- **Central Jet:** on color Doppler, jet area is visualized in multiple views, including apical 4-chamber and RV inflow views. It is analyzed qualitatively.
- **CV width:** using color Doppler, with a Nyquist limit of 50-60cm/s, measuring the width at its narrowest point.
- **PISA radius:** assessed by color Doppler with a Nyquist limit of 25-35cm/s, measures the radius of the hemispheric shell at the aliasing velocity. This radius is the distance from the regurgitant orifice to the first aliasing contour.

◊ **EROA:** calculated by PISA method, it is derived by dividing the flow rate by the peak velocity of the regurgitant jet obtained from CW Doppler, where Pk is the pressure in RV, V_{reg} is the regurgitant volume, and V_a is flow velocity through TV.

$$EROA = \frac{2\pi r^2 \cdot V_a}{Pk \cdot V_{reg}}$$

◊ **RVol:** calculated by PISA method by multiplying the EROA by the velocity-time integral of the regurgitant jet.

$$Rvol = EROA \cdot VTI_{reg}$$

◊ **CW Doppler velocity waveform and density:** using CW Doppler, the waveform should be analyzed for its density and early peaking.

Parameter	Mild	Moderate	Severe
Central Jet	Small, narrow, central	Moderate central	Large central jet or eccentric wall-impinging jet(s) of variable size swirling in the RA
Vena Contracta Width (cm)	<0.3	0.3-0.69	≥0.7
PISA Radius (cm)	≤0.5	0.6-0.9	>0.9
EROA (cm^2)	<0.20	0.20-0.39	≥0.40
RVol (mL)	<30	30-44	≥45
CW Doppler Velocity Waveform and Density	Faint/partial/parabolic	Dense, parabolic or triangular	Dense, often triangular

Table 3: Evaluation of TR via TTE.

Right Ventricular Function Evaluation

RV function will be evaluated using a multiparametric strategy, including:

◊ **TAPSE:** measured via M-mode echocardiography in the apical 4-chamber view, evaluates the longitudinal motion of the tricuspid annulus toward the apex. It is a

simple, reproducible, and recommended measure for assessing RV systolic function.

◊ **FAC:** determined by subtracting the right ventricular end-systolic area (ESA) from the end-diastolic area (EDA) and dividing the result by the EDA. This parameter is assessed in the RV-focused apical 4-chamber view and reflects both longitudinal and radial right ventricular function.

$$FAC = \frac{EDA - ESA}{EDA} \times 100\%$$

◊ **RVBD:** measured in the apical 4-chamber view at end-diastole. It represents the maximal short-axis dimension in the basal one-third of the right ventricle, at the level of the tricuspid valve annulus.

◊ **S':** measures the systolic motion of the tricuspid annulus using pulsed Doppler in an apical 4-chamber view.

◊ **MPI:** combines systolic and diastolic functions to evaluate overall efficiency via pulsed and tissue Doppler. Expressed as a unitless ratio, obtained by the sum of isovolumetric contraction time (IVCT) and isovolumetric relaxation time (IVRT), divided by ejection time (ET).

$$MPI = \frac{IVCT + IVRT}{ET}$$

◊ **RVLS:** evaluated through speckle-tracking echocardiography in the apical 4-chamber view, assesses myocardial deformation and contractility.

Parameter	RV Systolic Dysfunction
TAPSE (mm)	<16
FAC (%)	<35
RVBD (mm)	>41
S' (cm/s)	<10
MPI	>0.44 (pulsed Doppler) / >0.55 (tissue Doppler)
RVLS (%)	<-20

Table 4: Evaluation of RV function via TTE.

Safety and Complications

Procedure-related complications will be evaluated through anamnesis, clinical exploration, TTE and other laboratory tests and/or imaging techniques, according to professional criteria. To ensure accuracy, sonographers and cardiologists will undergo standardized training. Regular calibration sessions will be held throughout the study. Complications will be treated accordingly to ensure patient's safety.

Short-term complications, including pneumothorax, hematoma, pericarditis, perforation and dislodgement, will be addressed at either the 24h post-implantation or 2 weeks post-implantation follow-up, as for the hospital's protocol.

Infection, dislodgement, and other complications (e.g. device erosion, deep vein thrombosis) will comprehend long-term complications and will be evaluated at the 12 month endpoint.

Severe complications, as overseen by professionals, will constitute a withdrawal criterion for the study, although no increase of complications is expected in comparison to conventional pacemaker implantation.

Follow-Up

Patients will undergo regular follow-up to monitor clinical outcomes, device performance, and tricuspid valve function. Remote monitoring of the device, as well as clinical care, will be done according to standard clinical practice.

24h Post-Implantation: a clinical evaluation, device interrogation, chest X-ray and EKG will be performed, following routine practice.

2 Weeks Post-Implantation: during the patients wound check and dressing appointment, a clinical evaluation will be performed. If acute complications are present, they will be managed following standard routine practice.

12 Month Follow-Up: a standardized TTE will be performed one year after the procedure to assess TV function, as well as RV parameters. Any presence of TR or worsening of ventricular function will be documented. Long-term complications will be evaluated and treated if needed.

Additional Echocardiogram: for patients with intrinsic rhythm, a pacing-free TTE will be conducted to evaluate cardiac function without the influence of the pacing device.

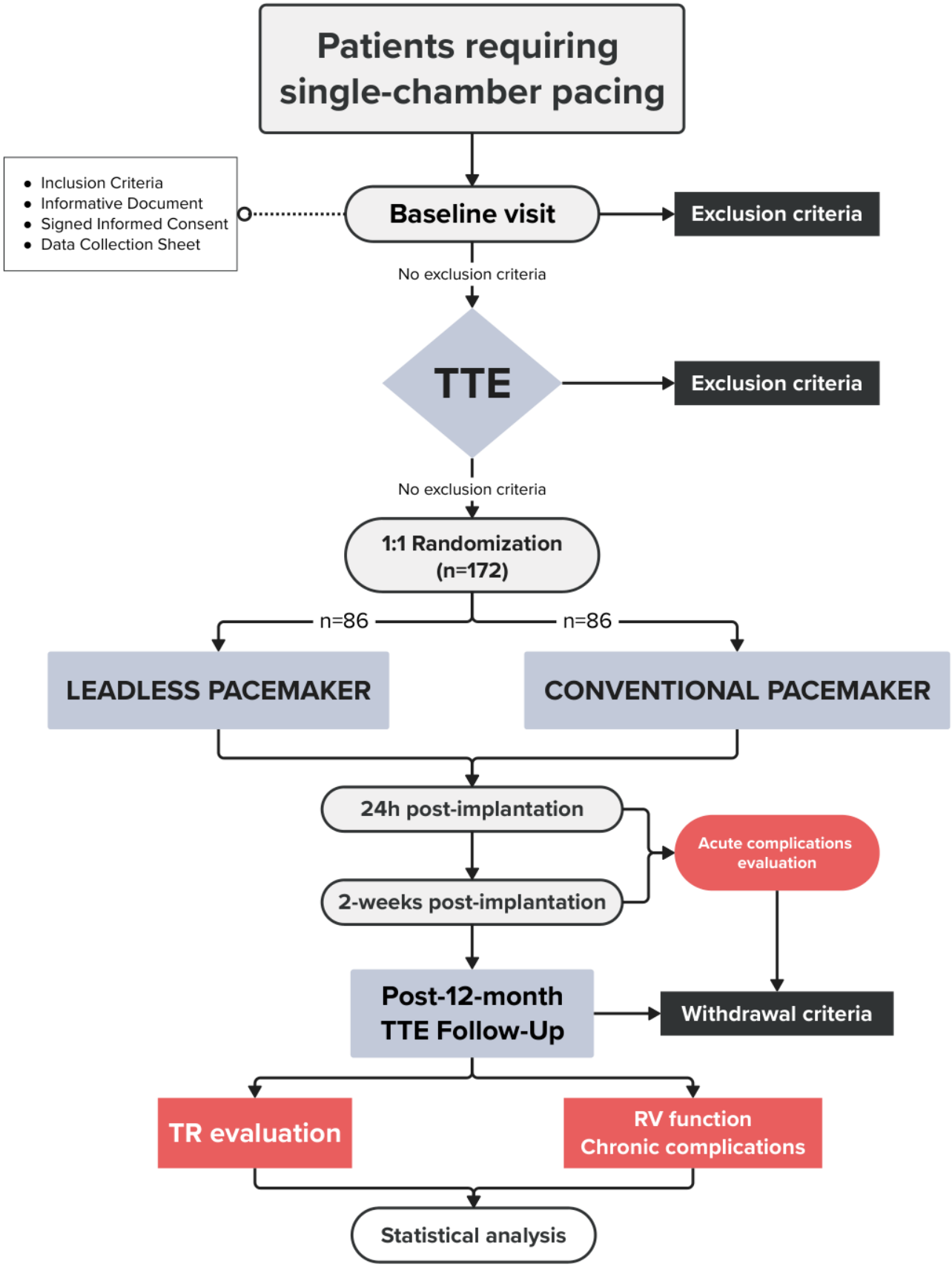

Figure 15: Flow chart.

Database

Column	Data	Description
Patient information		
Patient_ID	Integer	Unique identifier for each patient
Age	Integer	Age in years at the time of enrollment
Sex	Text	Male/Female
Group	Text	Leadless/Conventional
Comorbidities	Text	Coronary artery disease/diabetes/heart failure/hypertension/chronic renal disease/atrial fibrillation/ valvular disease
Indication	Text	AV block/SND/others
Implantation site	Text	Septal/Apical
Baseline TR	Text	None/Mild/Moderate
Baseline RV function:		
TAPSE	Decimal	mm
FAC	Decimal	%
RVBD	Decimal	mm
S’	Decimal	cm/s
MPI	Decimal	Unitless
RVLS	Decimal	%
RVPB	Decimal	%
TR assessment		
Patient_ID	Integer	Unique identifier for each patient
TR	Boolean	Yes/No
Central Jet	Text	Small/Moderate/Large
Vena Contracta	Decimal	cm
PISA radius	Decimal	cm
EROA	Decimal	cm^2
RVol	Integer	mL
CW Doppler Waveform	Text	CW waveform description

RV function assessment		
Patient_ID	Integer	Unique identifier for each patient
TAPSE	Decimal	mm
FAC	Decimal	mm
RVBD	Decimal	%
S’	Decimal	cm/s
MPI	Decimal	Unitless
RVLS	Decimal	%

Safety and complications		
Patient_ID	Integer	Unique identifier for each patient
Pneumothorax	Boolean	Yes/No
Pericarditis	Boolean	Yes/No
Perforation	Boolean	Yes/No
Hematoma	Boolean	Yes/No
Dislodgement	Boolean	Yes/No
Infection	Boolean	Yes/No
Others	Boolean	Yes/No
No complications	Boolean	Yes/No

Follow-up		
Patient_ID	Integer	Unique identifier for each patient
24h	Text	Summary of findings
2 weeks	Text	Summary of findings
12 months	Text	Summary of findings
Pacing-free	Text	For patients with intrinsic rhythm

Table 5: Database.

Statistical Analysis

The statistical analysis will be conducted by a professional statistician. A **p-value <0.05** will be considered statistically significant, with a **95% confidence interval** for all analyses.

All data will be collected in the online data forms created by **Research Electronic Data Capture Software (REDCap)** which will facilitate data integration and security.

The analysis will be conducted using version 30.0.0 of the **Statistical Package for the Social Sciences (SPSS)** software.

Univariate

All the variables in the study will be summarized and described as follows.

Qualitative Variables

The independent variable (Leadless Pacemaker vs. Conventional Pacemaker), the main variable (TR) and the secondary qualitative variable Complications will be summarized using **proportions**.

Quantitative Variables

Secondary quantitative variables:

- ◊ TAPSE: measured in millimeters.
- ◊ FAC: expressed as a percentage.
- ◊ RVBD: measured in millimeters.
- ◊ S': measured in cm/s.
- ◊ MPI: expressed as a unitless ratio.
- ◊ RVLS: expressed as a percentage.

Will be described using the **mean and standard deviation (SD)** if they follow a normal distribution, or the **median and interquartile range (IQR)** if they do not. Normality of the distribution will be assessed using the **Shapiro-Wilk test**.

Data Presentation

The results of the univariable analysis will be presented in tables, clearly displaying the **frequencies and percentages for categorical variables**, and the **means ± SD or medians with IQR for quantitative variables**, depending on their distribution.

Bivariate

The bivariate analysis will help determine the relationship between the type of pacemaker implanted (Leadless pacemaker or Conventional pacemaker) and the occurrence of TR or other secondary variables.

Main objective

For the main objective (effect of pacemaker type on TR at 12 months) we will calculate the **Relative Risk (RR)** to measure the association between the type of pacemaker (leadless vs. conventional) and the incidence of TR worsening. RR will be calculated using 2x2 contingency tables, comparing proportions of TR worsening between pacemaker types.

Secondary objectives

Quantitative continuous variables (TAPSE, FAC, RVBD, S', MPI, RVLS) will be tested for normality using Shapiro-Wilk or similar normality tests.

- ◊ If the variables follow a normal distribution, the **Student's T-test** will be used to compare means between groups.
- ◊ If the variables do not follow a normal distribution, the **Mann-Whitney U** test will be applied to compare medians.

For complications (expressed as a nominal qualitative variable) a **Chi-square test** will be used to assess the association between pacemaker type and the occurrence of each complication.

Multivariate

To examine the relationship between the independent (predictor) variable and one or more dependent (outcome) variables simultaneously, considering potential confounding factors or interactions between variables.

RV function metrics are included because they are known predictors of TR progression and may confound the relationship between pacemaker type and TR risk.

Main objective

To analyze the effect of pacemaker type on the risk reduction of TR worsening, adjusting for potential confounders, a **Logistic Regression Model** will be used for the primary outcome.

Secondary objectives

For quantitative continuous variables related to RV function (TAPSE, FAC, RVBD, S', MPI, RVLS), a **General Linear Model for Repeated Measurements** will be applied if the data follows a normal distribution. If the distribution is not normal, **Generalized Estimating Equations** will be used. Normality will be tested using Shapiro-Wilk or other appropriate tests.

A **Multinomial Logistic Regression** will be applied to assess the likelihood of different complications occurring based on pacemaker type, while adjusting for relevant covariates such as age, sex, and comorbidities.

Stratification

Stratification allows for subgroup analysis to understand the differential effects of pacemaker type across demographic and clinical factor. All descriptive statistics will be stratified based on relevant covariates, such as sex, comorbidities, or baseline right ventricular function parameters. This will allow a detailed understanding of how these factors influence the primary and secondary outcomes.

Ethical and Legal Considerations

This clinical trial will adhere to the ethical principles established by the Declaration of Helsinki (65) and the Principles of Biomedical Ethics by Beauchamp and Childress (66). These include:

- ◊ **Autonomy:** participation will be voluntary, and all patients will provide informed consent after being fully informed about the study's objectives, procedures, potential risks, and benefits. If the patient is unable to do so, their legal representative will review and sign the consent document.
- ◊ **Beneficence:** the study is designed to evaluate whether leadless pacemaker implantation offers clinical benefits, particularly regarding the preservation of tricuspid valve function, improving outcomes for patients needing cardiac pacing.
- ◊ **Non-maleficence:** potential risks, such as device-related complications or procedural adverse events, will be closely monitored and minimized. Patients who do not meet inclusion criteria will be excluded to prevent harm.
- ◊ **Justice:** inclusion and exclusion criteria will ensure that all eligible patients, regardless of demographics, are considered, and patient selection will avoid any form of discrimination.

Regulatory Compliance

The trial will comply with Spanish and European legislation on biomedical research and medical devices, including:

- ◊ **Real Decreto 1090/2015:** regulates clinical trials with medicines and ethical review boards.
- ◊ **Real Decreto 192/2023:** governs medical devices.
- ◊ **Reglamento (UE) 2017/745:** European regulation on medical devices.
- ◊ **Ley 14/2007:** Spanish law on biomedical research.

Data Protection and Confidentiality

Participants' privacy will be safeguarded following **Reglamento (UE) 2016/679 (GDPR)** and **Ley Orgánica 3/2018**. All patient data will be anonymized, assigning a unique identification code to ensure confidentiality. Access to data will be restricted to the research team and the Ethics Committee when required for study evaluation.

Ethical Approval and Monitoring

The study protocol will be submitted to **Institut d'Investigació Biomèdica de Girona Dr. Josep Trueta (IDIBGI)** and **Comitè d'Ètica d'Investigació Clínica (CEIC)** at the Hospital Universitari Doctor Josep Trueta for approval. Recommendations from both institutions will be implemented into the protocol. The study will also be registered in the **Registro Español de Estudios Clínicos (REec)** and monitored via **EudraCT** to ensure compliance with regulatory standards. Approval from the **Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)** will be required.

Transparency and Conflicts of Interest

All results, including unfavorable outcomes, will be published to ensure transparency and prevent publication bias. Investigators declare no conflicts of interest in conducting or reporting this study.

Study Work Plan and Chronogram

Overview

This single-center, randomized clinical trial at HUJT in Girona aims to compare the progression of CIED-related TR between patients receiving leadless versus conventional pacemakers. A total of 172 participants will be enrolled, with equal distribution between the two study groups. This study is designed to be conducted over a period of approximately **3 years**, including recruitment, follow-up, data analysis, and dissemination phases.

Research Team

Main investigator: individual whose roles in the research include directing the execution of the project, ensuring proper protocol application and supervising the functioning of all centers. Additionally, they will be responsible for participating in result discussions, drawing conclusions and contributing to dissemination efforts.

Co-investigators: includes all the cardiologists that actively participate in the research at the hospital.

Healthcare personnel: includes all personnel necessary to conduct the study such as anesthesiologists, medical engineers, nurses, other cardiologists nonparticipating in the study, etc.

Other personnel: statistical analyst, data controller and English corrector.

Study Work Plan

Stage 1: Protocol Development

Initial Meeting (January 2025): the research team will meet to wrap up the study objectives, define the primary and secondary outcomes, and discuss the intervention procedure. Outcome assessment methods, including TTE parameters, will be discussed and detailed ensure consistency and reliability in data collection.

Bibliographic Research and Protocol Preparation (January/February 2025): a thorough review of the literature will be conducted to ensure the study design aligns with the latest evidence. A detailed protocol will be drafted, including inclusion/exclusion criteria, randomization, and follow-up protocols.

Database Creation (February 2025): a database will be developed to systematically record clinical, echocardiographic, and procedural data.

Stage 2: Ethical Approvals

Ethical Review and Approval (March/April 2025): the protocol will be submitted to the CEIC and IDIBGI at HUJT, AMEPS, and the Spanish regulatory authorities (REec and EudraCT). All recommendations from these bodies will be incorporated into the protocol to ensure compliance.

Stage 3: Recruitment, Intervention and Follow-up

Patient Recruitment and Device Implantation (May 2025/August 2026): candidates for pacemaker implantation will be identified, informed about the study, and assessed for eligibility. Recruitment will include obtaining informed consent. Implantation of the leadless or conventional pacemaker will be conducted following standard techniques.

Follow-Up and Data Collection (May 2026/August 2027): echocardiographic assessments will be conducted pre- and post-implantation (TTE at 12 months), documenting TR progression, RV function, and complications. For patients with intrinsic rhythm, a pacing-free TTE will also be performed. All necessary data for each variable will be collected and evaluated as specified in the Data Collection section.

Stage 4: Data Analysis

Data Compilation and Quality Control (May 2026/August 2027): patient data will be collected, verified, and stored in a centralized, anonymized database.

Statistical Analysis (September/October 2027): blinded statistician will analyze the entire database using univariate, bivariate and multivariate analysis.

Interpretation of Results (October/November) 2027): the research team will evaluate findings and determine the clinical significance of the results.

Stage 5: Dissemination

Scientific Publications (December 2027): the project coordinator will draft the final manuscript, incorporating the results, discussion, and conclusions of the study. It will undergo revision by an English language editor before being submitted for publication in an ESC-endorsed journal to maximize visibility and relevance in the cardiovascular research community. Attendance at major conferences will be expected.

Table 6: Chronogram.

STAGE	TASKS	TIME																		CREW
		2025						2026						2027						
		1-2	3-4	5-6	7-8	9-10	11-12	1-2	3-4	5-6	7-8	9-10	11-12	1-2	3-4	5-6	7-8	9-10	11-12	
STAGE 1	Initial Meeting	■																		Research Team
	Protocol Preparation	■																		
	Database Creation	■																		
STAGE 2	Ethical Review		■																	CEIC
STAGE 3	Recruitment and Intervention			■	■	■	■	■	■	■	■									Research Team
	Follow-Up and Data Collection									■	■	■	■	■	■	■	■			
STAGE 4	Data Compilation									■	■	■	■	■	■	■	■			
	Statistical Analysis																	■		Professional Statistician
	Interpretation of Results																	■		Research Team
STAGE 5	Scientific Publications																		■	

Budget

This project is funded by a grant from the Cardiac Stimulation Section of the Spanish Society of Cardiology, awarded at the annual congress on October 29, 2021. A total of **12,500€** will ensure specific training and support the development of a research project.

Personnel

The members of the research team participating in this clinical trial will comprehend physicians, nurses and other healthcare personnel. As such, their involvement will be integrated into their routine clinical duties and will not generate any additional expenses. It is also deemed appropriate that their participation in the study should not be driven by financial incentives.

A statistician will be hired to analyze the data and provide the final results. This will involve 100 hours during patient recruitment and 100 hours for final analysis, at a rate of 20€/hour, resulting in a total cost of **4,000€.**

A data controller will also be hired for 200 hours, at a rate of 20€/hour, resulting in a total cost of **4,000€.**

Review by CEIC will not be charged.

Material and Resources

The intervention will involve the use of leadless conventional pacemakers. Both are standard medical devices utilized in clinical practice, so these devices will be supplied by the hospital as part of its existing resources. No additional costs for equipment or materials is anticipated according to established protocols for pacemaker implantation.

The costs for conventional Medtronic® pacemakers range from $20,753 to $78,140. The Micra™ Transcatheter Pacing System, also designed by Medtronic®, comes at a higher price due to its advanced technology, with reported hospitalization costs for its implantation around $34,098 in recent years. These devices will be supplied by the hospital as part of its existing resources.

The printing cost for the informative document, informed consent, and withdrawn consent forms, at 0.03€/page for 172 participants, results in a total of **30.96€.**

Insurance

Insurance prices around 200€ per participant. The study will qualify as a low-intervention clinical trial, as all procedures are part of routine clinical practice. Participants will be covered under the hospital's insurance.

Scientific Dissemination

For the publication of the study's findings, an English editor will be engaged to ensure the accuracy and clarity of the manuscript. Their services are expected to cost **€200.** Fees associated with publishing the study as a journal article are expected to cost **2,000€.** Attendance at national congress of cardiology, including registration and accommodation for one investigator, is expected to cost **2,000€.**

Contingency

To cover any unforeseen expenses, a contingency amount of **500€** is included.

Total Budget

TYPE	UNITS	COST
STATYSTICAL ANALYST	200 hours	4,000€
QUALITY DATA CONTROLLER	200 hours	4,000€
INSURANCE	-	0€
MATERIAL	-	0€
PRINTING	6/participant	30.96€
ARTICLE EDITION	1	200€
PUBLICATION EXPENSES	1	2,000€
CONGRESS ATTENDANCE	1	2000€
CONTINGENCY	-	500€
		Total budget: 12,730€

Table 7: Estimated budget.

Strengths and Limitations

Strengths

Impact: the study investigates the effect of leadless pacemakers versus conventional transvenous pacemakers on TR, a complication with significant morbidity. Given the growing use of leadless pacemakers, evidence about their long-term safety and impact on tricuspid valve function is critical for improving clinical outcomes. Conducting this clinical trial provides scientific evidence to address these gaps.

Unicentric design: conducting the trial exclusively at HUJT ensures strict protocol adherence, uniform data collection, and consistent echocardiographic evaluations, reducing inter-observer variability while maintaining high internal validity.

Percutaneous approach: implantation procedure for leadless pacemakers is performed percutaneously, offering a less invasive alternative to conventional pacemaker placing, therefore improving patients' willingness to enroll and adhere to the study protocol.

Echocardiography: TTE remains the gold standard for cardiac imaging in routine patient follow-up due to its non-invasive nature, widespread availability, and ability to assess a variety of cardiac parameters. The use of high-resolution echocardiographic equipment with 2D imaging, M-mode echocardiography, Doppler modalities and speckle-tracking capabilities enhances the precision of assessing left and right ventricular function, as well as valve mechanics, allowing for detailed, real-time evaluation.

Integrative evaluation: the combination of echocardiographic parameters comprehensive assessment of both right and left ventricular function. TAPSE and S' are excellent indicators of RV systolic function, while FAC and RVLS offer valuable insights into the overall performance and myocardial function of the RV. RVBD allows for evaluation of the chamber size, contributing to a complete assessment of RV morphology, and MPI serves as an integrated measure of both systolic and diastolic function. Together, these parameters form a well-rounded approach for assessing right cardiac performance.

Limitations

Confounding factors: the complexity of patients receiving pacemakers, including varying comorbidities and baseline characteristics, introduces confounding variables. While statistical adjustments and covariate analysis will mitigate these issues, residual confounding may persist.

Non-probabilistic sampling: the consecutive sampling method introduces potential selection bias. However, random allocation to intervention groups and a significant sample size will help reduce this limitation.

Blinding challenges: blinding is unfeasible for treating clinicians and patients due to the nature of the interventions.

Regional scope the single-center approach ensures consistency but limits generalizability to broader populations and diverse healthcare settings. Prospective multicenter clinical trials are needed to further investigate the topic.

Echocardiography: while valuable, TTE it has limitations in imaging the right ventricle and assessing valve function. Its accuracy can be affected by the RV's anatomical position, variability in shape, and suboptimal imaging angles. The assessment of TV function is operator-dependent and may be influenced by patient factors such as obesity, leading to variable image quality. Advanced equipment and Doppler modalities improve precision, but operator expertise and patient-specific conditions still impact the results.

Follow-up: while a 12 month follow-up provides important early findings, a longer follow-up period may be necessary to capture late-onset complications or recurrences of TR. Although loss to follow-up can affect data completeness, the Arrhythmia Unit currently maintains a 0% loss rate.

Health Impact

CIED-related TR is increasingly recognized as a significant clinical issue, linked to higher heart failure and mortality rates. Meta-analyses highlight TR as a key prognostic factor linked to higher mortality and worse clinical outcomes.

The introduction of leadless pacemakers marks a significant advancement in pacing technology, reducing complications associated with traditional devices. By eliminating transvenous leads, they reduce the risk of TV damage and help prevent the progression of TR. Leadless devices also offer benefits such as fewer infections and reduced vascular complications, improving patient outcomes and optimizing healthcare resources.

The present study focuses on assessing the impact of leadless pacemakers versus conventional transvenous pacemakers on the progression of TR. Our aim is to evaluate whether the use of leadless pacemakers can reduce CIED-related TR progression after a 12 month period. The lack of evidence on this subject, with existing studies being limited and often observational in design, has led to inconsistent results. To date, clinical trials have been performed, but no randomized studies have specifically evaluated the functional effects on the TV in patients with leadless pacemaker stimulation.

Given the limitations of previous research, this randomized clinical trial aims to provide more robust clinical evidence on whether leadless pacemakers can reduce the incidence and progression of TR. By addressing this gap, our study will contribute valuable insights that could shape future treatment strategies for patients requiring pacemaker implantation.

The outcomes of this trial could help clarify the potential benefits of leadless pacemakers. This could lead to more targeted and personalized treatment approaches, ultimately improving long-term cardiovascular health and quality of life for patients. Moreover, by clarifying the effects of leadless pacemakers on TR, this research has the potential to impact healthcare resource allocation, reducing the need for subsequent interventions and hospitalizations related to TR progression.

Feasibility

This study will be conducted at the Arrhythmia Unit of Hospital Universitari Dr. Josep Trueta, which performs over 700 device implantations annually, including conventional pacemakers, transvenous and subcutaneous defibrillators, resynchronization devices, and leadless pacemakers.

Regarding leadless pacemaker implantation, HUJT performs over 65 leadless pacemaker implantations annually. Given the volume of procedures and the growing trend of leadless pacemaker implantation, the unit has the capacity to recruit, implant, and follow-up the required patient sample efficiently. Conventional pacemaker implantations are performed at a rate of approximately 500 per year, given the hospital's established experience.

Considering the available resources, the hospital's infrastructure, and the experienced personnel, this study has a strong potential for successful implementation within a reasonable timeline, ensuring the feasibility of the project.

Furthermore, the catheter-based design of the leadless pacemaker implantation procedure, coupled with its relatively low risk, suggests that patients will likely be open to participation in the study. Clinical trials have reported a 98.3% success rate in achieving low and stable pacing capture thresholds at 6 months, with a 96% freedom from major complications.

As a non-invasive imaging tool, TTE will provide essential data on RV function, TR severity and complications. This technique offers the advantage of being safe, widely accessible, and easily repeatable, making it ideal for monitoring patient progress throughout the study.

The Arrhythmia Unit is equipped to ensure thorough and high-quality follow-up, facilitating evaluation of the study's outcomes after the 12-month period. Furthermore, considering the fast and non-invasive nature of TTE, it may be feasible to extend the study by incorporating protocol-based TTEs into the standard follow-up protocol for pacemaker patients, thereby yielding additional data on long-term outcomes.

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Annex

Annex 1 / Conventional Pacemaker Implantation Technique

I. Preoperative Preparation:
   - ◊ Confirm the indication for implantation and evaluate the patient's medical history, comorbidities, and risk factors like anticoagulation needs or infection risks.
   - ◊ Perform preoperative tests: EKG, echocardiography, and blood work to assess heart function and rule out contraindications.

II. Operative Environment:
   - ◊ Ensure a sterile environment with necessary equipment and personnel trained in pacemaker implantation and emergency procedures.

III. Skin Preparation and Anesthesia:
   - ◊ Local anesthesia with 1% lidocaine is standard, potentially mixed with long-acting anesthetics (e.g. bupivacaine 0.25% or ropivacaine 0.5%).
   - ◊ Anesthetics containing epinephrine are avoided due to increased hematoma risk.
   - ◊ Deep sedation or general anesthesia may be used in agitated patients or for complex cases (e.g. submuscular pockets).

IV. Venous Access:
   - ◊ Via cephalic, subclavian, or axillary veins. Extra-thoracic approach (cephalic and axillary veins) is preferred to minimize complications like pneumothorax. Fluoroscopy, venography, or ultrasound, with a caudal tilt view (35°) are often employed to target the vein safely.

V. Incision and Pocket Creation:
   - ◊ The pocket is usually created at the beginning of the procedure to enhance anesthesia effectiveness and monitor bleeding. A horizontal incision below the clavicle or an oblique incision along the deltopectoral groove is made, depending on operator preference. Both provide similar healing outcomes.
   - ◊ Oblique incisions facilitate cephalic vein access but require careful medial pocket preparation to avoid shoulder interference.
   - ◊ Dissection is performed down to the subfascial plane to avoid complications.

VI. Ventricular Lead Placement:

- ◊ The right ventricular lead is typically placed before the atrial lead to ensure backup pacing and minimize dislodgment risks.
- ◊ Common target sites include the right ventricular apex (RVA), right ventricular septum (RVS), and the right ventricular outflow tract (RVOT). Fluoroscopy will be used to ensure proper lead placing.
- ◊ Check lead stability by withdrawing the stylet and ensuring appropriate slack formation.
- ◊ Test pacing outputs to exclude phrenic nerve stimulation or inadvertent coronary sinus placement.

VII. Atrial Lead Placement:

- ◊ An atrial lead is essential for maintaining AV synchrony, detecting atrial arrhythmias, and improving arrhythmia monitoring in ICDs, though it does not reduce mortality. Dual-chamber devices that include atrial leads carry a 1.5 to 2 times greater risk of complications compared to single-chamber systems. Main issues include lead dislodgment and perforation.
- ◊ Right Atrial Appendage (RAA) placement is commonly used. Anterior RAA placement is preferred for safety. Other sites like Bachmann's bundle or the interatrial septum have not shown significant advantages over RAA pacing and may add complexity or risks. Fluoroscopy will be used to ensure proper lead placing.

VIII. Lead Placement:

- ◊ Resorbable braided sutures around lead insertion sites are useful to control bleeding. Avoid tying directly to the lead body to prevent insulation damage.
- ◊ Secure the lead to the muscular plane, not the subcutaneous fat, as fat is mobile and may cause dislodgement, especially in obese patients.

IX. Generator Placement:

- ◊ Manually check the device before implantation to confirm proper lead connection and parameters, as auto-initialization methods differ by manufacturer. Wipe lead pins with a dry swab to prevent blood clots obstructing wireless communication
- ◊ Irrigate the pocket with saline to clear clots and debris. Coiling the excess lead length and placing it under the generator reduces the risk of damage. Position the generator header towards the incision for easier access during future replacements. Fixation of the generator is optional.

X. Programming and Testing:

- ◊ Test the pacing system intraoperatively to confirm effective lead placement, appropriate sensing, and stimulation thresholds. Program the pacemaker based on patient-specific needs.

XI. Closure:

- ◊ The pocket should be closed with 2 or 4 separate stitches using resorbable braided suture to prevent migration and reduce wound tension.
- ◊ Skin can be closed with a running stitch using a 3-0 resorbable braided suture for the subcutaneous layer, followed by a 4-0 absorbable monofilament subcuticular stitch. Staples are used by some operators but require removal.

XII. Follow up:

- ◊ A chest X-ray (PA and lateral) should be performed within 24 hours post-lead implantation to check for pneumothorax and verify lead position.
- ◊ A 12-lead EKG and full device check should be done before discharge.
- ◊ Patients can mobilize once sedation wears off, and same-day discharge is possible for some.
- ◊ Arm movement restrictions are unnecessary, and shoulder exercises may reduce pain. Post-op care includes a dressing for 2–10 days, with showers allowed after a week.
- ◊ Patients should receive written care instructions and be seen in-office within 1–3 months for follow-up, as delays beyond 12 weeks are linked to worse outcomes.
- ◊ Remote monitoring can help detect issues early.

Annex 2 / Leadless Pacemaker Implantation Technique

I. Preoperative Preparation:
   - ◊ Confirm the indication for implantation and evaluate the patient's medical history, comorbidities, and risk factors like anticoagulation needs or infection risks.
   - ◊ Perform preoperative tests: EKG, echocardiography, and blood work to assess heart function and rule out contraindications.

II. Operative Environment:
   - ◊ Ensure a sterile environment with necessary equipment and personnel trained in pacemaker implantation and emergency procedures.

III. Skin Preparation and Anesthesia:
   - ◊ Local anesthesia with 1% lidocaine is standard, potentially mixed with long-acting anesthetics (e.g. bupivacaine 0.25% or ropivacaine 0.5%).
   - ◊ Anesthetics containing epinephrine are avoided due to increased hematoma risk.
   - ◊ Deep sedation or general anesthesia may be used in agitated patients or for complex cases.

IV. Vascular Access:
   - ◊ Femoral Access: The right femoral vein is the preferred entry point due to its straighter path to the heart. Ultrasound guidance is recommended to reduce vascular complications.
   - ◊ Insert a large introducer sheath (up to 27 French) into the femoral vein using the Seldinger technique.

V. Delivery and Positioning:
   - ◊ Attach the leadless pacemaker (e.g. helix-based or tined system) to the delivery catheter and introduce it into the right ventricle through the femoral access.
   - ◊ Use fluoroscopic imaging to guide the catheter into the desired location within the right ventricle (commonly the apical or septal region).

VI. Fixation:
   - ◊ For helix-based systems, the device is secured with clockwise rotations of the fixation helix to engage myocardial tissue.
   - ◊ For tined systems, self-expanding nitinol tines anchor the device to the ventricular wall.
   - ◊ Evaluate fixation stability using fluoroscopy and pacing thresholds.

VII. Testing:

- ◊ Perform electrical testing to verify sensing, impedance, and capture thresholds. Adjust placement if electrical parameters are suboptimal.

VIII. Completion:

- ◊ Detach the pacemaker from the delivery system.
- ◊ Withdraw the delivery catheter and sheath.
- ◊ Achieve hemostasis at the femoral access site using techniques such as a figure-of-eight suture.

IX. Postoperative Management:

- ◊ A chest X-ray (PA and lateral) should be performed within 24 hours post-lead implantation to check for pneumothorax and verify lead position.
- ◊ A 12-lead EKG and full device check should be done before discharge.
- ◊ Advise bed rest for 4–6 hours and follow standard postoperative care protocols.
- ◊ Patients may be discharged the same day or after 24 hours based on recovery.
- ◊ Patients should receive written care instructions and be seen in-office within 1–3 months for follow-up, as delays beyond 12 weeks are linked to worse outcomes.
- ◊ Remote monitoring can help detect issues early.

Annex 3 / Participant Information Sheet

HOJA DE INFORMACIÓN PARA EL/LA PARTICIPANTE

Nombre del estudio: Evaluation of CIED-related Tricuspid Regurgitation in Single-chamber Leadless Pacing.

Centro asistencial: HUJT
Investigador principal:

Bienvenido/a:

Gracias por su interés en participar en nuestro estudio. Nos gustaría invitarle a formar parte de un proyecto de investigación que se llevará a cabo en varios hospitales. Este estudio ha sido aprobado por el Comité de Ética e Investigación Clínica (CEIC) de [ubicación] y los hospitales participantes, de acuerdo con las leyes vigentes y respetando los principios establecidos en la Declaración de Helsinki.

Este documento proporciona información detallada sobre el estudio, su objetivo y lo que su participación implicará. Es importante que lea esta hoja cuidadosamente para entender el estudio y su posible participación, de modo que pueda tomar una decisión informada. Si tiene alguna pregunta o inquietud, no dude en preguntarnos.

La participación en este estudio es **completamente voluntaria**. Si decide no participar, su decisión no afectará en nada su atención médica. Puede retirarse del estudio en cualquier momento, y esto no cambiará el tratamiento que reciba.

Objetivos del estudio:

El estudio tiene como objetivo evaluar la posibilidad de reducir la regurgitación tricuspídea en pacientes que reciben un marcapasos, comparando la implantación de un marcapasos sin cable frente al marcapasos convencional transvenoso. Queremos explorar si el marcapasos sin cable puede ofrecer una alternativa menos invasiva y con menos impacto mecánico sobre el aparato valvular, lo que podría resultar en una menor incidencia de regurgitación tricuspídea en nuestra población. Además, observaremos si existen diferencias en la función del ventrículo derecho y la fracción de eyección del ventrículo izquierdo, comparando los resultados entre los dos tipos de marcapasos. Este estudio también evaluará posibles complicaciones relacionadas con ambos tipos de dispositivos.

Descripción del estudio:

Para evaluar nuestros objetivos, se asignarán dos grupos de 86 personas, quienes recibirán tratamiento con marcapasos convencionales o con marcapasos sin cable. Para evitar sesgos de confusión e información, todos los pacientes recibirán un tratamiento asignado de manera aleatoria, con un seguimiento de un año. Se realizará un seguimiento de la evolución clínica de los participantes a través de visitas periódicas. En cada grupo, uno recibirá el tratamiento real y el otro recibirá un placebo. El estudio tendrá una duración total de X años, aunque su participación será de 12 meses.

En qué consiste su participación:

Si cumple con los criterios para participar en el estudio y está interesado/a en formar parte, será necesario que firme el documento de Consentimiento Informado durante su próxima visita, el cual se le entrega junto con esta información.

Una vez haya decidido participar y firmado el consentimiento informado, recopilaremos información básica sobre su historial clínico y se le asignará aleatoriamente a uno de los dos grupos del estudio: el grupo que recibirá un marcapasos convencional o el que recibirá un marcapasos sin cable.

Desde ese momento, se le hará un seguimiento tras 1 año a partir del inicio de su tratamiento (independientemente del tipo de marcapasos). Se realizará evaluación ecocardiográfica de los objetivos del estudio.

Confidencialidad y protección de datos:

Toda información referente a usted recogida durante el estudio será introducida en una base de datos con un código que garantice el anonimato para su análisis. Su nombre ni otra forma en la que pueda ser identificado aparecerá en ningún documento público, y el uso comercial de estos datos está prohibido.

Toda la información es guardada y gestionada de forma segura y confidencial, de acuerdo con la Ley Orgánica 03/2018, de 5 de diciembre y del Reglamento (UE) 2016/679 del Parlamento Europeo de 27 de abril de 2016 de protección de datos.

Contacto en caso de ayuda:

Si durante su participación tiene alguna duda o necesita obtener más información, puede ponerse en contacto con los principales responsables de la investigación. Contacte mediante el siguiente correo:

_____

Muchas gracias por su colaboración y atención, Atentamente,

El equipo de investigación

FIRMA DEL PACIENTE FIRMA DEL INVESTIGADOR

Annex 4 / Informed Consent

CONSENTIMIENTO INFORMADO:

Sober el estudio: Evaluation of CIED-related Tricuspid Regurgitation in Single-chamber Leadless Pacing.

Yo, (nombre y apellidos)_____, con DNI _____,

y la fecha (DD/MM/AAAA) ___/___/_____

declaro que:

- He leído y entendido el documento informativo que se me ha entregado sobre el estudio.
- He podido hacer todas las preguntas que me han surgido y han sido respondidas de forma satisfactoria por el personal del estudio.
- He recibido la información suficiente y necesaria sobre el objetivo del estudio, su desarrollo y los posibles riesgos y beneficios asociados a mi participación.
- Entiendo que mi participación en este estudio es voluntaria, y que puedo retirarme en cualquier momento, sin necesidad de dar explicación alguna y sin que esto afecte al seguimiento y tratamiento médico de mi enfermedad.
- Consiento que los datos personales y clínicos recogidos durante el estudio sean almacenados en una base de datos codificada, garantizando el anonimato, y que estos datos sean utilizados solo con fines científicos.

De acuerdo con el Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, sobre la protección de datos personales, declaro haber sido informado/a de:

- La existencia de una base de datos que incluirá mis datos personales.
- La finalidad de la recogida de los datos y destinatarios de la información.
- El proceso de codificación de los datos para garantizar su confidencialidad.

- La disponibilidad de ejercer mis derechos de acceso, rectificación y cancelación de los datos dirigiéndome por escrito al equipo investigador del estudio.

Doy libremente mi consentimiento para participar en este estudio clínico.

Firma del participante: _____

Fecha: _____

Annex 5 / Withdrawal Consent

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO:

Yo (nombre y apellidos) _____, con DNI_____, a fecha (DD/MM/AAAA)_____, revoco el consentimiento informado previamente firmado en el estudio Evaluation of CIED-related Tricuspid Regurgitation in Single-chamber Leadless Pacing.

FIRMA DEL PACIENTE FIRMA DEL INVESTIGADOR

Annex 6 / Data Collection Sheet

DATOS IDENTIFICATIVOS

Código del participante: _____

Hospital: HUJT

Fecha: _____

INFORMACIÓN DEMOGRÁFICA Y DE SALUD

Fecha de nacimiento (DD/MM/AAAA): _____

Edad: _____

Sexo: ☐ Mujer ☐ Hombre

Indicación para implantación de marcapasos (S/N): _____

Comorbilidades:

☐ Enfermedad arterial coronaria

☐ Diabetes

☐ Insuficiencia cardíaca

☐ Hipertensión arterial

☐ Enfermedad renal crónica

☐ Fibrilación auricular

☐ Enfermedad valvular

☐ Enfermedad pulmonar crónica

☐ Otras: _____

Sitio de Implantación del Marcapasos:

☐ Septal

☐ Apical

DATOS DEL DIAGNÓSTICO Y PROCEDIMIENTO

Indicación para marcapasos:

☐ Bloqueo auriculoventricular

☐ Bradicardia sinusal sintomática

☐ Otra (especificar): _____

Tipo de dispositivo implantado:

☐ Marcapasos convencional

☐ Marcapasos sin cable

Fecha de implantación (DD/MM/AAAA): _____

DIAGNÓSTICO INICIAL (ECOCARDIOGRAFÍA):

☐ Presencia de regurgitación tricuspídea basal: _____

☐ Fracción de eyección ventricular izquierda (FEVI, %): _____

☐ Función del ventrículo derecho:

♦ Diámetro basal del ventrículo derecho (DBVD, mm): _____

♦ Intercambio de área fraccional (FAC, %): _____

♦ Excursión sistólica del plano anular tricuspídeo (TAPSE, mm): _____

♦ Velocidad sistólica del anillo tricuspídeo (S', cm/s): _____

♦ Índice de Tei (MPI): _____

♦ Strain longitudinal de la pared libre del VD (RVLS, %): _____

SEGUIMIENTO Y EVENTOS ADVERSOS

Eventos adversos relacionados con el procedimiento:

☐ Neumotórax

☐ Pericarditis

☐ Perforación

☐ Hematoma

☐ Desplazamiento de cable o dispositivo

☐ Infección

☐ Otros (especificar): _____

Fecha de aparición del evento adverso (DD/MM/AAAA): _____

Resolución del evento adverso (S/N): _____

Fecha de resolución: _____

EVALUACIÓN DE LA REGURGITACIÓN TRICUSPÍDEA (RT)

Seguimiento de RT (ecocardiografía a los 12 meses):

Grado de RT: _____
Progresión de la RT (S/N): _____
Comentarios adicionales: _____

FUNCIÓN CARDÍACA EN EL SEGUIMIENTO

Fracción de eyección del ventriculo izquierdo:

A los 12 meses: _____

Función del ventrículo derecho (mediciones ecocardiográficas):

• Diámetro basal del ventrículo derecho (DBVD, mm): _____
• Intercambio de área fraccional (FAC, %): _____
• Excursión sistólica del plano anular tricuspídeo (TAPSE, mm): _____
• Velocidad sistólica del anillo tricuspídeo (S', cm/s): _____
• Índice de Tei (MPI): _____
• Strain longitudinal de la pared libre del VD (RVLS, %): _____

OBSERVACIONES ADICIONALES DEL INVESTIGADOR